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

PC 128831 5

CYFLUTHRIN **Carcinogenicity study in mice (83-2b)**

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DATA EVALUATION RECORD
Supplement to DER for MRID No. 00137304 Cyfluthrin: Carcinogenicity Mouse Study. **This supplement includes a revised executive summary which includes changing the NOEL and LOEL to a NOAEL and LOAEL.**

STUDY TYPE: Carcinogenicity Study in Mice
OPPTS Number: 870.4100, 870.4200 OPP Guideline Number: 83-1, 83-2b

DP BARCODE: N/A
P.C. CODE: 128831

SUBMISSION CODE: N/A
TOX. CHEM. NO.: 266E

TEST MATERIAL (PURITY): Cyfluthrin (49.7-51.0%); FCR 1272

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

CITATION: Suberg, H. and Loser, E. FCR1272 (Cyfluthrin) chronic toxicological study on mice. (Unpublished study No. 12035 prepared by Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, German for Mobay Chemical Corporation, Agr. Chem. Div., Kansas City, MO; dated August 24, 1983.)

SPONSOR: Mobay Chemical Corporation, Agricultural Chemical Division

EXECUTIVE SUMMARY:

In a carcinogenicity study (MRID No. 00137304), cyfluthrin (49.7-51.0% purity as a premix concentrate in Wessalon S) was administered in the diet for 23 months to SPF mice (50/sex/dose) at dose levels of 0, 50, 200 or 800 ppm (equivalent to 0, 11.6, 45.8 or 194.5 mg/kg/day in males and 0, 15.3, 63.0 or 259.9 mg/kg/day in females based on food consumption and body weights).

There were no treatment related changes noted in the clinical observations, food consumption, hematology, gross observations, organ weights and microscopic pathology data. No ophthalmologic examinations or urinalyses were performed. Fluoride did not accumulate in teeth or bones of mice as observed in the rat study (MRID No. 00137303).

The mortality data were equivocal with respect to treatment. The incidence of mortality in the mid- and high-dose females was somewhat higher than the controls throughout the study. However, only the mid-dose at termination was significantly ($p \leq 0.05$) different from controls. At study termination, mortality in the females was 52, 60, 74 and 68% for the control, low-, mid- and high-dose groups, respectively. Mortality in the males was 80, 78, 82, and 88% for the control, low, mid- and high-dose groups, respectively at study termination. Mean body weights relative to controls were no more than 10% less for mid- and high-dose males and 9% less for the mid- and high-dose females throughout the study. The mean body weights of the treated groups, however, were not significantly different at termination, possibly due to the mortality differences in the dosed groups compared to the concurrent controls.

In the clinical chemistry data, alkaline phosphatase activity was elevated in treated males at all dose levels when compared to controls at all time points except termination where there was evidence that the samples were hemolyzed, leading to spurious results. A dose-response was evident at months 6 (↑43-230%; $p \leq 0.05$ or 0.01) and 12 (↑37-73%; $p \leq 0.05$ or 0.01); however, it was somewhat flat for the low - and mid-dose groups at month 12. At month 18, there was no dose-response. The low-dose group had the highest elevation in alkaline phosphatase (↑ 114%, $p \leq 0.05$) while the mid- and high-dose groups remained somewhat flat (↑61 and 68%, respectively ($p \leq 0.05$ and 0.01: the odd significance values indicate some wide-ranging individual values in at least one dose group). The histopathology data did not confirm the liver as a target organ.

Under the conditions of this study, there was no evidence of carcinogenic potential.

This study is classified as **Acceptable guideline** for a carcinogenicity study in mice (870.4200, 83-2b).

This study is classified as **Uncceptable guideline** for a chronic feeding study in mice (870.4100, 83-1a). No urinalysis or opththalmological data were collected and the clinical chemistry data were limited. In addition, alkaline phosphatase levels are increased at all dose levels, indicating that a NOAEL could not be established.

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EPA: 68-01-6561
TASK: 90
January 25, 1985

DATA EVALUATION RECORD

FCR1272 (CYFLUTHRIN)

Chronic Toxicity and Oncogenicity Study in Mice

CITATION: Suberg, H. and Loser, E. FCR1272 (Cyfluthrin) chronic toxicological study on mice. (Unpublished study No. 12035 prepared by Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Germany for Mobay Chemical Corporation, Agr. Chem. Div., Kansas City, MO; dated August 24, 1983.)

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DATA EVALUATION RECORD

STUDY TYPE: Chronic toxicity and oncogenicity study in mice.

CITATION: Suberg, H. and Loser, E. FCR1272 (Cyfluthrin) chronic toxicological study on mice. (Unpublished study No. 12035 prepared by Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Germany for Mobay Chemical Corporation, Agr. Chem. Div., Kansas City, MO; dated August 24, 1983.)

ACCESSION NUMBER: 072366.

LABORATORY: Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Germany.

QUALITY ASSURANCE STATEMENT: Not present.

TEST MATERIAL: The test material was identified as an active ingredient sample designated as FCR 1272. It was received in batches as pre-mix concentrates in Wessalon S. The test compound content was 49.7 to 51.0% formulation 113. The common name of FCR 1272 is Cyfluthrin.

PROCEDURES:

1. Male and female SPF mice, strain CF1/W74, were obtained from Winkelmann, Borchen, Germany. The mice were 5-6 weeks of age at start of study and had mean weights of 27 g for males and 22 g for females. The animals were individually housed in cages in a room maintained at 21-23° C and 50-60% humidity on a 12-hour light/dark cycle. Food and tapwater were available ad libitum.

2. The test material was mixed with powdered feed to obtain the required concentrations. The active ingredient content and the test substance were verified at various intervals throughout the study.

3. Animals were randomly assigned to four dose groups which were fed diets containing 0, 50, 200, or 800 ppm. Each group consisted of 50 mice/sex.

4. Animals were observed twice daily (once a day on weekends and holidays) and changes and/or toxic symptoms were recorded when found. Individual body weights and group food consumption were determined weekly the first 15 weeks, every three weeks from week 18 to 66, and weekly thereafter. All surviving animals were sacrificed at 23 months of study.

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Hematology and clinical chemistry were performed on 10 mice/sex/group at 6, 12, 18, and 23 months. Blood was collected via the retro-orbital venous plexus under ether anesthesia. The hematology parameters measured were erythrocyte count, hematocrit, hemoglobin, red cell indices (MCV, MCH and MCHC), total and differential leucocyte counts, thrombocyte count, and reticulocyte count. The clinical chemistry parameters measured were alkaline phosphatase, SGPT, creatinine, urea, cholesterol, and bilirubin. Urinalyses were not performed.

Fluoride content in the bones and teeth were determined on 5 mice/sex/group at 23 months of study.

Gross examination was performed on mice that died or were sacrificed when moribund. The organs and tissues were preserved for all animals. At 23 months all survivors were anesthetized with diethyl ether and sacrificed by exsanguination. The mice were grossly examined and the following organs were weighed: heart, testes, lung, liver, spleen, kidneys, and ovaries.

All animals that died or were sacrificed moribund and animals at termination had the following tissues preserved in 10% buffered formaldehyde solution for histological examination: aorta, eyes, intestine (duodenum, jejunum, ileum, colon, cecum, and rectum), femur en bloc with skeletal musculature and sciatic nerve, gallbladder, brain, Harderian glands, urinary bladder, skin, heart, testes, pituitary, salivary glands, liver, lung, lymph nodes (mesenteric and non-mesenteric), stomach, mammary glands, spleen, adrenals, kidneys, ovaries, pancreas, prostate, spinal cord, seminal vesicle, sternum, (thyroids, esophagus, and trachea en bloc), uterus, and gross lesions.

5. Statistical Methods: The mean and standard deviations of tabular data were assessed at the upper and lower confidence limits at levels of 95 and 99%. The data for dose groups were compared to the control group with the significance test (U test) of Mann, Whitney, and Wilcoxon, at the alpha 5 and 1% significance level. Fisher's exact test was used to compare the incidence of mortality in the dose groups and controls. An IBM subroutine package was used to generate randomization lists.

RESULTS:

Dietary Analyses: No analytical results were given for stability, homogeneity, or concentration of cyfluthrin in the diet.

Mortality: The incidence of mortality of male and female mice is summarized in Table 1. The incidence of mortality in the mid- and high-dose females was somewhat higher than controls throughout the study. However, only the mid-dose at termination was significantly different from controls. The mortality data are equivocal with respect to relationship to the test material.

Body Weight: Selected body weight data are given in Table 2. Male and female high-dose animals lost weight during the first week on study. The body weight of females remained significantly less than that of controls

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TABLE 1. Mortality Incidence in Mice Fed Cyfluthrin

Dietary Level (ppm)	Incidence of Mortality at Week				
	26	52	64	78	99
Males					
0	4(92)[a]	13(74)	23(54)	34(32)	40(20)
50	3(94)	14(72)	20(60)	31(38)	39(22)
200	3(94)	13(74)	22(56)	33(34)	41(18)
800	5(90)	17(66)	19(62)	31(38)	44(12)
Females					
0	2(96)	6(88)	14(72)	20(60)	26(48)
50	1(98)	5(90)	13(74)	24(52)	30(40)
200	7(86)	15(70)	19(62)	29(42)	37(26)*
800	6(88)	12(76)	19(62)	27(46)	34(32)

Did
52
60
74
68

[a] Numbers in parenthesis are the percent survival based 50 animal/sex/group.

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

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TABLE 2. Selected Mean Body Weight Data in Mice Fed Cyfluthrin

Dietary Level (ppm)	Mean Body Weight (g) at Week							Percent of Control at Week	
	0	1	13	27	51	78	99	13	99
Males									
0	26.7	27.9	35.0	39.5	43.0	42.9	40.2	100	100
50	26.4	28.2	34.7	38.8	40.9	41.0	38.3	99	95
200	27.0	28.3	35.0	38.4	41.9	40.5	36.0	100	90
800	27.3	26.7*	34.6	37.9	39.7*	39.1*	38.9	99	97
Females									
0	21.6	22.2	27.8	31.6	34.9	35.3	33.8	100	100
50	21.7	22.5	28.4	30.8	33.9	35.0	32.7	102	97
200	21.6	22.3	28.1	30.5	34.1	33.2	36.2	101	107
800	21.1	20.9**	27.6	30.0**	33.2*	32.2*	32.1	99	95

* Significantly different from control value ($p \leq 0.05$).
** Significantly different from control value ($p \leq 0.01$).

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throughout the first 95 weeks of the study. The decreased mean body weight of high dosage level females (and possibly males) is likely to be related to the test material. At the mid dosage level, the data are equivocal. At 13 weeks and at termination, there were no significant differences in the mean body weight of treated animals as compared with controls.

Food Consumption: Selected food consumption and test compound intake data are given in Table 3. No significant differences between treated and control animals were noted for food consumption.

Hematology: Hematology results are summarized as follows:

6 Months - Male and female mice at 6 months exhibited no dose-related changes. In the male mice, there were sporadic significant differences in MCV and MCHC. (CBI page 13)

TABLE 3. Selected Food Consumption Data for Mice Fed Cyfluthrin

Dietary Level (ppm)	Mean Food Consumed (g/mouse/day) at Week 1	54	99	Overall Average	Mean Compound Intake (mg/kg/day)
Males					
0	10	9	9	9	-
50	10	9	9	9	11.6
200	10	8	8	9	45.8
800	10	8	9	9	194.5
Females					
0	11	10	8	10	-
50	11	9	7	9	15.3
200	11	10	9	10	63.0
800	10	10	9	10	259.9

12 Months - No dose-related changes were noted in male or female mice. There was a significant increase in MCH and MCHC in male mice and sporadic significant differences in RBC and platelet count (CBI pg 017). In the females there was a significant increase in platelet counts and sporadic significant differences in RBC, Hgb, MCH, Hct, MCH, and MCHC.

18 Months - No dose-related changes were noted in male or female mice. There was a significant decrease in MCH and MCHC in the low-dose males (CBI pg 021). In the female mice, there was a significant increase in the segmented neutrophiles with corresponding decreases in the lymphocytes (CBI pg 024).

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23 Months - No dose-related changes were noted in male or female mice. There was significant differences in Hct and MCHC in the low-dose male. (CBI pg. 025)

Clinical Chemistry: Significant differences noted in the liver enzyme activities are summarized in Table 4. Dose-related effects were most pronounced for alkaline phosphatase in males through 18 months. These effects were likely to have been related to the test material. No other differences were considered biologically relevant. Fluoride did not accumulate in teeth or bones.

Necropsy: Gross necropsies did not indicate any effects due to the test material.

Organ Weight: The absolute and relative organ weight data did not reveal any dose-related effects.

Histopathology: Frequently encountered non-neoplastic lesions are summarized in Table 5 and neoplastic lesions are given in Table 6. No dose-related differences were noted.

DISCUSSION:

According to Authors:

The only effect noted by the authors was decreased body weight in females fed 800 ppm as compared to controls. A target organ was not identified. They dismissed the alkaline phosphatase data since there was no significant finding for liver organ weight or histopathology data. Based on the body weight data, the NOEL for cyfluthrin in mice was 200 ppm and the LEL was 800 ppm.

According to This Review:

It appears that the effects of aging may have masked significant findings at termination of the study, especially in the alkaline phosphatase, body weight, and organ weight data.

In the body weight data, effects were noted throughout most of the study, but possibly due to mortality differences in all dosed groups of females and high-dose males as compared to their respective controls, the mean body weights of treated groups at termination were not significantly different from controls. Mean body weight differences were as high as 11% for mid- and high-dose males and 8% and 12% for mid- and high-dose females, respectively. Thus, the mid-dose (200 ppm) could be considered an effect level. This rationale also extends to mortality in females where excess mortality at termination was 8, 22, and 16% for the low-, mid-, and high-dose groups, respectively, as compared to controls. Excess mortality was 8% in the high-dose males at termination. Thus, the MTD may have been exceeded in this study.

In the clinical chemistry data, the dose-response of alkaline phosphatase activity in males was clearly evident at month 6, 12, and 18. At termination there was considerable evidence that many of the samples were hemolyzed, therefore leading to spurious results. The evidence is based

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TABLE 4. Selected Clinical Chemistry Data for Mice Fed Cyfluthrin

Dietary Level (ppm)	Alkaline Phosphatase (U/L) at Month 6	12	18	23	Glutamic-Pyruvic Transaminase (U/L) at Month 6	12	18	23
Males								
0	59	84	95	706[a]	35	55	33	637[a]
50	80*	115*	204*	238	32	35**	55	88
200	91**	120*	153*	106**	35	52	53	86
800	196**	146**	158**	371	45*	55	58**	192
Females								
0	155	163	162	431	39	31	35	135
50	124	122	193	310	33	30	34	65
200	120	150	259*	360	32	37	58*	56
800	154	117*	153	304	34	40	44	69

[a]Includes three animals with activities greater than 1200 U/L.
*Significantly different from control value ($p \leq 0.05$).
**Significantly different from control value ($p \leq 0.01$).

TABLE 5. Frequently Encountered Non-Neoplastic Lesions in Mice Fed Cyfluthrin

Organ/Finding	Males (ppm)				Females (ppm)			
	0	50	200	800	0	50	200	800
Heart	(47)[a]	(45)	(49)	(49)	(48)	(46)	(49)	(47)
myocardial degeneration	20	31	33	12	14	23	17	17
Trachea	(28)	(30)	(38)	(35)	(37)	(42)	(45)	(38)
round cell infiltration	7	5	8	16	22	11	16	11
Lungs	(46)	(44)	(49)	(45)	(48)	(45)	(48)	(47)
alveolar edema	11	10	20	6	2	2	8	7
Stomach	(38)	(38)	(45)	(46)	(47)	(44)	(44)	(46)
round cell infiltration	3	4	9	3	8	16	14	3
hermorrhagic erosion	3	4	2	8	3	2	2	10
Liver	(44)	(43)	(48)	(45)	(47)	(45)	(47)	(46)
lymphoid cell infiltration	5	11	5	1	6	15	11	7
Pancreas	(42)	(39)	(46)	(43)	(47)	(43)	(46)	(43)
lymphoid cell infiltration	2	8	8	1	10	12	11	5
atrophic acini	-	1	2	3	3	6	6	5
Kidney	(45)	(43)	(49)	(43)	(48)	(45)	(48)	(46)
tubular atrophy	26	19	29	28	22	13	17	19
calcification	15	17	19	15	1	3	1	-
glomerular cysts	14	17	16	12	7	5	1	3
degenerated tubuli	18	13	13	12	8	9	1	4
round cell infiltration	31	30	41	35	42	39	35	38
Testes	(46)	(42)	(49)	(47)				
tubular atrophy	9	10	9	8				
Ovaries					(48)	(44)	(48)	(46)
cyst(s)					22	17	11	16
Uterus					(48)	(45)	(48)	(40)
cystic hyperplasia					25	27	21	20

TABLE 5. Frequently Encountered Non-Neoplastic Lesions in Mice Fed Cyfluthrin (continued)

Organ/Finding	Males (ppm)				Females (ppm)			
	0	50	200	800	0	50	200	800
Adrenal Gland	(44)	(43)	(47)	(46)	(48)	(44)	(47)	(46)
A-cell proliferation	7	5	13	9	45	43	41	39
ceroid cell degeneration	2	1	-	3	30	26	25	19
Spleen	(44)	(41)	(47)	(43)	(48)	(44)	(47)	(45)
erythropoiesis	4	9	14	9	22	27	20	22
Lymph nodes	(42)	(37)	(45)	(37)	(48)	(43)	(48)	(39)
hyperplasia	16	11	8	5	23	21	21	19

[a] The numbers in parentheses are the number of tissues examined histologically.

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TABLE 6. Frequently Encountered Neoplastic Lesions in Mice Fed Cyfluthrin

Organ/Finding	Males (ppm)				Females (ppm)			
	0	50	200	800	0	50	200	800
Lungs	(46)[a]	(44)	(49)	(48)	(48)	(45)	(48)	(47)
brochioalveolar tumor	10	13	11	8	16	5	11	12
Liver	(44)	(43)	(48)	(45)	(47)	(45)	(47)	(46)
adenoma, hepatocellular	-	2	3	4	3	2	4	-
carcinoma, hepatocellular	6	10	5	4	2	1	1	3
Uterus					(48)	(45)	(48)	(46)
stromal polyp					-	2	3	1
leiomyosarcoma					2	1	1	1
carcinoma					-	1	2	-
Pituitary	(40)	(33)	(42)	(39)	(44)	(41)	(43)	(37)
adenoma	-	-	1	1	4	1	2	1
Adrenal glands	(44)	(43)	(47)	(46)	(48)	(44)	(47)	(46)
cortical tumor, non-invasive	-	2	2	1	-	1	-	-
cortical tumor, invasive	4	2	2	2	1	1	1	-
Hemolymphoreticular System	(47)	(45)	(49)	(49)	(48)	(46)	(49)	(47)
malignant lymphoma	7	5	9	3	12	11	10	12

[a]Number in parenthesis is the number of animals in that group for which the organ was examined.

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as well as bilirubin and cholesterol concentration are affected by hemolysis. Through 18 months, there were 2/120 bilirubin samples that were above 4.0 micromoles/liter and 2/120 cholesterol samples above 4.0 millimoles-liter (CBI pp. 214-225). However, at study termination 30/80 bilirubin samples and 25/80 cholesterol samples were above the same levels. For control males, 6/10 samples may have been hemolyzed based on cholesterol levels while 8/10 samples for control females may have been hemolyzed based on bilirubin concentration. Thus, the data for study based on the samples analyzed at termination were unacceptable. It is possible that the aging process increased the fragility of erythrocytes, however, fragility tests were not conducted.

There was no apparent reason to reject the alkaline phosphatase data in males. If a more conservative approach is used to assign biological significance i.e., when the means are two standard deviations above the control, then the mid- and high-dose results can be considered significant at 6 months; and it follows that all three treatment group means were significantly increased at 12 and 18 months. Since effects were observed at all doses, a no effect level could not be established for alkaline phosphatase activity.

For, organ weight data, all organs were included in the calculated means even if tissue masses were noted at necropsy. For those animals from which organ weights were taken, weight data are given in Table 7. The mean body weights at termination are different from those given in Table 2 because a number of animals were not included in the organ weight data. The reason for excluding these animals was not given. The standard deviations are included in the relative liver, spleen, and kidneys weight data. These large standard deviations are indicative of the wide variations in the data. Hence, an interim sacrifice might have provided usable data; however, the data at termination of the study were unacceptable for analysis.

Although the pathology data were adequate for this study, histopathology data did not confirm the liver as a target organ. The total number of tumors and the distribution of tumors within groups indicate that cyfluthrin is not an oncogen in mice.

CONCLUSIONS:

According to the Authors:

Cyfluthrin was not a carcinogen in mice, and the NOEL for the chronic study is 200 ppm while the LEL is 800 ppm based on body weight effects.

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TABLE 7. Selected Weight Data for Mice Fed Cyfluthrin

Dietary Level (ppm)	No. of Animals	Terminal Body Weight (g)	Percent of Control (%)	Relative[a] Liver Weight (%)	Relative[a] Spleen Weight (%)	Relative[a] Kidney Weight (%)
Males						
0	10	41.4	--	5.46 ± 1.43	0.23 ± 0.11	2.33 ± 1.36
50	11	38.4	93	6.32 ± 2.61	0.47 ± 0.59	2.26 ± 0.21*
200	9	36.7	89	4.65 ± 0.50	0.33 ± 0.23	2.35 ± 0.33*
800	6	38.2	92	6.02 ± 1.00	0.26 ± 0.07	2.43 ± 0.40
Females						
0	24	32.4	--	6.47 ± 2.75	0.87 ± 1.47	1.71 ± 0.28
50	19	32.7	101	6.19 ± 1.31	1.08 ± 1.05	1.75 ± 0.26
200	13	35.8	110	7.15 ± 4.64	1.02 ± 0.96*	1.72 ± 0.19
800	16	31.6	98	5.91 ± 1.06	0.79 ± 0.76	1.74 ± 0.15

[a]Relative to body weight.

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

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According to the Review:

Cyfluthrin is not an oncogen in male or female mice under the conditions of this study. For chronic toxicity the LEL is 50 ppm based on an increased alkaline phosphatase activity in dosed males. The NOEL for cyfluthrin in male mice was not established.

CORE CLASSIFICATION: Core minimum for oncogenicity.
Supplementary for chronic toxicity.

LOEL 50 ppm
NOEL not set.

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R058533

Chemical:	**Cyfluthrin**
PC Code:	**128831**
HED File Code	**13000 Tox Reviews**
Memo Date:	**02/16/2001 12:00:00 AM**
File ID:	**00000000**
Accession Number:	**412-04-0046**

HED Records Reference Center
03/25/2004