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DATA EVALUATION RECORD

CYHALOTHRIN (Grenade)

Chronic Toxicity Study in Rats

STUDY IDENTIFICATION: Pigott, G. H., Chart, I. S., Godley, M. J., Gore, C. W., Hollis, K. J., Robinson, M., Taylor, K., and Tinston, D. J. Cyhalothrin: Two-year feeding study in rats. (Unpublished report No. CTL/P/980 and study No. PRO414 prepared by Imperial Chemical Industries PLC (ICI), Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, U.K. for Coopers Animal Health, Inc., Kansas City, MO; dated 6/27/84.) Accession No. 073210-073213.

APPROVED BY:

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1. CHEMICAL: Grenade insecticide (containing cyhalothrin) [(Rs)α-cyano-3-phenoxybenzyl(Z)-(1RS,3RS)-3-(2,chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate]. Total pyrethroid content 92.2% (w/w) of which 96.8% (w/w) was cyhalothrin.

2. TEST MATERIAL: Cyhalothrin as described above. A single batch (ADM/46156/80) was used for the chronic study. It was supplied by Imperial Chemical Industries PLC, Pharmaceutical Division. The CTL reference number was Y00102/010/005.

3. STUDY/ACTION TYPE: Chronic feeding study in rats.

4. STUDY IDENTIFICATION: Pigott, G. H., Chart, I. S., Godley, M. J., Gore, C. W., Hollis, K. J., Robinson, M., Taylor, K., and Tinston, D. J. Cyhalothrin: Two-year feeding study in rats. (Unpublished report No. CTL/P/980 and study No. PR0414 prepared by Imperial Chemical Industries PLC (ICI), Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, U.K. for Coopers Animal Health, Inc., Kansas City, MO; dated 6/27/84.) Accession No. 073210-073213.

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7. CONCLUSIONS:

A. Groups of 52 male and 52 female Alpk/AP strain rats were fed 0, 10, 50, or 250 ppm cyhalothrin for two years. Additional groups of 20 males and females were added to each dose level as extras and for the purpose of interim sacrifice. Female rats fed 50 and 250 ppm cyhalothrin in the diet showed decreased adrenal weights (corrected for body weight). However, the control adrenal weights appeared high when compared to the males. Additional effects at 250 ppm cyhalothrin levels included reduced body weight gain and decreased feed consumption in both sexes. There were no neurological effects noted. The LOEL for chronic toxicity in rats is 250 ppm cyhalothrin in the diet and the NOEL is 50 ppm. There was no indication of oncogenic activity for this chemical.

B. This is a valid study with respect to study design, execution and reporting.

8. Classificantion: Core Guideline.

Items 9 through 10 - see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

The submitted Materials and Methods section for this study is appended in Appendix A.

A. Materials and Methods:

1. The test material was the insecticide Grenade; the active ingredient was cyhalothrin with a purity of 89.2%. The total pyrethroid content was 92.2%.

2. The test animal was a Specific Pathogen Free, Alderley Park, Alpk/AP strain rat. The rats were randomly distributed to dosage groups of 0, 10, 50, and 250 ppm, each containing 72 rats per sex.

3. The basal diet was Porton Combined Diet (PCD) supplied by Special Diet Services (SDS). It was formulated by adding cyhalothrin to acetone and the solution mixed with PCD. The air-dryed feed was fed as a pellet or as a powdered diet ad libitum.

4. Most of the measurement data was evaluated by analysis of variance or analysis of covariance on pre-experimental data. Group means were adjusted for missing values. Group means were compared to control means using Student's t-test

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[a]Only items appropriate to this DER have been included.

(two-sided). Mortality data were evaluated using Mantel (1966) logrank test. Neoplastic findings were analyzed with Fischer's exact test. One-sided significance tests were used according to Gart et al. (1979).

5. Test diet was analyzed for homogeneity and stability. Dietary cyhalothrin content was also analyzed at approximately monthly intervals. The treated feed was extracted with acetone in a Soxhlet apparatus and analyzed by gas-liquid chromatography using an electron capture detector after Florisil column cleanup.

B. Protocol: See Materials & Methods, Appendix A.

12. REPORTED RESULTS:

A. Feed and Chemical Analysis: Cyhalothrin was stable in the diet for at least 9 weeks. The mixing method produced homogeneous mixes both as pellets and powdered diet. Cyhalothrin concentrations found in treated diets were within ±10% of the nominal level.

B. Mortality: There were no statistically significant differences in mortality between the dosed and control rats. Survival at 18 months ranged from 83 to 94 percent and at 24 months survival among groups ranged from 34 to 48 percent.

C. Clinical Observations: There were no adverse clinical observations which could be related to the dietary exposure to cyhalothrin. Specifically, there were no signs of neurotoxicity in any treatment group.

D. Body Weight: Mean body weight was reduced in both sexes fed diets containing 250 ppm cyhalothrin. The body weight effect was significant for the females throughout the study, while in the males it was significant to week 84 as shown in Table 1.

E. Food Consumption and Food Efficiency: There was a consistently reduced food consumption in male rats fed 250 ppm cyhalothrin for the first twelve weeks of the study. This occurred as a trend in the high-level female rats, but rarely reached statistical significance.

Male rats fed 250 ppm showed statistically increased efficiency of food utilization during the first month of the study. Mean food utilization was significantly increased for the high-level females during weeks 9-12. Although the latter is related to the reduction in body weight, the effects in either sex is of little biological significance.

F. Ophthalmology: There were no compound-related eye changes noted following ophthalmoscopic examination.

TABLE 1. Selected Body Weight Data for Rats Fed Cyhalothrin for Two Years

Dietary Level (ppm)	Group Mean Body Weight at Week					
	0	1	13	27	79	105
Males						
0	137.2	191.7	506.7	608.7	647.0	549.0
10	136.8	191.5	506.5	609.1	653.5	577.9
50	135.8	189.5	508.7	605.1	636.1	538.5
250	135.9	171.4	469.2*	561.9*	596.4*	505.5
Females						
0	125.4	158.1	286.1	320.1	405.4	379.6
10	125.8	159.4	288.9	321.8	410.1	352.3
50	123.4	156.9	286.6	314.2	400.2	351.5
250	126.4	151.0*	270.4*	299.4*	371.3*	332.2*

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

TABLE 2. Selected Hematology Data for Rats Fed Cyhalothrin for Two Years

Period (weeks) and Hematology Parameter	Dietary Concentrations (ppm)							
	Males				Females			
	0	10	50	250	0	10	50	250
Pre-experimental	-	-	-	-	-	-	-	-
4								
M.C.Hb.Conc.	37.84	37.63	37.58	37.29*	36.49	36.32	36.33	36.32
M.W.B.C.	9.75	9.97	9.49	10.08	7.20	7.54	7.49	8.44*
M.E.C.	0.15	0.06	0.12	0.05*	0.08	0.23**	0.11	0.07
13	-	-	-	-	-	-	-	-
26								
M.RBC	8.79	8.66	8.95	9.15*	7.91	8.02	7.90	7.98
M.P.C.	570	560	578	505	529	488	561	395*
39								
M.RBC	8.77	8.83	8.80	8.94	7.69	8.01*	7.96	8.04*
M.C.V.	49.1	49.5	49.3	48.3	55.0	54.5	54.7	53.4*
M.WBC	8.43	7.69	8.48	8.09	5.03	5.49	6.37*	6.78**
M.L.C.	5.78	5.27	5.76	5.32	3.53	3.83	4.09	4.86*
52								
M.Hb	15.66	15.87	15.84	15.57	15.92	15.38*	15.39*	15.35*
M.H.crit	0.422	0.430	0.430	0.422	0.439	0.427	0.422**	0.422**
M.P.C.	948	660**	813	720**	679	730	636	608
65								
M.H.crit	0.412	0.429	0.426	0.415	0.424	0.430	0.423	0.402*
M.L.C.	5.29	5.32	5.14	5.43	3.90	3.91	4.62	6.54*
M.E.C.	0.30	0.26	0.23*	0.21*	0.14	0.10	0.12	0.10
78	-	-	-	-	-	-	-	-
91								
M.WBC	10.69	10.80	12.56	9.97	5.89	6.12	8.52*	7.38
MMC	0.27	0.29	0.48	0.52*	0.05	0.18	0.28*	0.17
104								
M.RBC	7.17	7.89*	7.14	7.40	7.72	7.39	7.26	7.76
MEC	0.09	0.12	0.09	0.08	0.06	0.04*	0.05*	0.01*

Key:

M.C.Hb.Conc. = mean cell hemaglobin concentration
M.W.B.C. = mean white cell count
M.E.C. = eosinophil count
M.WBC = mean white cell count
M.Hb = mean hemoglobin
MMC = mean monocyte count
M.RBC = mean red blood cell
M.P.C. = mean platelet count
M.C.V. = mean cell volume
M.L.C. = mean lymphocyte count
M.H.crit = mean hematocrit

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

G. Hematology: Selected results of hematology studies are presented in Table 2. There was a small but statistically significant decrease in hemoglobin at week 52 in female rats in all groups receiving cyhalothrin. The effect was not dose-related and may have been significant as a result of an unusually high control value.

H. Clinical Chemistry: Rats in the group that were fed 250 ppm cyhalothrin showed a tendency for reduced levels of plasma glucose, triglycerides, and alkaline phosphatase activity. The effect on triglycerides was most marked and was primarily evident in the female rats. Plasma urea levels were higher in the 250 ppm group with the females showing the effect more than the males.

There were occasionally other parameters that were significantly different from the controls, but in the absence of a consistent dose-effect relationship or time pattern the effects were considered unrelated to the treatment with cyhalothrin. Selected clinical chemical findings are summarized in Table 3.

I. Urinalysis: According to the study authors, there was a trend to a lower urine volume with an associated increase in urine specific gravity in the 250 ppm cyhalothrin group. These findings seldom were of statistical significance. The urinary glucose levels of the female test animals tended to be lower than the controls through the course of the study. This parameter reached statistical significance only twice during this study.

There were isolated statistically significant differences between other dosed and control animals for other parameters, but due to the lack of a dose-effect relationship or a pattern over time, none of these effects were considered to be test compound related.

J. Organ Weights: For the rats killed at 52 weeks, liver weights (when adjusted for body weights) were elevated for both sexes fed 250 ppm cyhalothrin. Brain weights of the female rats fed 10 or 50 ppm cyhalothrin were reduced, but this is not considered to be compound induced because of lack of dose-effect relationship.

In the animals killed at termination, adrenal weights (when corrected for body weight) were significantly decreased in female 50 or 250 ppm groups when compared to controls. No other organs showed treatment related effects. Table 4 presents selected organ weight data.

K. Gross Pathology: The majority of the gross lesions were similar to those expected in the rat strain used. A significant number of rats at all levels, including the controls, had unilateral or bilateral oro-nasal fistulation (erosion of the palate). Additionally, erosion of the gum (cavities) of the lower jaw occurred in a number of rats. The oro-nasal pathological lesions were not compound related.

TABLE 3. Selected Clinical Chemistry Data (Means) Rats Fed Cyhalothrin for Two Years

Period (weeks)	Dietary Concentration (ppm)															
	0				10				50				250			
	P.glucose[a]	P.urea	Alk.phos	Trigly.	P.glucose	P.urea	Alk.phos	Trigly.	P.glucose	P.urea	Alk.phos	Trigly.	P.glucose	P.urea	Alk.phos	Trigly.
Males																
Pre-experimental	143	34.3	422	88	145	32.7	445	93	141	35.8	486	95	138	35.6	458	116
4	150	48.5	263	133	154	51.0	279	146	149	52.2	268	125	145	47.7	267	123
13	150	50.6	149	167	151	51.5	147	172	145	53.4	150	139	142	54.9	144	118**
26	139	48.3	130	134	136	48.3	126	131	136	47.4	115*	126	127**	49.4	126	104*
39	135	42.5	115	152	133	40.8	123	137	135	42.3	133*	127*	131	45.0	115	140
52	138	39.8	130	198	138	38.4	128	123	133	41.4	152	145	126*	43.1	115	180
65	127	45.0	125	194	128	39.7	131	156	122	45.0	125	164	124	51.1	112	174
78	116	49.5	114	211	120	45.9	128	195	110	47.4	124	204	116	51.5	122	157
91	116	43.3	127	104	118	37.9	115	162	110	58.7	107	202	110	51.4	112	136
104	116	54.6	122	189	117	46.4	111	160	123	52.8	106	201	115	60.2	117	140
Females																
Pre-experimental	141	39.3	394	80	138	39.4	382	91	134	38.2	379	86	138	38.7	359	83
4	137	55.3	175	97	141	53.8	181	104	139	52.9	173	88	137	55.1	153	98
13	142	62.7	108	109	145	61.2	102	100	143	63.7	90*	107	140	63.8	82**	90
26	141	57.3	67	151	136	55.8	73	126	128**	62.3	59	126	131*	68.3**	54	110**
39	139	56.4	66	144	137	53.7	62	139	133	55.6	54	152	127**	64.8**	49*	105**
52	140	54.8	59	203	132	49.3	55	132*	134	53.4	50	176	131	58.6	48	125**
65	128	50.2	53	202	125	52.0	57	201	121	58.6	48	221	133	55.3	49	148
78	112	49.7	54	270	113	47.5	53	279	110	49.8	48	255	116	55.3	49	164*
91	111	46.8	52	272	107	45.3	45	177	115	44.5	50	205	114	47.2	41	139**
104	119	44.0	67	270	119	46.8	63	219	111	50.5	54	180	117	50.0	40	175

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

[a] P. glucose = plasma glucose.
P. urea = plasma urea.
Alk. phos. = plasma alkaline phosphotase.
Trigly = plasma triglycerides.

TABLE 4. Intergroup Comparison of Selected Organ Weights from Rats Fed Cyhalothrin for Two Years

Interval & Tissue	Dietary Concentration (ppm)							
	Males				Females			
	0	10	50	250	0	10	50	250
52 Weeks								
Brain								
mean	2.283	2.313	2.369	2.328	2.140	2.085*	2.088*	2.110
mean adjusted for body weight	2.283	2.308	2.358	2.344	2.140	2.085*	2.088*	2.109
Liver								
mean	22.0	23.06	24.0	25.0	12.4	12.1	12.6	12.6
mean adjusted for body weight	22.0	23.4	23.6	25.7*	11.9	11.7	12.1	13.8**
Terminal								
Adrenals								
mean	0.066	0.106	0.075	0.072	0.120	0.111	0.097	0.093*
mean adjusted for body weight	0.066	0.109	0.074	0.069	0.127	0.109	0.095**	0.087**
Spleen								
mean	1.75	1.66	1.60	1.42	0.86	1.04	1.26	0.87
mean adjusted for body weight	1.74	1.59	1.62	1.49	0.69	1.10	1.32*	1.02

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

Several rats in all groups had gaseous distention of the intestines. This lesion was not treatment related.

L. Histopathology: The majority of pathological lesions in dosed animals, both neoplastic and nonneoplastic, were similar to those present in control rats in this study. Except for oro-nasal fistulation and other associated lesions, there were no compound-related pathological lesions in any tissue in either sex.

Noteworthy lesions were associated with the fibrous nature of the feed and consisted of oral food granuloma and oro-nasal fistulation. This was first noted at week 65 and the incidence was greater in the males than females in all groups. Also associated with the oro-nasal fistulation was marked rhinitis which was the leading cause of death or moribund kill in male rats and second in female rats. Also associated with the oro-nasal finding was the gaseous distention of the intestine (observed grossly) and a reactive lymphoid hyperplasia of the cervical lymph nodes with an increase in the number of plasma cells.

The number of animals with bronchopneumonia or chronic pneumonitis was higher than expected in SPF rats of this strain. The animals with marked lung lesions also had severe oro-nasal lesions.

The highest incidence of tumors occurred in the pituitary gland. This was the most common cause of death in the females. However, the incidence of pituitary adenoma, the most frequent type, was consistent with historical incidence of this strain of rat.

Selected histopathologic findings are tabulated in Tables 5 and 6. Table 5 summarizes histologic lesions in animals at the terminal sacrifice; similar incidences were seen in animals that died on study.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The authors concluded that 250 ppm cyhalothrin fed in the diet to rats for two years caused decreased body weight and produced other minor indications of toxicity. Although there was a high incidence of palatine fistulation and marked rhinitis this was not compound related but was produced by long pointed fibers in the food. There were no neurologic or carcinogenic effects associated with ingestion of cyhalothrin. They concluded that 50 ppm is the NOEL.

B. The protocol and an amendment to the protocol were examined by the quality assurance staff. The conduct of the study was examined 16 times during the course of the study. The draft report and the final report were audited for consistency of performance according to the protocol and that the reports accurately represented the data.

TABLE 5. Incidence of Selected Histologic Lesions in Two-Year Feeding Study on Cyhalothrin (Results are in Rats Killed at Termination)

Pathologic Findings	Dietary Concentration of Cyhalothrin (ppm)							
	Males				Females			
	0	10	50	250	0	10	50	250
Mouth - Number Examined	21	23	25	28	22	20	25	30
Not remarkable	0	1	0	2	1	0	2	0
Malocclusion	1	0	1	3	0	1	1	0
Periodontitis	15	16	15	17	18	14	12	22
Hyperplasia palate	0	0	2	0	1	0	0	0
Food granuloma palate	6	4	3	5	8	5	5	10
Food granuloma lower gum	8	11	13	11	6	6	9	5
Granuloma maxilla	0	0	0	0	0	0	1	0
Food granuloma palate (gross finding)	0	1	1	2	1	2	1	2
Food granuloma lower (gross finding)	2	0	0	1	0	0	1	0
Palatine fistula	9	12	12	11	5	6	10	11
Granuloma gum	0	0	0	1	0	0	0	0
Broken incisor	0	0	0	0	0	0	1	0
Mononuclear cell infiltration palate	0	0	1	0	0	0	0	0
Nasal Passage - Number Examined	21	23	25	28	22	20	25	30
Not remarkable	7	5	4	9	10	5	6	12
Rhinitis	12	15	20	18	12	15	16	15
Maxillary sinusitis	8	8	5	3	2	4	5	4
Squamous metaplasia	9	7	12	12	7	4	8	9
Cervical Lymph Node - Number Examined	20	23	25	28	22	20	25	30
Not remarkable	0	2	4	4	6	2	5	9
Cystic change	12	16	14	20	12	12	15	18
Congested	1	1	0	0	0	0	0	0
Lymphoid hyperplasia	8	9	9	7	8	7	9	8
Increased plasma cells	14	13	14	14	11	14	12	12
Reactive	0	1	1	0	0	0	0	1
Dilated blood filled sinus	0	0	1	1	0	0	1	0
Pigmented	0	0	0	0	1	0	0	0

TABLE 5. Incidence of Selected Histologic Lesions in Two-Year Feeding Study on Cyhalothrin (Results are in Rats Killed at Termination) (continued)

Pathologic Findings	Dietary Concentration of Cyhalothrin (ppm)							
	Males				Females			
	0	10	50	250	0	10	50	250
Colon - Number Examined	21	23	24	27	22	20	25	28
Not remarkable	17	19	15	26	20	19	24	28
Dilated	4	4	8	1	1	1	1	0
Dilated (gross only)	0	0	0	0	1	0	0	0
Lung - Number Examined	21	23	25	28	22	20	25	30
Not remarkable	16	18	18	23	21	15	22	27
Congested	0	0	0	0	0	0	1	0
Alveolar histocytosis	1	5	4	3	0	1	1	3
Alveolar cell calcification	1	0	1	0	0	0	1	0
Chronic pneumonia	0	0	1	1	0	3	0	0
Granuloma	0	0	0	1	0	0	0	0
Hemorrhage	1	0	1	0	1	1	0	0
Alveolar cell hyperplasia	1	0	2	0	0	0	0	0
Mononuclear cell infiltration	1	0	0	0	0	0	0	0
Adrenal - Number Examined	21	23	25	28	20	20	24	28
Not remarkable	7	10	7	9	1	1	2	0
Vascular ectasia	4	2	3	1	18	18	20	24
Hyperplasia cortex	2	0	0	0	1	0	1	0
Vascular degeneration	10	9	17	18	3	2	3	4
Hyperplasia medulla	0	0	0	0	0	0	0	1
Cortical necrosis	0	1	0	0	0	1	0	0
Cortex reduced	0	1	0	0	0	0	0	0
Mononuclear cell infiltration medulla	0	1	0	0	0	0	0	0

TABLE 5. Incidence of Selected Histologic Lesions in Two-Year Feeding Study on Cyhalothrin (Results are in Rats Killed at Termination) (continued)

Pathologic Findings	Dietary Concentration of Cyhalothrin (ppm)							
	Males				Females			
	0	10	50	250	0	10	50	250
Mammary Gland - Number Examined					22	20	24	30
Not remarkable					9	3	2	2
Increased secretory activity					13	17	21	27
Granuloma					0	1	0	0
Cyst					1	1	0	1
Hyperplasia					0	0	1	1
Abcess					0	0	1	1
Prominent nipple					0	0	1	0
Adenocarcinoma					1	1	1	1
Fibroadenoma					1	1	2	5
Cyst adenoma					1	0	0	0
Adenoma					0	0	1	2
Squamous cell adenoma					0	1	0	0
Cyst fibroadenoma					0	1	0	1
Pituitary Gland - Number Examined	20	19	25	23	20	20	24	29
Adenoma	10	5	13	8	17	18	19	24
Neurofibrosarcoma	0	0	0	0	0	0	0	1
Adenocarcinoma	0	0	0	0	0	0	1	0

TABLE 6. Incidence of Selected Mammary Gland Lesions
In Two-Year Feeding Study on Cyhalothrin

Pathologic Findings	Dietary Concentration of Cyhalothrin (ppm)							
	Males				Females			
	0	10	50	250	0	10	50	250
Mammary Gland - Number Examined					71	72	69	72
Adenocarcinoma					6	4	5	4
Fibroadenoma					5	4	6	9
Cyst adenoma					2	1	0	2
Adenoma					1	2	2	3
Squamous cell adenoma					0	2	0	0
Cyst fibroadenoma					0	1	0	1

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. The cyhalothrin in the diet was stable and homogeneously mixed. The dietary content generally met the intended level. Ingestion of diets containing up to 250 ppm cyhalothrin for two years produced no changes in the following parameters as compared to the control values: signs toxicity or clinical observations, mortality, ophthalmoscopic findings, mean cell volume, mean cell hemoglobin, mean neutrophil counts, prothombin time, Kaolin-cephalin time, gross pathology, and histopathology. The following values had occasional statistically different values as compared to control values but the differences were not considered by our reviewers to be related to the test material because of lack of dose-effect relationship, a consistent time relationship, or due to an unusual control values: hemoglobin, mean hematocrit, red blood cell counts, cell volume, cell hemoglobin concentration, cell hemoglobin, white blood cell count, lymphocyte, monocyte count, eosinophila, platelet count, plasma glucose, plasma urea, alkaline phosphatase, alanine transaminase, and aspartate transaminase activity, albumin, protein, urinary pH, protein, and glucose.

Mean plasma triglyceride values were consistently lower than controls from 13 to 78 weeks. These values were statistically significant primarily in the females. Although this is felt by our reviewers to be compound related, the toxicological significance is not highly meaningful.

Body weights were decreased in both sexes due to ingestion of feed containing 250 ppm cyhalothrin. The effect was more significant in the female rats. There was consistently reduced feed consumption in male rats fed 250 ppm cyhalothrin. A similar but less severe effect was seen in the high level females, but the effect was not often statistically significant. Slightly increased feed efficiency was apparent in the male 250 ppm group in the first 4 weeks of the study. The females fed 250 ppm cyhalothrin showed reduced feed efficiency in the period 9-12 weeks. Neither of these feed efficiency effects are large and are of little biological significance.

Liver weights (corrected for body weight) were elevated for both sexes when fed 250 ppm cyhalothrin for 52 weeks. Since there were no similar effects at termination and no correlative pathology at either times this is not considered biologically significant. Reduced brain weights at 52 weeks in female rats fed 10 or 50 ppm are likewise of no significance as there was no morphologic effect. Adrenal weights (when corrected for body weight) at termination showed a significant decrease in the female 50 or 250 ppm group as compared to the controls. No morphologic effect correlated with this weight change; nevertheless, the effect cannot be dismissed due to its dose-effect relationship and the high degree of significance. However, since the adrenals are difficult to trim properly at necropsy and since the female control values appear high when compared to males; the decrease in adrenal weights are probably not of toxicological significance.

B. There were no problems, discrepancies, or inaccuracies in the design, conduct or reporting of this study, so the study must be considered a valid study.

Item 15 - see footnote 1.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 3-15.