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[CYFLUTHRIN-Technical] Chronic Toxicity/Oncogenicity Study (83-5)

EPA Reviewer: Pamela M. Hurley, PhD Pamela M Hurley . Date 2/16/2001
Registration Action Branch 2 (7509C)

EPA Secondary Reviewer: Alan C. Levy, PhD Alan C. Levy . Date 2/16/2001
Registration Action Branch 2 (7509C)

DATA EVALUATION RECORD

Supplement to DER for MRID No. 44459301: Cyfluthrin: [Chronic/Oncogenicity Study in Rats] **This supplement includes a revised executive summary, including a discussion on why the increase in the incidence of mammary gland adenocarcinomas is not considered to be toxicologically significant.**

STUDY TYPE: Chronic Toxicity/Oncogenicity Study, OPPTS 870.4300(83-5), Feeding - Rat

DP BARCODE: D247250 ✓

SUBMISSION CODE: S541724

P.C. CODE: 128831 (CYFLUTHRIN) ✓

TOX. CHEM. NO.: 266E

TEST MATERIAL (PURITY): CYFLUTHRIN (BAYTHROID 94.7% a.i)

SYNONYMS: BAYTHROID, Cyano(4-fluoro-3-phenoxyphenyl)methyl 3(2,2,-dichloroethenyl)-2.2-dimethyl-cyclopropanecarboxylate.

CITATION: B. S. Wahle and W. R. Christenson (1997). Technical Grade Cyfluthrin: A Combined Chronic Toxicity/Oncogenicity Testing Study in the Rat. Bayer Corporation Agriculture Division, Toxicology, 17745 South Metcalf, Stillwell, KS 66085-9104. Laboratory Report No: 107769. December 12, 1997. MRID No.: 44459301, Unpublished.

SPONSOR: BAYER CORP, Agriculture Division, Box 4913, Hawthorn Road, Kansas City, MO 64120-0013

EXECUTIVE SUMMARY:

In a combined chronic toxicity/carcinogenicity study (MRID 44459301), **cyfluthrin** (94.7% a.i.), was administered to separate 1- and 2-yr sacrifice groups of Fischer 344 rats. The 1-year sacrifice group consisted of 40 animals (20 males and 20 females) in both the control and high-dose groups and 20 animals (10 males and 10 females) in both the low and intermediate dose levels for a total of 120 animals. The two-year sacrifice group consisted of 100 animals (50

males and 50 females) in all 4 dose groups for a total of 400 animals. Nominal dietary concentrations of 0, 50, 225, 450 ppm, corresponding to mean daily intake of the test substance of approximately 0,2.6,11.6,22.8 mg/kg/day/male rat or 0, 3.3, 14.4, 28.3 mg/kg/day/female rat, was achieved.

At 225 ppm, mean body weights were up to 7% less than the control groups in both sexes and mean body weight gains were up to 12% and 10% less than the control groups for males and females, respectively. At 450 ppm , mean body weights were up to 13% and 14% less than the control groups and mean body weight gains were up to 23% and 24% less than the control groups for males and females, respectively. An increased frequency of alopecia was also observed in 450-ppm males and females (M:17,16,17,30; F:30,35,34,43).

There were no compound related effects on mortality, food consumption, hematology, urinalysis, or gross pathology. **The LOAEL is 225 ppm (11.6 and 14.4 mg/kg body wt/day for male and female rats, respectively)**, based on decreases in body weight gain relative to controls by 12% and 10% in males and females, respectively. **The NOAEL is 50 ppm (2.6 and 3.3 mg/kg body wt/day for male and female rats, respectively).**

At the doses tested, there was a treatment related increase in tumor incidence of mammary gland adenocarcinomas in 2-yr 450-ppm females when compared to controls (M: 0/50 (0%), 1/50 (2%), 0/50 (0%), 1/50 (2%); F: 1/50 (2%), 0/50 (0%), 0/50 (0%), 4/50 (8%)). Dosing was considered adequate based on decrease in body weight, compared to controls, as a critical endpoint in this study. The increase in incidence of mammary gland adenocarcinomas is not considered to be toxicologically significant because none of the increases in mammary tumors were statistically significant and, with the exception of one fibroadenoma observed on day 668 when the animal died, all the hyperplasia and mammary tumors were observed at terminal sacrifice. Neither the incidences of hyperplasia nor fibroadenomas appeared to be dose-related. Historical control data are as follows: 1/50 adenomas and 1/50 adenocarcinomas in one study and 0/50 for both in a second study from the same laboratory; 3.8% (mean) and 2-15% (range) for carcinomas in the Hazleton laboratories; 1.5% (mean) and 0-4.3% (range) for carcinomas in the Charles River (1990) laboratories and 1.5% (mean) and 0-4% (range) for the National Toxicology Program (1985). A 1983 study on cyfluthrin using Wistar rats was negative at doses up to 25.5 mg/kg/day and cyfluthrin is not mutagenic in multiple assays. Out of 19 other pyrethroids, only cyhalothrin has a possible increase in mammary tumors; however the study involved mice, the tumors were considered to be equivocal, and the highest dose level attained was not considered to be adequate for fully assessing the carcinogenic potential of cyhalothrin.

This combined chronic toxicity/carcinogenicity study in the rat is acceptable, and satisfies the guideline requirement for a chronic toxicity/carcinogenicity study (83-5) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

EPA Reviewer: Ayaad Assaad, D.V.M., Ph.D. , Date: 10/22/1998
Toxicology Branch II (7509C)
EPA Secondary Reviewer: William Greear, MPH, DABT , Date
Toxicology Branch II (7509C)

DATA EVALUATION RECORD

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In a combined chronic toxicity/carcinogenicity study (MRID 44459301), **cyfluthrin** (94.7% a.i.), was administered to separate 1- and 2-yr sacrifice groups of Fischer 344 rat. The 1-year sacrifice group consisted of 40 animals (20 males and 20 females) in both the control and high-dose groups and 20 animals (10 males and 10 females) in both the low and intermediate dose levels for a total of 120 animals. The two-year sacrifice group consisted of 100 animals (50 males and 50 females) in all 4 dose groups for a total of 400 animals. A nominal dietary concentrations of 0, 50, 225, 450 ppm, corresponding to mean daily intake of the test substance of approximately 0,2.6,11.6,22.8 mg/kg/day/male rat or 0, 3.3, 14.4, 28.3 mg/kg/day/female rat, was achieved.

There were compound-related declines in body weight gain of 6 and 7% in 225-ppm males and females, respectively, while 8% and 13% declines were measured in males and females, respectively at 450 ppm. An increased frequency of alopecia was also observed in 450-ppm males and females (M:17,16,17,30; F:30,35,34,43).

There were no compound related effects in mortality, food consumption, hematology, urinalysis, or gross pathology. **The LOAEL is 225 ppm (11.6 and 14.4 mg/kg body wt/day for male and female rats, respectively)**, based on overall declines in body weight gain by 6 and 7% in males and females, respectively. **The NOAEL is 50 ppm (2.6 and 3.3 mg/kg body wt/day for male and female rats, respectively).**

At the doses tested, there was a treatment related increase in tumor incidence of mammary gland adenocarcinomas in 2-yr 450-ppm females when compared to controls (M;0,1,0,1; F:1,0,0,4). Dosing was considered adequate based on decrease in body weight, compared to controls, as a critical endpoint in this study.

This combined chronic toxicity/carcinogenicity study in the rat is acceptable, and does satisfy the guideline requirement for a chronic toxicity/carcinogenicity study (83-5) in the rat.

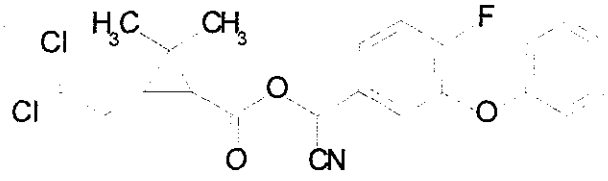
COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** CYFLUTHRIN (BAYTHROID)
   Description: CYFLUTHRIN (BAYTHROID) is a chemical with insecticidal properties, used as an agrochemical
   Physical Status: Viscous liquid
   Color: Brown
   Lot/Batch #: 4030059/BF9340-71
   Purity: 94.7% a.i.
   Stability of compound: at least 40 months (~-23°C)
   CAS #: 68359-37-5

Structure:



2. **Vehicle and/or positive control:**
   Acetone/corn oil mixture.
   Lot/Batch #: Not reported in the study.

3. **Test animals:**
   Species: Rat
   Strain: CDF[Fischer-344]/BR
   Age and weight at study initiation:
   approximately 8 weeks old, and weighed 175,
   and 127 grams for males and females, respectively
   Source: Charles River Breeders, Inc. (Kingston, NY)
   Housing: Individually, in suspended stainless steel wire-mesh cages
   Diet: Purina Mills Rodent lab Chow 5001-4 in "etts" form *ad libitum*
   Water: Tap water, *ad libitum*

Environmental conditions:
Temperature: 18-26°C
Humidity: 40-70%
Air changes: Not reported in the study
Photoperiod: 12 hr/daily

Acclimation period: at least 6 days

B. **STUDY DESIGN:**

1. **In life dates:**
   Start of the study: December 5, 1994
   End of the study: December 12, 1996

2. **Animal assignment**
   Animals were assigned randomly to the test groups in table 1.

TABLE 1: STUDY DESIGN[1]

Test Group	Conc. in Diet *(ppm)*	dose (mg/kg/day)[a]		1-Year Sacrifice[b]		2-year Sacrifice[b]	
		Male	Female	Male	Female	Male	Female
Control	0	0	0	20	20	50	50
Low (LDT)	50	2.6	3.3	10	10	50	50
Mid (MDT)	225	11.6	14.4	10	10	50	50
High (HDT)	450	22.8	28.3	20	20	50	50

[1]Data extracted from P.21, study report # 107769, MRID 44459301
[a]Time-weighted average based on food consumption, dietary concentration, and body weight; calculated by authors.
[b]No. Of animals/dose/treatment group.

3. **Dose Selection:** The authors stated that the doses were selected based on data generated from subchronic, chronic toxicity/oncogenicity, and reproductive bioassays conducted with cyfluthrin in the rat (MRID No. 44371401, MRID No. 00131532, MRID No. 00131524, MRID No. 00137303). Briefly, in these studies body weight was the principal endpoint affected following exposure to cyfluthrin. At a dose of 450 ppm, statistically significant body weight declines (relative to controls) at conclusions of a 2-year bioassay were 8.6% and 10.6% in males and females, respectively. Based on these results it was anticipated that the low and high doses chosen of 50 and 450 ppm would constitute a no-observed-adverse-effect level and a maximum tolerated dose, respectively, with the intermediate dosage of 225 ppm serving to confirm any dose response relationships that may have emerged.

4. **Diet preparation and analysis:**

Diet was prepared weekly by mixing appropriate amounts of test substance with Purina Mills Rodent lab Chow 5001-4 in "etts" form. An acetone/corn oil mixture was used as a vehicle to dissolve the test substance prior to mixing in the diet. The control diet (including acetone/corn oil mixture) was prepared the same as the treated diet, excluding only the test substance. The prepared diet was stored under freezer conditions (~-23°C) until presented to animals. Homogeneity and stability were tested at 25 and 2000 ppm. During the study, samples of treated food were analyzed for four concentrations, 0,50,225, and 450 ppm at week 1,14,17,40, 53,66,79,92, and 105. Stability was assessed for two concentrations, 25 and 2000 ppm under two different storage conditions. At freezer temperature (-23°C), stability was assessed for 28 days (at day 7,14,21,28), and at room temperature storage (22°C), stability was assessed for 14 days (at day 0,1,3,7,10,14).

Results:

Homogeneity Analysis: The mean concentration of cyfluthrin in the 25 ppm test level was 24.5 ppm (97.9% initial conc.), and in the 2000 ppm level, it was 2170 ppm (108% initial conc.).

Stability Analysis: Stability of cyfluthrin in rodent ration was assessed for two concentrations, 25 and 2000 ppm, at room temperature (~22°C, table 2), or at freezer temperature (~-23°C, table 3)

Table 2. Stability of cyfluthrin in rodent ration stored at room temperature[1].

Time/Day	25 ppm	%INITIAL	2000 PPM	%INITIAL
0	26.8	100	2271	100
1	29.1	109	2312	102
3	26.3	98.1	2196	96.7
7	28.7	107	2270	100
10	25.4	94.8	2302	101
14	28	104	2234	98.4

[1]Data extracted from P.3962, study report # 107769, MRID 44459301

Table 3. Stability of cyfluthrin in rodent ration stored at freezer temperature[1].

Time/Day	25 ppm	%INITIAL	2000 PPM	%INITIAL
0	27.5	100	2251	100
7	26.8	97.5	2271	101
14	27.4	99.6	2359	105
21	28.4	103	2011	89.3
28	30.8	112	2510	112

[1]Data extracted from P.3962, study report # 107769, MRID 44459301

Concentration Analysis:

Mean for 50 ppm = 51.1±5 ppm, % Nominal=102%
Mean for 225 ppm = 221±16 ppm, % Nominal=98.1%
Mean for 450 ppm = 429±29 ppm, % Nominal=95.3%

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5. Animals received fresh diet weekly *ad libitum*.

6. **Statistics:**

Continuous data were evaluated initially for equality or homogeneity of variance using Bartlett's test. Group means were further analyzed by a one-way variance analysis (ANOVA) followed by Dunnett's test. Unequal variances were subject to non-parametric procedures consisting of a Kruskal-Wallis ANOVA followed by a Mann-Whitney-U test for between-group comparisons. Frequency data were initially examined for trends; data suggestive of potential effect were then statistically evaluated using the chi-square, Fisher exact, or chi-square and Fisher exact tests. For the Bartlett test, a (p) value $\leq$ 0.001 was considered significant; for all other statistical tests, differences with p values $\leq$ 0.05 were considered significant.

C. **METHODS:**

1. **Observations:**
Animals were inspected weekly for clinical signs of toxicity, and twice daily for moribundity and mortality.

2. **Body weight:** Animals were weighed once each week.

3. **Food consumption and compound intake:**
Food consumption for each animal was determined, and mean daily diet consumption was calculated as g food/kg body wt/day. Compound intake (mg/kg body wt/day) was calculated as time-weighted averages from feed consumption, body weight gain data, and diet analysis data.

4. **Ophthalmoscopic examination:** Eyes were examined prior to administration of test substance, and again on all survivors of the 12-and 24-month groups prior to termination of the study. Pupillary response, conjunctiva, cornea, lens were evaluated using a slit lamp microscope. The vitreous, retina, and choroid and optic disc were examined with an indirect ophthalmoscope.

5. **Blood collection:** Blood was collected from fasted rats via the orbital sinus (20 rats/sex/dose of 2-yr sacrifice group) at 3, 6, 12, 18, and 24 months into the study for hematology and clinical chemistry studies.

The CHECKED (X)parameters were examined.

a. **Hematology**

X	Hematocrit (HCT)	X	Leukocyte differential count
X	Hemoglobin (HGB)	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)	X	Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)	X	Mean corpusc. volume (MCV)
X	Platelet count	X	Reticulocyte & Heinz bodies counts
	Blood clotting measurements	X	Erythrocyte morphology
	(Thromboplastin time)		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

b. **Clinical Chemistry**

	ELECTROLYTES
X	Calcium
X	Chloride
	Magnesium
X	Phosphorus
X	Potassium
X	Sodium
	ENZYMES
X	Alkaline phosphatase (ALK)
	Cholinesterase (ChE)
X	Creatine phosphokinase (CPK)
X	Lactic acid dehydrogenase (LDH)
X	Serum alanine amino-transferase (also SGPT)
X	Serum aspartate amino-transferase (also SGOT)
X	Gamma glutamyl transferase (GGT)
	Glutamate dehydrogenase

	OTHER
X	Albumin
X	Blood creatinine
X	Blood urea nitrogen
X	Total Cholesterol
X	Direct bilirubin
X	Globulins
X	Glucose
X	Total bilirubin
X	Total serum protein (TP)
X	Triglycerides
	Serum protein electrophores
X	Uric acid

6. **Urinalysis**

Urine was collected from animals at 3, 6, 12, 18, and 24 months into the study. THE CHECKED (X) parameters were examined.

X	Appearance		
X	Color & Clarity	X	Glucose
	Volume	X	Ketones
X	Specific gravity	X	Bilirubin
X	pH	X	Blood
X	Sediment (microscopic)	X	Nitrate
X	Protein	X	Urobilinogen

7. **Sacrifice and Pathology**:
All animals that died and those sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASCULAR/ HEMATOPOIETIC	X	NEUROLOGIC
X	Tongue	X	Aorta	XX	Brain
X	Salivary glands	XX	Heart	X	Periph.nerve
		X	Bone marrow	X	Spinal cord (3 levels)
X	Esophagus	X	Lymph nodes		
X	Stomach	XX	Spleen	X	Pituitary
X	Duodenum	X	Thymus	X	Eyes (optic n.)
X	Jejunum				
X	Ileum		UROGENITAL		GLANDULAR
X	Cecum	XX	Kidneys	XX	Adrenal gland
X	Colon	X	Urinary bladder	X	Lacrimal gland
X	Rectum	XX	Testes	X	Mammary gland
XX	Liver	X	Epididymides	X	Parathyroids
	Gall bladder	X	Prostate	X	Thyroids
X	Pancreas	X	Seminal vesicle	X	Clitoral gland
		XX	Ovaries	X	Prostate
	RESPIRATORY	X	Uterus	X	Preputial glands
X	Trachea	X	Vagina	X	Harderian glands
XX	Lung	X	Cervix		
X	Nose, Pharynx (Whole skull)	X	Epididymis		OTHER
				X	Bones & joints
X	Larynx			X	Skeletal muscle
				X	Skin
				X	All gross lesions and masses
				X	Identifier (Tail)

II. **RESULTS:**

A. **Observations:**

1. **Toxicity:** With the exception of an increased incidence of alopecia noted in the 450-ppm, 2-year sacrifice group (30/50 and 43/50 vs control 17/50 and 30/50 for males and females, respectively), clinical and/or cageside observations attributable to exposure to the test substance were not observed in this study.

2. **Mortality:** Survival was unaffected by administration of cyfluthrin as the incidence of mortality was comparable between treated and control animals (table 4).

Table 4: Mortality Data in 2-Year Oncogenicity Study[1]

Dose (ppm)		0	50	225	450
No. Of Animals	Males	50	50	50	50
	Females	50	50	50	50
Time to death (days)	Males	703	690	697	708
	Females	694	687	690	700
Found dead on study	Males	7	3	3	3
	Females	5	4	3	2
Unscheduled killed	Males	16	16	12	7
	Females	8	15	13	15
Scheduled killed	Males	27	31	35	41
	Females	37	31	34	33

[1]Data extracted from P.292, study report # 107769, MRID 44459301

B. **Body weight:** At the highest dose tested (450 ppm), body weight gain declined relative to controls of approximately 10, 13, and 8% in the male and 7, 10, and 13% in female at 3, 12, and 24 months into the study, respectively. Decline in body weight, assessed by comparing the grand mean of weekly averages to that of controls, were 6 and 5% in 225-ppm males and females, respectively. Body weight remained unchanged in both sexes at 50 ppm (Table 5).

TABLE 5: MEAN ABSOLUTE BODY WEIGHTS IN RATS FED CYFLUTHRIN FOR 104 WEEKS[1]

Group	1-week weight (g)[a]		3-month weight (g)		6-month weight (g)	
	Male	Female	Male	Female	Male [b]	Female [c]
Control	175±2 (n=55)	126±1 (n=55)	315±3 (n=50)	181±1 (n=50)	356±3 (n=50)	200±1 (n=49)
50 ppm	174±2 {-0.6%}[d] (n=55)	125±1 {-0.8%} (n=55)	311±3 {-1.3%} (n=50)	179±1 {-1.1%} (n=50)	350±3 {-1.7%} (n=50)	197±1 {-1.5%} (n=50)
225 ppm	175±2 {0.0%} (n=55)	124±1 {-1.6%} (n=55)	299±3* {-5.1%} (n=50)	175±1* {-3.3%} (n=50)	335±4* {-5.9%} (n=50)	192±1* {-4.0%} (n=50)
450 ppm	173±2 {-1.1%} (n=55)	122±1* {-3.2%} (n=55)	282±3* {-10.5%} (n=50)	167±1* {-7.7%} (n=50)	319±3* {-10.4%} (n=50)	181±2* {-9.5%} (n=50)

TABLE 5. (Continued):

Group	12-month weight (g)[a]		18-month weight (g)		24-month weight (g)	
	Male	Female	Male	Female	Male [b]	Female [c]
Control	399±4 (n=50)	218±2 (n=49)	402±5 (n=50)	262±3 (n=48)	367±7 (n=31)	276±3 (n=38)
50 ppm	392±4 {-1.8%} (n=49)	215±2 {-1.4%} (n=49)	398±4 {-1.0%} (n=46)	253±3 {-3.4%} (n=48)	355±7 {-3.3%} (n=32)	263±4* {-4.7%} (n=32)
225 ppm	372±4* {-6.8%} (n=50)	211±2* {-3.2%} (n=50)	375±4* {-6.7%} (n=47)	246±2* {-6.7%} (n=45)	347±6* {-5.4%} (n=37)	259±4* {-6.2%} (n=35)
450 ppm	346±3* {-13.3%} (n=50)	196±2* {-10.1%} (n=50)	353±3* {-12.2%} (n=48)	226±3* {-13.7%} (n=49)	338±3* {-7.9%} (n=42)	241±3* {-12.7%} (n=33)

[1]Data extracted from p.127-134, study report #107769 , MRID 44459301.

[a] Mean weight ± sem (g).

[b] Male weights were recorded at week 104.

[c] Female weights were recorded at week 103.

[d] {%} Percent change from control group

* Statistically significant from the control group ($p<0.05$).

C. **Food consumption and compound intake:**

1. **Food consumption:** Food consumption was assessed for each group in terms of both grams (g) consumed/animal/day and (g) consumed/kg body weight/day and expressed as a grand mean of weekly averages. The grand mean of each chemically-treated group was then compared to that of the untreated control group. Based on this criteria, food consumption and utilization remained unaffected in both sexes at all doses tested.

2. **Compound consumption:** Compound intake (mg/kg body wt/day) was calculated as time-weighted averages from feed consumption, body weight gain data, and diet analysis data (table 1).

3. **Food efficiency:** Food efficiency remained unaffected in both sexes at all doses tested.

D. **Ophthalmoscopic examination:** Corneal opacity, varied in severity from minimal to moderate and was principally bilateral, was observed in all rats during the pre-and post-treatment ophthalmic examination. This lesion was considered to be a background findings specific to the Fischer 344 rats, and is characterized by the presence of small mineral deposits along the anterior corneal basement membrane. Ophthalmological examinations of the pupillary response, conjunctiva, cornea, lens, the vitreous, retina, and choroid and optic disc were all within the normal limit.

E. **Blood work:**

1. **Hematology:** Evaluation of the data from blood collected at approximately 3, 6, 12, 18, and 24 months into the study provided no indication of compound-induced hematological toxicity in either sex at any dose tested.

2. **Clinical Chemistry:** A decline in serum triglyceride concentration (and to a lesser extent serum cholesterol) was observed in 450 ppm males; however, the alterations did not appear to be toxicologically significant.

F. **Urinalysis:** Evaluation of urine chemistries from samples collected at approximately 3, 6, 12, 18, and 24 months into the study provided no evidence of compound-induced toxicity in either sex at any dose tested.

G. **Sacrifice and Pathology:**

1. **Organ weight:** Declines in absolute organ weight were observed in the adrenal gland (22%), kidney (8%), and liver (13 and 20%, respectively) of 2-year 225- and 450-ppm males, and in the liver (12%) of 2-yr 450-ppm females; a corresponding decrease in relative liver weight was noted in the liver of 2-year 450-ppm males (Tables 7 & 8).

TABLE 7: CHANGES IN ABSOLUTE AND RELATIVE ORGAN WEIGHTS (M±SD) IN MALE RATS FED CYFLUTHRIN FOR 104 WEEKS[$]

Dose (ppm)	(n)[1]	TermBW (g)[2]	Adrenals		Kidneys		Liver	
			Absol[3]	Relat[4]	Absol[3]	Relat[4]	Absol[3]	Relat[4]
0	27	367±38	.09±.03	.02±.01	3.6±.4	1±.1	18.3±3.9	5.0±1.2
225	35	344±37*	.07±.01*	.02±.01	3.3±.4*	1±.1	16±3.1*	4.6±.8
450	41	341±21*	.07±.01*	.02±.00	3.3±.3*	1±.1	14.7±2.5*	4.3±.7*

[$]Data extracted from p.513 & 519, study report #107769 , MRID 44459301.
[1]n=Number of animals/group.
[2]TermBW=Terminal body weight in grams.
[3]Absol=Absolute organ weight in grams.
[4]Relat=The ratio between organ weight/absolute body weight (%).
*Statistically significant from the control group ($p<0.05$).

TABLE 8: CHANGES IN ABSOLUTE AND RELATIVE ORGAN WEIGHTS (M±SD) IN FEMALE RATS FED CYFLUTHRIN FOR 104 WEEKS

Dose (ppm)	(n)[1]	TermBW (g)[2]	Adrenals		Kidneys		Liver	
			Absol[3]	Relat[4]	Absol[3]	Relat[4]	Absol[3]	Relat[4]
0	37	275±21	.071	.026±.003	2.4±.2	.87±.06	11.5±2	4.2±.7
225	34	256±29*	.075±.02	.03±.006*	2.4±.2	.94±.1*	11.1±3	4.3±.6
450	33	236±15*	.073	.031±.004*	2.4±.2	1±.01*	10.1±1.2*	4.3±.5

[$]Data extracted from p.514 & 520, study report #107769 , MRID 44459301.
[1]n=Number of animals/group.
[2]TermBW=Terminal body weight in grams.
[3]Absol=Absolute organ weight in grams.
[4]Relat=The ratio between organ weight/absolute body weight (%).
* Statistically significant from the control group ($p<0.05$).

2. **Gross pathology**: Provided no indication of cyfluthrin-induced change in either sex at any dose tested.

3. **Microscopic Pathology**:
a) Non-neoplastic: microscopic lesions associated with exposure to cyfluthrin were not observed in this study.
b) Neoplastic: the incidence of mammary gland adenocarcinomas was numerically increased over controls (Appendix A) in 2-year 450 ppm females (M:0,1,0,1; F:1,0,0,4). Despite being out of the range of both in-house (1/50 adenoma and 1/50 adenocarcinoma, study # 91-272-LJ, Appendix B), and published historical control data (not provided by the authors, and not indexed in any data base searched by the EPA reviewer), the authors considered the difference as spurious and insignificant.

III. DISCUSSION

A. **Cyfluthrin** (94.7% a.i.), an agrochemical with insecticidal properties, was administered to separate 1- and 2-yr sacrifice groups of Fischer 344 rat (70-80 animals/ dose/sex total) at nominal dietary concentrations of 0, 50, 225, 450 ppm, corresponding to mean daily intake of the test substance of approximately 0,2.6,11.6,22.8 mg/kg/day/male rat or 0, 3.3, 14.4, 28.3 mg/kg/day/female rat. The doses were selected based on data generated from previous studies, in which decline in body weight was the principal endpoint affected following exposure to cyfluthrin.

There were no compound related effects in mortality, food consumption & efficiency, hematology, urinalysis, or gross pathology of organs and tissues examined.

The corneal and retinal changes observed in the ophthalmoscopic examinations were attributed to the strain of rat used in the study, and the technique of blood collection (orbital sinus bleeding). An increased frequency of alopecia was also observed in 450-ppm males and females. Serum cholesterol and triglycerides declined slightly.

There were compound-related declines in body weight in the mid-and the high doses tested, when compared to controls. A corresponding decline was also observed in Organ/body weight ratios of the liver, kidneys, and adrenals, and it was interpreted as a secondary response to the decline in body weight observed in both sexes administered the mid-and the high doses tested. The EPA reviewer agrees with the interpretation of the authors. The authors concluded that the compound did not induce neoplasia, however, at the doses tested, there was a treatment related increase in tumor incidence of mammary

gland adenocarcinomas in 2-yr 450-ppm females when compared to controls. Despite the fact that the increases in mammary adenocarcinomas observed in this study was out of the range of both in house and published historical data, the authors provided the following explanations to justify for such high incidence of mammary tumors: a)the increase was statistically insignificant, compared to concurrent controls; b)the change occurred in one sex in the absence of a dose response; c) the incidence of mammary gland hyperplasia, fibroadenomas, or adenomas did not change to parallel the increases observed in mammary gland adenocarcinomas; d)the compound has shown to be non-genotoxic in previous studies (MRID 00157798, MRID 00131539, MRID 00157796); e) no proliferative lesions were noted at 1-yr; f) a similar 2-year study in Wistar rat showed no evidence of oncogenicity (MRID 00137303).

Conclusions: Except for the declines in body weight observed in the mid-and the high doses tested, there was no treatment-related toxicity in this rat feeding study (104 weeks). However, the incidence of mammary gland adenocarcinomas in female rats at the high dose level was higher than control.

The LOAEL is 225 ppm (11.6 and 14.4 mg/kg body wt/day for male and female rats, respectively), based on overall declines in body weight gain by 6% and 7% in males and females, respectively. The NOAEL is 50 ppm (2.6 and 3.3 mg/kg body wt/day for male and female rats, respectively). This combined chronic toxicity/carcinogenicity study in the rat is acceptable, and does satisfy the guideline requirement for a chronic toxicity/carcinogenicity study (83-5) in the rat.

B. **Study deficiencies:**

a) the lot/batch # of the vehicle substance (acetone/corn oil mixture) was omitted.
b) the number of air changes in animal rooms was omitted.
c) some serum chemistry parameters were not measured e.g. Serum protein electrophoresis, Glutamate dehydrogenase, and Magnesium), these parameters are included in the guideline.
d) urine volume was not measured.
e) historical published control data referenced were not provided in the study report, or indexed in any data base.

The reviewer considers these as minor deficiencies that have no major impact on the classification of the study.

APPENDIX A

Histopathological Incidence of Proliferative Mammary Lesions in Rats Fed **Cyfluthrin**
For 1-year (pp 528, MRID # 44459301)
and 2-year (pp 558-559, MRID # 44459301)

BAYER Agriculture Division - Toxicology

Date: 07OCT1997
Time: 14:52:34

Table MP 1-SUM-INT
MICROPATHOLOGY INCIDENCE AND AVERAGE GRADE SUMMARY
A Combined Chronic Toxicity/Oncogenicity Feeding Study with Technical Grade Cyfluthrin in the Rat - One Year Animals
Study Number 94-272-BK

ORGAN and LESION		Males Level (PPM) CONTROL	50	225	450	Females Level (PPM) CONTROL	50	225	450
LYMPH NODE,CERVICAL	# Tissues Examined	20	0	0	20	19	0	0	20
No Abnormality Detected		18	-	-	19	19	-	-	20
Tissue Missing		-	-	-	-	1	-	-	-
Congestion		1 (1.0)	-	-	-	-	-	-	-
Cyst		1 (1.0)	-	-	-	-	-	-	-
Hyperplasia,Lymphoid		-	-	-	1 (1.0)	-	-	-	-
LYMPH NODE,MESENTERIC	# Tissues Examined	20	0	0	20	20	0	0	20
No Abnormality Detected		20	-	-	19	20	-	-	20
Cyst		-	-	-	1 (1.0)	-	-	-	-
MAMMARY GLAND	# Tissues Examined	20	0	0	20	20	0	0	20
No Abnormality Detected		11	-	-	16	19	-	-	20
Galactocele(s)		9 (1.7)	-	-	4 (2.0)	1 (1.0)	-	-	-
Physiologic Status,Inactive		1	-	-	1	-	-	-	-
MULTICENTRIC LESIONS[t]	# Tissues Examined	0	0	0	0	20	10	10	20
No Abnormality Detected		-	-	-	-	18	7	6	11

() = Average severity of animals with lesion: 1 (minimal) to 5 (severe).
Blank severity field = neoplasm or lesion which is not graded.
* = Significantly different from control ($p<=0.05$).
- = No incidence.
ER = At least one ungraded lesion.
[t] Note: This entry contains the actual number of animals with multicentric lesions.

BAYER Agriculture Division - Toxicology

Date: 08OCT1997
Time: 11:06:40

Table MP 1-SUM
MICROPATHOLOGY INCIDENCE AND AVERAGE GRADE SUMMARY
A Combined Chronic Toxicity/Oncogenicity Feeding Study with Technical Grade Cyfluthrin in the Rat - Two Year Animals
Study Number 94-272-BK

ORGAN and LESION		Males Level (PPM) CONTROL	50	225	450	Females Level (PPM) CONTROL	50	225	450
LYMPH NODE,MESENTERIC (continued)									
Hyperplasia,Reticuloendothelial Cell		-	-	-	-	-	2 (2.5)	-	-
Hemangiosarcoma		-	-	-	-	-	-	1	-
Mesothelioma		-	-	-	1	-	-	-	-
Neoplasm,Metastatic		-	-	-	-	1	-	-	-
Lymphoreticular Neoplasm		1	9 *	2	2	4	5	5	5
MAMMARY GLAND	# Tissues Examined	50	48	50	50	50	50	50	50
No Abnormality Detected		29	19	33	32	15	11	12	18
Tissue Missing		-	2	-	-	-	-	-	-
FREE TEXT		-	1	-	1	-	-	1	-
Dilatation		-	-	-	1 (3.0)	-	-	-	-
Edema		-	1 (2.0)	-	-	-	-	-	-
Galactocele(s)		17 (2.6)	21 (2.2)	16 (2.4)	13 (2.2)	31 (1.9)	37 (2.2)	35 (2.1)	29 (1.7)

() = Average severity of animals with lesion: 1 (minimal) to 5 (severe).
Blank severity field = neoplasm or lesion which is not graded.
* = Significantly different from control ($p<=0.05$).
- = No incidence.
ER = At least one ungraded lesion.

BAYER Agriculture Division - Toxicology

Date: 08OCT1997
Time: 11:06:41

Table MP 1-SUM
MICROPATHOLOGY INCIDENCE AND AVERAGE GRADE SUMMARY
A Combined Chronic Toxicity/Oncogenicity Feeding Study with Technical Grade Cyfluthrin in the Rat - Two Year Animals
Study Number 94-272-BK

ORGAN and LESION		Males Level (PPM) CONTROL	50	225	450	Females Level (PPM) CONTROL	50	225	450
MAMMARY GLAND (continued)									
Hyperplasia		2 (2.0)	-	-	1 (1.0)	-	1 (3.0)	-	2 (3.0)
Inflammation,Chronic		-	2 (2.5)	-	-	-	-	-	-
Mineralization		-	2 (1.5)	-	-	-	-	-	-
Physiologic Status,Inactive		2	-	2	-	-	-	-	-
Pigmentation		1 (1.0)	2 (2.5)	1 (2.0)	-	-	-	-	-
Adenocarcinoma		-	1	-	1	1	-	-	4
Fibroadenoma		1	4	-	1	9	15	9	4
Fibroma		-	1	-	-	-	-	-	-
Lymphoreticular Neoplasm		-	1	-	-	-	-	-	-
MESENTERY	# Tissues Examined	0	0	2	1	0	0	0	0
Necrosis,Fat		-	-	1 (4.0)	-	-	-	-	-
Mesothelioma		-	-	1	1	-	-	-	-

() = Average severity of animals with lesion: 1 (minimal) to 5 (severe).
Blank severity field = neoplasm or lesion which is not graded.
* = Significantly different from control (p<=0.05).
- = No incidence.
ER = At least one ungraded lesion.

APPENDIX B

Historical Control Data on Mammary
Lesions in Female Rats
(pp 4187, MRID # 44459301)

Bayer Corporation
Micropathology Historical Control Data on Mammary Proliferative Lesions in Female Rats[f]

Toxicology Study ID Number 94-272-SK

Study Number	Hyperplasia	Adenoma	Adenocarcinoma
92-272-SC	0	0	0
91-272-LJ	0	1	1

[f]50 Control animals evaluated per study

4187

Bayer Corporation Agriculture Division Report Number 107769

Cyfluthrin: Mammary Tumor Incidences in Chronic/Oncogenicity Bioassay in Female Rats

Lesion	Control	50 ppm	225 ppm	450 ppm
Hyperplasia (moderate, focal)	0/50	1/50	0/50	2/50
Adenocarcinoma	1/50	0/50	0/50	4/50
Fibroadenoma	9/50	15/50	9/50	4/50
Fibroma	0/50	0/50	0/50	0/50
Lymphoreticular neoplasm	0/50	0/50	0/50	0/50

None of these incidences were statistically significant. Frequency data were initially examined for trends: data suggestive of a potential effect were then statistically evaluated using the chi-square, Fisher exact, or chi-square and Fisher exact tests. I counted the top dose females individually and they checked out with the above. One of the adenocarcinomas had parts which resembled a fibroadenoma, suggesting that the adenocarcinoma arose from a fibroadenoma. One of the animals had both hyperplasia and a fibroadenoma.

With the exception of one fibroadenoma observed on day 668 when the animal died, all hyperplasia and mammary tumors were observed at terminal sacrifice. Days adenocarcinoma were found: 450 ppm: 731, 736, 736, 731. Control: at terminal sacrifice.

Historical controls:

From same lab: 1/50 adenomas and 1/50 adenocarcinomas in one study, 0/50 for both in second study.

Hazelton: 3.8% (mean); 2-15% range carcinomas
Charles River (1990): 1.5% (mean); 0-4.3% range
NTP: 3.1% (mean)

Mortality summary (females):

Dose # of Animals	Control 50	50 ppm 50	225 ppm 50	450 ppm 50
Mean time of death (days)	694	687	690	700
Total found dead on study	5	4	3	2
Total unscheduled killed	8	15	13	15
Total scheduled killed	37	31	34	33
Total number dead animals	50	50	50	50

Old rat study: Wistar rats (1983) negative. - Doses may not be adequate (up to 450 ppm)

Mutagenicity: Negative in multiple assays.

Mouse studies: negative in 1983 study: CF1/W74 mice (doses may not be adequate - up to 800 ppm). 1998 study: negative in CD-1 mice (up to 1400/1600 ppm).

SAR: Out of 19 other pyrethroids, only cyhalothrin has an equivocal result concering mammary tumors and these were in mice. The dose levels were inadequate.

13544

R058392

Chemical:	**Cyfluthrin**
PC Code:	**128831**
HED File Code	**13000 Tox Reviews**
Memo Date:	**02/16/2001 12:00:00 AM**
File ID:	**DPD247250**
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03/25/2004