004992
004993 3/14/86

G. Ghali
W. Burns
J.W. Hanswirth
S. Saunders
D. Bowers

REFERENCE DOSES (RFDs) FOR ORAL EXPOSURE

Chemical: Baythroid

CAS #: 68359-37-5
Caswell #: 266E

Carcinogenicity: Not oncogenic in mice and rats

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD
Bayer AG Institute for Toxicology (1983) 2-Year Feeding/ Oncogenic Rat Study decreased body weights in males, inflammatory foci in kidneys of females	50 ppm (2.5 mg/kg) Systemic NOEL 150 ppm (7.5 mg/kg) Systemic LOEL	100	-	0.025 mg/kg/day

Endpoint and Experimental Doses:

Suberg, H., and Loeser, E.
Two Year Feeding/Oncogenic Rat Study
Bayer AG Institute for Toxicology
Study No. 11949; July 19, 1983

Sixty-five male and 65 female Wistar SPF rats, 5-6 weeks of age, were assigned to 4 groups which were fed diets containing 0, 50, 150, and 450 ppm of baythroid. Animals were observed for clinical signs twice daily and once daily on weekends and holidays. Individual body weights and group food consumption were determined weekly the first 26 weeks, biweekly during week 27 through 74, and then weekly until termination. Hematology, clinical chemistry, and urinalysis were performed on 10 rats/sex/group at 6, 12, 18, and 24 months of study. Observed results included decreased body weights in males and inflammatory foci in kidneys of females.

Preparation Date: 3/12/86

1/26

REFERENCE DOSES (RFDs) FOR ORAL EXPOSURE

Chemical: Baythroid

CAS #: 68359-37-5
Caswell #: 266E

Carcinogenicity: No evidence of carcinogenicity in two adequate animal (rat and mice) tests.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD
Bayer AG Institute for Toxicology (1983)	50 ppm (2.5 mg/kg) Systemic NOEL	100	-	0.03 mg/kg/day
2-Year Feeding/ Oncogenic Rat Study	150 ppm (7.5 mg/kg) Systemic LOEL			
decreased body weights in males, inflammatory foci in kidneys of females				
3-Generation Reproduction	50 ppm (Systemic NOEL) 150 ppm (Systemic LEL)			

Endpoint and Experimental Doses:

Suberg, H., and Loeser, E.
Two Year Feeding/Oncogenic Rat Study
Bayer AG Institute for Toxicology
Study No. 11949; July 19, 1983

Sixty-five male and 65 female Wistar SPF rats, 5-6 weeks of age, were assigned to 4 groups which were fed diets containing 0, 50, 150, and 450 ppm of baythroid. Animals were observed for clinical signs twice daily and once daily on weekends and holidays. Individual body weights and group food consumption were determined weekly the first 26 weeks, biweekly during week 27 through 74, and then weekly until termination. Hematology, clinical chemistry, and urinalysis were performed on 10 rats/sex/group at 6, 12, 18, and 24 months of study. Observed results included decreased body weights in males and inflammatory foci in kidneys of females.

Preparation Date: 3/12/86

Uncertainty Factors (UFs):

A 100 fold UF has been used to compensate for the interspecies differences in extrapolating from the rat to the human.

Modifying Factors (MFs):

None

Additional Comments:

Data Considered for Establishing the RfD

1) 2-Year Feeding/Oncogenic - Rat Systemic NOEL=50 ppm (2.5 mg/kg), Systemic LOEL= 150 ppm (7.5 mg/kg)(decreased boody weights in males, inflammatory foci in kidneys of the females); Oncogenic NOEL = >450 ppm (22.5 mg/kg); core grade minimum

2) 1-Year Feeding - Dog NOEL=160 ppm (4 mg/kg), LOEL=640 ppm (16 mg/kg)(slight ataxia in 2 dogs, one occasion each; increased vomiting; increased pasty-to-liquid feces; and decreased body weights in males); core grade minimum

3, 3-Generation Reproduction - Rat Systemic NOEL=50 ppm (2.5 mg/kg), Systemic LEL= 150 ppm (7.5 mg/kg)(body weight decrease in the pups); Reproductive NOEL= 50 ppm, Reproductive LEL=150 ppm (decreased viability index); core grade minimum

4) Teratology - Rat Maternal NOEL=3 mg/kg/day, Maternal LEL=10 mg/kg/day (behavioral changes in gait and coordination); Teratogenic NOEL >30 mg/kg/day (HDT); Fetotoxic NOEL >30 mg/kg/day; core grade minimum

5) Teratology - Rabbit Maternal NOEL=15 mg/kg, Maternal LEL=45 mg/kg (abortion and resorption); Teratogenic NOEL = >45 mg/kg/day (HDT); Fetotoxic NOEL = > 45 mg/kg/day (HDT); core grade minimum

Data Gap(s)

None

Other Data Considered

1) 23-Month Feeding/Oncogenic - Mice Oncogenic NOEL = >800 ppm (120 mg/kg)(HDT); core grade minimum; Systemic NOEL = <50 ppm (7.5 mg/kg) (increased alkaline phosphates activity in males); core grade supplementary

.....

Confidence in the RfD:

Study: High Data Base: High RfD: High

The critical study appears to be of good quality and is given a high rating. Since there are no data gaps existing for baythroid and additional studies are also of good quality, the RfD is given a high confidence.

.....

Documentation of RfD and Review:

.....

Agency RfD Review:

First Review:
Second Review:
Verification Date:

U.S. EPA Contact:

Primary: Reto Engler FTS 557-7491

Secondary: George Ghali FTS 557-4382

DATA EVALUATION RECORD

STUDY TYPE: Chronic toxicity.

CITATION: Suberg, H. and Loeser, E. FCR1272 (Cyfluthrin the active ingredient of Baythroid) chronic toxicity study in rats. (Unpublished report No. 11949 prepared by Bayer AG Institut Fuer Toxikologie for Mobay Chemical Corp., Agr. Chem. Div., Kansas City, MO., dated July 19, 1983.)

ACCESSION NUMBER: 072365.

LABORATORY: Bayer AG Institut Fuer Toxikologie, Wuppertal, Federal Republic of Germany.

QUALITY ASSURANCE STATEMENT: Not present for this report.

TEST MATERIAL: The test material was identified as FCR1272, the active ingredient of Baythroid, an insecticide. It was a composite sample of batches received prior to the study and was available as a premix concentrate in Wessalon S, with 49.7 to 51.0% active ingredient. The purity of the technical material was not reported.

PROTOCOL:

1. Male and female Wistar SPF rats were obtained from Winkelmann, Borchen, Federal Republic of Germany. The rats were individually housed in Type II Makrolon cages in rooms maintained at 21-23° C and 50-60% humidity with 12 hour light/dark cycle. The rats were 5-6 weeks of age at the start of the study. Tapwater was available ad libitum.

   It was not reported whether the animals were acclimated to laboratory conditions prior to treatment. Animals were weighed prior to dosing and assigned to 4 groups with initial mean body weights of 80 g for males and 81 g for females.

2. The premix concentrate in Wessalon S, formulation 113, was mixed with pulverized feed to obtain the required concentrations of the active ingredient. The frequency of diet preparation throughout the study was not reported. The control group was fed the basal diet. The concentration, homogeneity, and stability of the diet was determined by gas chromotography at various intervals during the study.

EPA: 68-01-6561
TASK: 90
January 24, 1985

DATA EVALUATION RECORD

CYFLUTHRIN

Chronic Toxicity

CITATION: Suberg, H. and Loeser, E. FCR1272 (Cyfluthrin the active ingredient of Baythroid) chronic toxicity study in rats. (Unpublished report No. 11949 prepared by Bayer AG Institut Fuer Toxikologie for Mobay Chemical Corp., Agr. Chem. Div., Kansas City, MO., dated July 19, 1983.)

REVIEWED BY:

Nicolas P. Hajjar, Ph.D.
Senior Scientist
Dynamac Corporation

Signature: Nicolas P. Hajjar
Date: January 24, 1985

William McLellan, Ph.D.
Senior Scientist
Dynamac Corporation

Signature: William L. McLellan
Date: 24 January 1985

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I Cecil Felkner
Date: 1-24-85

APPROVED BY:

Edwin R. Budd
EPA Scientist

Signature: Edwin R. Budd
Date: January 31, 1985

3. Groups of 65 males and 65 females were fed diets containing 0, 50, 150, and 450 ppm of test material. Dose selection was based on a subchronic feeding study.

4. Animals were observed for clinical signs twice daily and once a day on weekends and holidays.

Individual body weights and group food consumption were determined weekly the first 26 weeks, bi-weekly during week 27 through 74, and then weekly until termination. Food consumption was determined by weighing the unconsumed feed and substracting this value from the amount of food offered.

On day seven of the study 5 rats/sex/group were sacrificed and the activities of N-demethylase and O-demethylase as well as the concentration of cytochrome P_{450} in the liver were determined.

Hematology, clinical chemistry, and urinalysis were performed on 10 rats/sex/group at 6, 12, 18, and 24 months of study. Serum protein electrophoresis was performed at 12 months of study. Blood samples were collected with a Pasteur pipette via the retroorbital venous plexus after ether anesthesia. Blood glucose determinations were performed on blood samples obtained from the tail vein without anesthesia. Blood for thromboplastin time was obtained by cardiac puncture. Urine samples were collected during 16 hr fasting periods.

The following is a list of parameters analyzed: Hematology - erythrocyte count, hemoglobin, hematocrit, red cell indices (MCV, MCH, MCHC), total and differential leukocyte count and thrombocyte count. Clinical chemistry - alkaline phosphatase, SGOT, SGPT, creatinine, urea, glucose, cholesterol bilirubin, total protein, sodium, potassium, and calcium. Urinalyses - glucose, blood, protein, ketone, bilirubin, urobilinogen, pH, specific gravity and total volume.

The fluoride content in bones and teeth of 5 males and 5 females from each group was determined at the 12-month interim and final sacrifices.

Gross examination was performed on rats that died or were sacrificed moribund during the study, interim sacrifice animals, and on all survivors at termination. Rats were anesthetized with ether and sacrificed by exsanguination. At 12 months and termination, 5 rats/sex/group were perfused with 10% buffered formaldehyde, and then examined grossly.

The following organs from each animal were weighed at the interim and terminal sacrifices: heart, testes, lung, liver, spleen, kidneys, adrenals and ovaries. The organs from perfused rats were not weighed.

7

The following tissues from all animals that died or were sacrificed moribund and all animals sacrificed at weeks 52 and 104, were fixed in 10% formaldehyde:

Aorta	Liver	Thymus (if present)
Eyes	Lung	Uterus
Intestine (duodenum, jejunum ileum, colon and in some cases cecum and rectum)	Lymph nodes	Gross Lesions
	Stomach	
	Spleen	
	Adrenals	
Femur enbloc with skeletal musculature and* sciatic nerve	Kidneys	
	Ovaries	
	Pancreas	
Brain	Prostate	
Urinary bladder	Spinal cord	
Heart	Seminal vesicles	
Testes	Sternum	
Pituitary	Thyroids, esophagus, and trachea enbloc	
Salivary glands		

Microscopic examination was performed on all the above tissues for each animal on the study.

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

RESULTS:

Diet Analysis: There were no data presented or diet analyses for content, homogeneity, and stability of test material.

Clinical Signs: It was stated in the report that there were no differences noted among dosed and control animals in appearance, behavior, activity or condition of coat during the study. However, individual or group data were not presented. Ophthalmologic examinations were apparently not performed.

---

* For perfused rats the sciatic nerve was isolated and fixed.

Mortalities: There were no differences in survival among dosed and control animals throughout the two-year study (Table 1).

TABLE 1. Percent Survival of Rats Fed Diets Containing Cyfluthrin for Two Years

Group/Dose (ppm)	Percent Survival Month: 18	24
Males		
Control	98(49/50)[a]	88(44/50)
50	98(49/50)	88(44/50)
150	100(50/50)	96(48/50)
450	96(48/50)	82(41/50)
Females		
Control	96(48/50)	86(43/50)
50	98(49/50)	90(45/50)
150	100(50/50)	90(45/50)
450	94(47/50)	82(41/50)

[a] Number of animals alive/number of animals in each group.

Body Weights: The mean body weights of males and females receiving the high-dose were significantly lower than control values throughout the study (Table 2). The mean body weights of males receiving the mid-dose was also significantly lower than the control group during the first year of the study, but the animals recovered thereafter. There were no effects on the body weights of animals receiving the low-dose.

Food Consumption: Food consumption was similar throughout the study among compound-treated and control groups (Table 3 and CBI Report Appendix, pp. 63-70). Based on mean food consumption and body weight data, it was reported that the average intake of test compound throughout the study was 2.02, 6.19, and 19.20 mg/kg/day in males and was 2.71, 8.15, and 25.47 mg/kg/day in females for the low-, mid-, and high-dose groups, respectively.

Hematology: There were a few isolated changes in certain hematologic parameters in compound-treated animals as compared to control values, at months 6, 12, 18, or 24 of the study, but none were dose- and/or time-related (CBI Report Tables 3-6). At the end of the study there was a significant decrease in leukocyte count in all dosed male groups.

TABLE 2. Mean Body Weights of Rats Fed Diets Containing Cyfluthrin for Two Years

Group/Dose (ppm)	Week:	Body Weight (g) 0	13	26	51	78	104
Males							
Control		81	320	370	407	420	422
50		81	313	365	405	412	409
150		80	304**	356*	392*	407	407
450		80	295**	346**	378**	391**	382**
Females							
Control		81	199	221	239	261	266
50		81	197	219	238	259	267
150		81	195*	217	234	249*	257
450		81	189**	210**	221**	233**	239**

* Significanly different from control value $p < 0.05$.
** Significanly different from control value $p < 0.01$.

TABLE 3. Mean Food Consumption Data for Rats Fed Diets Containing Cyfluthrin for Two Years

Group/Dose (ppm)	Mean Food Intake (g/rat/day) at Week									
	1	7	13	20	26	39	51	65	78	104
Males										
Control	12.58	18.30	18.30	17.5	17.2	17.55	16.88	16.32	15.65	16.18
50	12.17	17.91	18.24	17.41	16.52	17.60	16.20	16.31	15.41	11.68
150	11.99	16.42	17.62	16.98	16.41	16.26	16.18	15.97	15.56	14.94
450	9.99	17.46	17.69	17.43	16.15	16.57	16.32	16.06	15.21	10.73
Females										
Control	11.23	13.06	13.44	14.81	13.79	13.47	12.41	13.29	13.34	14.78
50	10.39	12.53	13.85	13.11	12.69	13.26	13.18	13.17	12.77	13.61
150	11.09	12.36	13.36	13.06	12.23	13.59	12.16	13.21	12.42	13.25
450	10.60	12.04	13.43	12.70	12.15	12.57	11.47	13.04	12.65	13.87

Blood Chemistry: There were a few isolated changes in certain parameters in dosed animals as compared to control values, at months 6, 12, 18, or 24 of the study, but none were dose and/or time-related (CBI Report Tables 7-15). At the end of the study there was a significant decrease in plasma protein and cholesterol in females receiving the high-dose and in SGPT activity and calcium in males receiving the high-dose. At 12 months, the relative amounts of protein fractions in the serum were determined by electrophoresis. The results indicated a dose-related increased in alpha-1-globulins; there were no other differences noted between control and compound-treated animals.

Urinalysis: There were no dosed-related differences in urinalysis parameters between treated and control animals at months 6, 12, 18, or 24 of the study (CBI Report Appendix pp. 313-328).

Liver Enzyme Activities and Cytochrome P_{450} Content: The hepatic N- and O-demethylase activities and cytochrome P_{450} content in rats were determined one week after study initiation. There were no differences noted in N- or O-demethylase activities or cytochrome P_{450} levels in treated animals when compared to control values, except for a significant increase in N-demethylase activity in females receiving the high-dose (Table 4).

TABLE 4. Hepatic N-Demethylase Activity in Rats Fed Diets Containing Cyfluthrin for Two-Years

Group Dose (ppm)	N-Demethylase Activity (nmol/g/min) Male	Female
Control	107.8	59.3
50	107.7	69.1
150	108.7	71.3
450	135.4	103.8**

** Significantly different from control at $p < 0.01$.

Fluoride Content in Teeth and Bones: The fluoride content in teeth and bones of treated animals was similar to those of control values at month 12 of the study (CBI Report Table 17). Increased fluoride levels were noted in the teeth and bones of males receiving the high-dose, and in the bones of males receiving the mid-dose and females receiving the high-dose (Table 5).

Gross Examinations: Summary data for gross-findings were not presented. It was stated that "gross examination revealed no changes in any of the rats that could be attributed to treatment." (CBI report p 496 - 1177).

TABLE 5. Fluoride Content in Teeth and Bones of Rats Fed Diets Containing Cyfluthrin for Two Years

Group/Dose (ppm)	Fluoride Content (mg/g ash)	
	Teeth	Bones
Males		
Control	0.097	0.464
50	0.125	0.503
150	0.113	0.514*
450	0.116**	0.560*
Females		
Control	0.144	0.654
50	0.144	0.665
150	0.140	0.698
450	0.164	0.779**

* Significantly different from control at $p < 0.05$
** Significantly different from control at $p < 0.05$

Organ Weights: At interim sacrifice, the mean liver weight (5 rats/sex/group) of males and females receiving the high-dose were significantly lower than control values. The liver to body weight ratios of treated male rats were similar to those of control, but the liver to body weight ratios of treated females were significantly lower than control values (Table 6). There were no other changes noted.

TABLE 6. Mean Organ Weight Data of Rats Fed Cyfluthrin for Two-Years

Group/Dose (ppm)	Body Weight (g)	Liver (g)	Liver:BW %	Kidney (g)	Kidney:BW %
		12 Month Sacrifice			
Males					
Control	435	15.61	3.58	2.37	0.543
50	418	14.83	3.55	2.43	0.582
150	385**	13.25	3.43	2.23	0.580
450	371**	12.90**	3.48	2.32	0.627
Females					
Control	234	8.36	3.57	1.54	0.658
50	235	7.31	3.10*	1.58	0.671
150	247	7.51	3.04**	1.58	0.643
450	208*	6.78**	3.26*	1.44	0.692
		24 Month Sacrifice			
Males					
Control	418	14.19	3.42	2.56	0.618
50	408	14.61	3.57*	2.66	0.655*
150	410	14.24	3.47	2.58	0.633
450	382**	12.98**	3.40	2.47	0.650**
Females					
Control	265	9.33	3.53	1.78	0.673
50	266	9.16	3.46	1.79	0.679
150	252*	8.51**	3.40	1.70*	0.679
450	237**	8.33**	3.53	1.65**	0.701

* Significantly different from control value $p < 0.05$.
** Significantly different from control value $p < 0.01$.

At final sacrifice, the mean liver weight of male rats receiving the high-dose was significantly lower than the control value (Table 6). Similarly, the mean liver and kidney weights in females receiving the mid- and high-dose were significantly lower than control values. However,

liver- and kidney-to-body weight ratios in both dosed males and dosed females were similar to control values. There was also an increase in lung- and adrenals-to-body weight ratios in females receiving the high-dose as compared to controls.

Histopathology: At the 12 month sacrifice, pituitary gland adenomas were found in one male receiving the low-dose, one male receiving the high-dose, and in two females receiving the mid-dose. Several non-neoplastic lesions were also observed in the interim sacrifice animals, but the incidences were similar among control and dosed rats. The neoplasms observed most frequently in animals that died or were sacrificed at study termination are summarized in Table 7.

The incidences of all neoplastic lesions observed in dosed animals were comparable to those observed in the control animals. Non-neoplastic lesions observed most frequently are summarized in (Table 8). There were increased incidences of the following histopathologic lesions in dosed animals when compared to controls: inflammatory foci of the kidneys of females receiving the mid- and high-doses; cortical hyperplastic nodules in the adrenals of males receiving the low- and high-doses and females receiving the high-dose; and medullary hyperplasia in the adrenals of males receiving the high-dose. The incidences of other histologic lesions were similar among control and dosed animals.

DISCUSSION:

The authors stated that the only compound-related effects observed in dosed rats were decreased body weights in males receiving the mid- and high-doses and females receiving the high-dose. They concluded that the NOEL was 50 ppm of test material in the diet.

Our evaluation of the data is in agreement with the authors statements, although we identified some additional compound-related histopathologic lesions. These effects include increased incidences of inflammatory foci of the kidneys of females receiving the mid- and high-dose; and cortical and/or medullary hyperplastic nodules in the adrenal gland of males and females receiving the high-dose. In addition, there was a significant increase in hepatic N-demethylase activity in females receiving the high-dose for 7 days, indicating enzyme induction by Cyfluthrin. Increased levels of fluoride in teeth and/or bones were also noted in males and females receiving the mid- and high-doses, but in the absence of metabolic studies the toxicological significance of these findings is unclear. We view effects on liver and kidney weights at the end of the study as being primarily due to decreased body weight, since the organ-to-body weight ratio were similar among control and treated animals. Finally, the incidences of neoplastic lesions in treated animals were similar to those observed in controls.

The following deficiencies were noted: individual clinical observations and eye examinations were not reported; no data were presented for diet analyses and stability.

TABLE 7. Summary of Neoplastic Lesions Most Frequently Observed in Rats Fed Cyfluthrin for Two Years

Lesion	Group:	Males				Females			
		0	50	150	450	0	50	150	450
Liver	N[a]	49	50	49	50	50	50	50	49
carcinoma		0	0	0	1	0	0	0	0
Kidneys	N	49	49	49	50	50	50	50	49
adenoma		0	0	1	0	0	0	0	0
Testes	N	49	49	49	50				
leydig cell tumor		3	5	5	3				
Uterus	N					50	50	50	49
polyp						14	7	20	17
adenocarcinoma						5	4	4	3
Pituitary gland	N	47	49	47	47	49	50	48	48
adenoma		10	11	19	6	14	23	10	12
Thyroid gland	N	49	48	47	48	49	48	49	47
adenoma		4	2	2	1	2	1	1	0
Adrenal glands	N	48	48	49	50	50	49	50	49
pheochromocytoma		4	3	5	6	0	2	1	1
Mammary glands	N					5	5	5	5
fibrosarcoma						5	3	3	3
Skin	N	1	2	0	5	4	10	4	4
fibrosarcoma		0	0	0	2	0	2	1	0

[a] The numbers of tissues examined microscopically.

TABLE 8. Summary of Non-Neoplastic Lesions Most Frequently Observed in Rats Fed Cyfluthrin for Two-Years[a]

Lesion	Group:	Males 0	Males 50	Males 150	Males 450	Females 0	Females 50	Females 150	Females 450
Heart	N	49	50	49	50	50	50	50	49
myocardial fibrosis		25	27	27	32	34	17	15	27
myocarditis		11	-	9	4	7	1	0	3
Trachea	N	49	50	47	50	49	49	50	48
chronic tracheitis		5	15	10	11	6	2	6	5
Lungs	N	49	50	49	50	50	50	50	49
macrophage		9	9	16	11	11	6	4	4
perivascular cuffing		18	22	16	9	8	13	10	9
Liver	N	49	50	49	50	50	50	50	49
inflammation		24	21	17	14	16	13	11	6
bile duct proliferation		31	34	32	29	14	8	8	13
clear cell foci		33	34	32	29	10	3	1	3
Kidneys	N	49	49	49	50	50	50	50	49
inflammatory foci		3	4	9	1	1	1	7*	7*
chronic nephropathy		38	43	45	38	29	35	34	17
Urinary bladder	N	48	48	49	50	50	49	48	49
cystitis		14	17	14	12	6	6	17	8
urothel. hyperplasia		2	1	2	2	0	2	2	4
Testes	N	49	49	49	50				
tubular atrophy		15	16	15	19				
leydig cell hyperplasia		8	11	12	7				
Prostate	N	49	49	49	50				
inflammation		4	3	2	2				
Ovaries	N					50	50	49	49
cyst						21	24	21	26
stromal hyperplasia						3	6	9	9
Uterus	N					50	50	50	49
cystic hyperplasia						10	9	10	5
Thyroid gland	N	49	48	47	48	49	48	49	47
follicular cyst		23	36	42	38	37	27	29	44
nodular hyperplasia		8	13	19	10	11	14	3	9
Adrenal glands	N	48	48	49	50	50	49	50	49
altered cell foci		23	23	23	17	10	24	30	14
cort. hyperpl. nodule		10	21*	14	20*	4	9	11	18*
medull. hyperplasia		4	8	8	14*	5	4	1	4
Spleen	N	49	48	49	50	50	50	50	49
hemopoiesis		28	14	15	18	33	23	17	23
Lymph nodes	N	49	49	46	50	50	47	48	49
hyperplasia		13	18	10	15	13	8	15	12
Eyes	N	49	47	49	50	49	49	47	49
retinal atrophy		16	13	9	14	23	15	16	25

* Statistically different from control value at $p < 0.05$.

[a] Statistical analyses conducted by the reviewers, using the Fisher Exact test.

CONCLUSIONS:

Under the conditions of this 2-year feeding study, Cyfluthrin was not oncogenic to male and female Wistar CRF rats. There was a compound-related effect on body weight of males receiving the mid- and high-doses and females receiving the high-dose. In addition, increased incidences of inflammatory foci of the kidneys of females receiving the mid- and high-doses and hyperplastic nodules of the adrenals of males and females receiving the high-dose were observed. There were no other effects noted except for increased levels of fluoride in teeth and/or bones of male and females receiving the mid- and high-doses and increased liver N-demethylase activity in females receiving the high-dose. Hence, the NOEL and LEL for chronic toxicity based on mean body weights of male rats were 50 and 150 ppm, respectively.

CORE CLASSIFICATION: Minimum for both chronic toxicity and oncogenicity.

Tox Chem No. 266E File Last Updated _____ Current Date 1/23/85

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No
28-day oral - rat; Bayer AG Institute for Toxicology; #9039; March 28, 1980	Technical 85% Batch 16001/79 Lot #2151	072008	Levels tested: 0, 5, 20 and 40/80 mg/kg/day by gavage in SPF Wistar strain. NOEL = 20 mg/kg/day. LEL = 40/80 mg/kg/day. (nerve stimulation, body weight loss, liver and adrenal weight changes increases).	N/A	Minimum 004285
28-day feeding - rat; Nihon Tokushu Noyaku Seizo K.K. (Japan); #215; March 15, 1982	Technical	072008	Dose levels: 0, 100, 300, 1000 ppm. NOEL = 100 ppm. LEL = 300 ppm (minimal decrease in blood glucose). At 100 ppm, behavioral changes, body weight loss, urobilinogen and ketone bodies in urine, decreased blood parameters, increased weight of submaxillary glands, liver weight change and some transient changes in nerve fibers.	N/A	Supplementary 004285
28-day feeding - mice; Nihon Tokushu Noyaku Seizo K.K.; #221; April 14, 1982	Technical	072008	Dose levels: 0, 300, 1000, 3000 ppm. NOEL = 300 ppm. LEL = 1000 ppm (behavioral changes, decreased body weight gain, increased liver weight, cytoplasmic swelling of the submaxillary glands).	N/A	Supplementary 004285

Tox Chem No. 266E | File Last Updated _____ | Current Date 1/23/85

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No
28-day feeding - mice; continued			At 3000 ppm - possible decrease in WBC, increase in "AIP" and BUN, increase weight of submaxillary glands, decreased spleen, adrenal, and ovary weights (in addition to above effects at 1000 ppm).		
90-day feeding - rats; Bayer AG Institute for Toxicology; #9386; June 4, 1980	Technical 84.2% pure Batch 16003/79	072008	Dose levels: 0, 30, 100, 300 ppm in SPF Wistar (TNO W.74) strain. NOEL >300 ppm (HDT). No definite test chemical effects noted.	N/A	Minimum 004285
21-day dermal - rabbit; Bayer AG Institute for Toxicology; #8928; February 5, 1980	Technical 83.5% Batch 16001/79	072009	Dose levels: 0, 50 and 250 mg/kg/day in New Zealand White strain. NOEL >250 mg/kg/day (HDT).		Minimum 004285
21-day inhalation - rat; Bayer AG Institute for Toxicology; #9373; August 20, 1980	Technical 85.3% Lot #16001/79	072009	Atmospheric concentration levels: 0, 0.4, 1.4, 2.3, 10.5, 11.5 and 69.6 mg/m^3/6 hrs/5 day/3 weeks. NOEL = 1.4 mg/m^3. LEL = 2.3 mg/m^3 (decreased body weight gain). At $\geq$ 10.5 mg/m^3 (behavioral changes, body weight changes, and organ weight changes in liver, spleen and possibly other organs.		Minimum 004285

Chem No. 266E | File Last Updated _____ | Current Date 1/23/85

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No
21-day inhalation - chicken; Bayer AG Institute for Toxicology; #11558; February 14, 1983	Technical 95%	072008	Atmospheric concentration 614 mg/m^3/6 hrs/15 days. Nonspecific symptomology at this level, 1 hen died.		Minimum 004285
5-month oral neurotoxicity - rat; Bayer AG Institute for Toxicology; #10705; March 10, 1982	Technical 83.3% Batch #1601/79	072009	Dose levels: 60-80 mg/kg and solvent control in Wistar TNO W74. Study was designed to assess effects on the structure of the nervous system. No effects on the structure of the nervous system were noted (no axonal degeneration or myelin effects).		Minimum 004285
3 Generation reproduction - rat; Bayer AG Institute for Toxicology; #11870; (also Mobil 85881); June 8, 1983	Technical Batch #'s 2/80; 3/80; 5/80; 6/80; 7/80	072009	Dose levels: 0, 50, 150, and 450 ppm in BOR:WIS W strain. Reproductive NOEL = 50 ppm. Reproductive LEL = 150 ppm (decreased viability index). Systemic ~~effects~~ NOEL = 50 ppm. Systemic LEL = 150 ppm (body weight decrease in the pups).		Minimum 004285
Teratology - rat; Bayer AG Institute for Toxicology; #10562; January 20, 1982	Technical 85% Batch 16001/79	072009	Dose levels: 0,3, 10 and 30 mg/kg/day by gavage in BAY:FB30. Teratogenic NOEL >30 mg/kg/day. (HDT) Fetotoxic NOEL >30 mg/kg/day. maternal NOEL = 3 mg/kg/day. maternal LEL = 10 mg/kg/day (behavioral changes in gait and coordination).		Minimum 004285

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Teratology - rabbit; Bayer AG Institute for Toxicology; #11855; (also Mobay 85879); June 1, 1983	Technical 95% Batch # 816170017	072009	Dose levels: 0, 5, 15 and 45 mg/kg/day by gavage in Himalayan strain. Teratogenic NOEL = >45 mg/kg/day (HDT). Fetotoxic NOEL = >45 mg/kg/day. (HDT) NOEL = 15 mg/kg. LEL = 45 mg/kg (abortion and resorption).		Minimum 004285
6-month feeding - dog; Bayer AG Institute for Toxicology; #9991 June 2, 1981	Technical 84.8%	072009	Dose levels: 0, 65, 200, and 600 ppm in beagles. NOEL = 200 ppm. LEL = 600 ppm (stiff gait, incoordination, arched backs late in study, vomiting, diarrhea, possibly decreased thymus weights).	N/A	Minimum 004285
12-month feeding - dog; Bayer AG Institute for Toxicology; #11983; (Mobay #86031); August 3, 1983	Technical PCR 1272 (cyfluthrin)	073256	Dose levels: 0, 40, 160 and 640 ppm in beagles. NOEL = 160 ppm. LOEL = 640 ppm (slight ataxia in 2 dogs, on one occasion each; increased vomiting; increased pasty-to-liquid feces; and decreased body weights in males).	N/A	Minimum 004285

Tox Chem No. 266E | File Last Updated _____ | Current Date 1/23/85

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
2-year feeding/oncogenic - rats; Bayer AG Institute for Toxicology; #11949; July 19, 1983	Technical FCR 1272 (cyfluthrin)	072365	Oncogenic NOEL = >450 ppm (HDT). Systemic NOEL = 50 ppm. Systemic LOEL = 150 ppm (decreased body weights in males, inflammatory foci in kidneys of females). Dosage levels: 0, 50, 150 and 450 ppm in Wistar SPF strain.		Minimum for ~~chronic toxicity~~ 004285
23-month feeding/ oncogenic-mice; Bayer AG Institute for Toxicology; #12035; August 24, 1983	Technical FCR 1272 (cyfluthrin)	072366	Oncogenic NOEL = >800 ppm (HDT). Systemic NOEL = <50 ppm (increased alkaline phosphates activity in males). Dosage levels: 0, 50, 200 and 800 ppm in SPF strain.		Supplementary for chronic ~~toxicity~~ finding 004285 Minimum for oncogenicity 004285
Delayed neurotoxicity - hen; Bayer AG Institute for Toxicology; #9753; January 27, 1981	Technical Batch 16001/79 85.3% pure and Batch 16003/79	072009	Part 1 Acute oral $LD_{50} \approx 5000$ mg/kg (in polyethylene glycol). 2/10 hens showed behavioral changes and some possible signs of nerve fiber degeneration ("moderate" in degree).	N/A	Supplementary 004285
	84.8% pure Batch # 16003/80 94.3% pure		Part 2 (two oval applications at 3 week intervals, 5000 mg/kg each time). Four birds showed nerve fiber degeneration and behavioral changes.		

REFERENCE DOSES (RFDs) FOR ORAL EXPOSURE

Chemical: Baythroid

CAS #: 68359-37-5
Caswell #: 266E

Carcinogenicity: No evidence of carcinogenicity in two adequate animal (rat and mice) tests.

Systemic Toxicity: See below.

Preparation Date: 3/12/86

Endpoint	Experimental Doses	UF	MF	RfD
Bayer AG Institute for Toxicology (1983)	50 ppm (2.5 mg/kg/day) Systemic NOEL	100	-	0.025 mg/kg/day
2-Year Feeding/ Oncogenic Rat Study	150 ppm (7.5 mg/kg/day) Systemic LOEL			
decreased body weights in males, inflammatory foci in kidneys of females				
3-Generation Reproduction	50 ppm (Systemic NOEL) 150 ppm (Systemic LEL)			

Conversion factor (rat): 1 ppm = 0.05 mg/kg/day

Endpoint and Experimental Doses:

Suberg, H., and Loeser, E.
Two Year Feeding/Oncogenic Rat Study
Bayer AG Institute for Toxicology
Study No. 11949; July 19, 1983

Sixty-five male and 65 female Wistar SPF rats, 5-6 weeks of age, were assigned to 4 groups which were fed diets containing 0, 50, 150, and 450 ppm of baythroid. Animals were observed for clinical signs twice daily and once daily on weekends and holidays. Individual body weights and group food consumption were determined weekly the first 26 weeks, biweekly during week 27 through 74, and then weekly until termination. Hematology, clinical chemistry, and urinalysis were performed on 10 rats/sex/group at 6, 12, 18, and 24 months of study. Observed results included decreased body weights in males and inflammatory foci in kidneys of females.

24

.....

Uncertainty Factors (UFs):

A 100 fold UF has been used to compensate for both the interspecies differences in extrapolating from the human, and the expected intra-human varibility to the toxicity of this chemical in lieu of specific data.

.....

Modifying Factors (MFs):

None

.....

Additional Comments:

Data Considered for Establishing the RfD

1) 2-Year Feeding/Oncogenic - Rat Systemic NOEL=50 ppm (2.5 mg/kg/day), Systemic LOEL 150 ppm (7.5 mg/kg/day)(decreased boody weights in males, inflammatory foci in kidneys of the females); Oncogenic NOEL = >450 ppm (22.5 mg/kg/day); core grade minimum

2) 1-Year Feeding - Dog NOEL=160 ppm (4 mg/kg/day), LEL=640 ppm (16 mg/kg/day)(slight ataxia in 2 dogs, one occasion each; increased vomiting; increased pasty-to-liquid feces; and decreased body weights in males); core grade minimum

3) 3-Generation Reproduction - Rat Systemic NOEL=50 ppm (2.5 mg/kg/day), Systemic LEL= 150 ppm (7.5 mg/kg/day)(body weight decrease in the pups); Reproductive NOEL= 50 ppm, Reproductive LEL=150 ppm (decreased viability index); core grade minimum

4) Teratology - Rat Maternal NOEL=3 mg/kg/day, Maternal LEL=10 mg/kg/day (behavioral changes in gait and coordination); Teratogenic NOEL >30 mg/kg/day (HDT); Fetotoxic NOEL >30 mg/kg/day; core grade minimum

5) Teratology - Rabbit Maternal NOEL=15 mg/kg, Maternal LEL=45 mg/kg (abortion and resorption); Teratogenic NOEL = >45 mg/kg/day (HDT); Fetotoxic NOEL = > 45 mg/kg/day (HDT); core grade minimum

Data Gap(s)

None

Other Data Considered

1) 23-Month Feeding/Oncogenic - Mice Oncogenic NOEL = >800 ppm (120 mg/kg)(HDT); core grade minimum; Systemic NOEL = <50 ppm (7.5 mg/kg) (increased alkaline phosphates activity in males); core grade supplementary

.....

Confidence in the RfD:

Study: High Data Base: High RfD: High

The critical study appears to be of good quality and is given a high rating. Since there are no data gaps existing for baythroid and additional studies are also of good quality, the RfD is given a high confidence.

Documentation of RfD and Review:

Registration files

Agency RfD Review:

First Review:
Second Review:
Verification Date:

U.S. EPA Contact:

Primary: Reto Engler FTS 557-7491

Secondary: George Ghali FTS 557-4382

END