

US EPA ARCHIVE DOCUMENT

9-30-91



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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September 6, 1991

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: ID# 57883-1. Pyrethrum extract (technical). Evaluation of a Two-Generation Rat Reproduction Study to support reregistration of Pyrethrum Extract.

Tox. Chem. No.: 715
Shaughnessey No.: 069001
Project No.: 0-0454
Record (Submission) No.: 257715

TO: Linda DeLuise, PM Team 50 Product Manager
Special Review and Reregistration Division. (H7508W)

FROM: Linnea J. Hansen, Ph.D.
Toxicology Branch I, Section IV
Health Effects Division (H7509C)

Linnea J. Hansen
9/16/91

THRU: Marion P. Copley, D.V.M., D.A.B.T., Section Head
Toxicology Branch I, Section IV
Health Effects Division (H7509C)

Marion Copley 9/16/91

CONCLUSIONS:

The two-generation reproduction study in rat submitted on behalf of the Pyrethrin Joint Venture for the reregistration of pyrethrin satisfied the guideline requirements and is acceptable for regulatory purposes.

Pyrethrum extract, a blend of 3 pyrethrins, caused no specific reproductive effects in rats up to 3000 ppm in the diet (196 mg/kg/day, dietary estimate). Under the conditions of this study a NOEL of 100 ppm (6.4 mg/kg/day, dietary estimate) was observed for both parental and offspring animals. A LEL of 1000 (65 mg/kg/day, dietary estimate) was established for both parental (decreased male F₁ body weight during growth) and offspring (decreased F_{1b} pup body weights during lactation) animals.

Core-classification: guideline

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ACTION REQUESTED:

On December 15, 1989 the Chemical Specialties Manufacturers' Association submitted for review a two-generation reproduction study in the rat treated with pyrethrum extract. This report was submitted on behalf of the Pyrethrin Joint Venture, an organization of nine companies involved in reregistration of pyrethrin. This study is submitted as part of the guideline requirements for reregistration of pyrethrin.

HANSEN/PC-1/PYRETH.MEM/0005/PYRETHRUM EXTRACT/PROJ #0-
0454/2GENREP,RAT/9-6-91

Reviewed by: Linnea J. Hansen, Ph.D.
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DATA EVALUATION REPORT

STUDY TYPE: 2 generation repro. - rat (83-4) TOX. CHEM NO: 715

MRID NUMBER: 413275-01 SHAUGHNESSEY NO.: 069C01

TEST MATERIAL: Pyrethrum Extract (Task Force Blend)

SYNONYMS: Pyrethrin, Prentox, Pyroicide, Pyrenone, Pyronyl

STUDY NUMBERS: IRDC 556-005

SPONSOR: Pyrethrin Joint Venture/Chemical Specialties,
Manufacturers' Association, Suite 1120, 1001
Connecticut Ave., N.W., Washington, D.C.

TESTING FACILITY: International Research and Development
Corporation, 500 N. Main St., Mattawan, MI
49071

TITLE OF REPORT: Two Generation Reproduction Study in Rats with
Pyrethrum Extract

AUTHOR: James L. Schardein, M.S., D.A.T.S.

REPORT ISSUED: December 14, 1989

CONCLUSION:

Doses Tested: 0, 100, 1000 and 3000 ppm

Parental Systemic Toxicity NOEL = 100 ppm (6.4 mg/kg/day, dietary estimate); LEL = 1000 ppm (65 mg/kg/day, dietary estimate) based on body weight reduction in F₁ parental rats during growth (males). At 3000 ppm (196 mg/kg/day), body weight reduction observed in males and females during growth and reduction of body weights in F₁ females during F_{2a} and F_{2b} lactation.

Reproductive (Offspring) NOEL = 100 ppm (6.4 mg/kg/day); LEL = 1000 ppm (65 mg/kg/day) based on reduction of F₁ pup body weights during lactation. 3000 ppm (196 mg/kg/day): decreased mean pup weights during lactation (all generations), decreased birth weights in F_{2a} generation pups.

No specific reproductive effects on mating, fertility, gestation or lactation were observed in this study.

Classifier: Core-Guideline

This study satisfied guideline requirements and is acceptable for regulatory purposes.

A signed Quality Assurance Statement was present.

Special Review Criteria (40 CFR 154.7) Not triggered by this study.

A. MATERIALS:

1. Test compound: Pyrethrum Extract, amber liquid, lot - #PEK-99, equal parts of lot# 3910 from Mclaughlin Gormly King, lot# 344 from Pyrethrum Board of Kenya and no lot number from Pyrethria an Rwanda; prepared by Fairfield American Corp. and sent in 3 shipments. Purity - 57.57% (w/w), stability - stable at 4° C; stable in diet under storage conditions (room temperature) for at least 10 days.
2. Test animals. Species: rats, Strain: Charles River COBS CD; Age: 28 days; Weight: Males 172-228 g, females 125-171 g; Source: Charles River Laboratories, Inc., Portage, MI; and acclimated for 14 days (clinical and viral screens performed pretest on 10 males and 10 females to assess health of animals).

B. STUDY DESIGN:

1. Animal assignment

Animals were assigned randomly to test groups (see Table 1). F₀ rats were fed the appropriate test diet throughout the entire study. An attempt was made to put a male and female from each F₁ litter into each treatment group. F₁ progeny produced during the experiment (F₂) were placed on the same diets as their parents immediately following weaning and continuing until sacrifice. Dose levels were chosen based on results from a 90-day range finding study.

TABLE 1

Test Group	Conc. in diet		F ₀ (parents of f ₁ pups)		F ₁ (parents of f ₂ pups)		Time Weighted Ave.* (mg/kg/day)
	%	(ppm)	male	female	male	female	
1 Cont	0.0	(0)	28	28	28	28	0.0
2 Low (LDT)	.01	(100)	28	28	28	28	6.4
3 Mid (MDT)	.1	(1000)	28	28	28	28	65
4 High (HDT)	.3	(3000)	28	28	28	28	196

* calculated from compound consumption and averages during growth periods of the study

Rats in the F₀ generation were maintained on the test diet for 77 days prior to mating (about 17 weeks of age), then

bred to obtain the F_{1a} litters. These progeny were raised until weaning age (Postpartum (PP) day 21). The F_0 rats were then bred again to produce the F_{1b} litters. Following a 70 day feeding period (15 weeks of age) the F_{1b} (F_1) rats were bred to obtain the F_{2a} litters. After the F_{2a} litters were weaned, the F_1 parents (about 26 weeks old) were mated again to produce the F_{2b} litters.

2. Mating procedure

Twenty-eight males and females per group were used for each mating (see Table 1). Each female was mated to a non-sibling male from the same treatment group. The pairs were checked daily for copulatory plugs and vaginal sperm (by vaginal smears). Females with confirmed matings were separated into individual plastic cages with chip bedding. Those females that showed no signs of mating within 7 days of cohabitation were re-housed with a second male from the same treatment group and, if necessary after another 7 days, a third male (total of 21 days for mating if needed).

3. Diet preparation

Test diet was prepared every week and stored at room temperature in closed containers until used. Prior to initiation of the study, trial batches were tested for homogeneity and chemical stability. During the study, samples of freshly prepared treated food were analyzed for chemical presence and concentration weekly from Weeks 1-4 and every 4 weeks thereafter. Diets were considered within acceptable range if the means of analyzed samples were within $\pm 10\%$ of target, differences between duplicate analyses were within $\pm 15\%$ and individual analyses were within $\pm 15\%$ of target. Samples which did not fall within acceptable range were re-analyzed and, if necessary, prepared again.

Results -

Homogeneity: Samples removed from different places in batches contained 94 to 111% of target concentration. Means and standard deviations at each concentration were $100 \pm 2.9\%$, $104 \pm 3.4\%$ and $102 \pm 3.0\%$ for 100, 1000 and 3000 ppm, respectively.

Stability: Test compound was stable in diets for at least 20 days under storage conditions (room temperature). Concentrations varied between 100-106% of target.

Routine Analysis: Test compound concentrations in diet ranged between 91-109% of target. Means were $100 \pm 5\%$ (100 ppm), $99 \pm 3.9\%$ (1000 ppm) and $100 \pm 3.9\%$ (3000 ppm).

- 4. Animals received food, as a mash (Purina Certified Rodent Chow No. 5002) and water ad libitum.

- 5. Statistics

Data was evaluated for statistical significance relative to controls at the level of $p < 0.05$ or $p < 0.01$.

Parental body weights, food consumption, number of live-born pups/litter and mean pup body weights were analyzed by analysis of variance (one-way classification), Bartlett's test for homogeneity of variances (Steel, R.G.D. and Torrie, J.H., 1960, Principles and Procedures of Statistics, McGraw-Hill, NY) and t test using Dunnett's multiple comparison tables (Dunnett, C.W., 1964, Biometrics 20: 482-421) to determine significances of differences .

Fertility indices were compared using Chi-square test criterion with Yates correction for 2 x 2 contingency tables and/or Fishers exact probability test to determine significance of differences (Siegal, S., 1956, Nonparametric Statistics for the Behavioral Sciences, McCraw-Hill, NY).

Pup survival indices were compared using the Mann-Whitney U-test to determine significance of differences (Siegal, S., see above and Weil, C.S., 1970, Food Cosmet. Toxicol. 8: 177-182)

C. METHODS AND RESULTS:

- 1. Observations:

Animals were inspected twice daily for signs of toxicity and mortality. A more detailed examination was conducted weekly. Pregnant females were examined 3 times daily towards end of gestation.

Mortality - Mortality among F_0 and F_1 animals did not increase with dose and did not appear to be treatment-related. Among F_0 animals, 1 low dose female died on lactation day 21, 1 high dose female on lactation day 17 and a low dose female was sacrificed at parturition in poor condition. Four F_1 animals died prior to sacrifice. One male each from low, medium and high dose groups died at 9, 21 and 31 weeks of age, respectively. A control female also died at 24 weeks of age (lactation day 14, F_{2a} mating).

Toxicity - Clinical observations did not appear to be treatment-related. Some of the more common findings included hair loss, dark red/brown/black matter around eyes, malocclusion and missing teeth.

2. Parental Body Weight

Animals were weighed weekly during the growth phase. Males were weighed weekly during mating until sacrifice. Females were weighed weekly during mating until conception, then on gestation days (G) 0, 6, 15 and 20 and on PP 0, 7, 14 and 21.

Males: Mean body weights of treated male F_0 rats did not differ significantly from controls during the study.

F_0 Females: There were no statistically significant differences in mean body weights among treated and control animals during growth, gestation or lactation. High dose females showed decreased weight gain relative to controls between matings (Table 2). This did not appear to be treatment-related since F_0 males were not affected and since the decrease did not continue into gestation.

TABLE 2: MEAN BODY WEIGHT GAIN BETWEEN MATING, F_0 FEMALES¹

MEAN BODY WEIGHT GAIN, G (NO. ANIMALS)				
STUDY WEEK	PYRETHRUM EXTRACT, 0 PPM	PYRETHRUM EXTRACT, 100 PPM	PYRETHRUM EXTRACT, 1000 PPM	PYRETHRUM EXTRACT, 3000 PPM
19	-9 (27)	-16 (27)	-21 (26)	-14 (25)
20	12 (28)	14 (27)	12 (28)	6 (27)
21	5 (28)	9 (27)	6 (28)	6 (27)
22	7 (28)	8 (27)	7 (28)	3 (27)
23	14 (13)	16 (10)	9 (10)	6 (15)
24	25 (4)	8 (5)	39 (5)	4 (3)

¹ Body weight gain data for parental animals during growth was not calculated in the study; the weight gain information presented here was calculated from mean body weights in Table 6 (Summary of Body Weight Values) of study (current weekly body wt. - previous weekly body wt.). Table 6 from the study is included in Appendix 1.

High dose females also showed decreased mean body weights relative to controls during F_{1a} lactation (net weight loss in high dose animals vs net weight gain in controls) as shown in Table 3. The study authors considered this to be unrelated to treatment since weight fluctuations are common during lactation in the strain of rat used.

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TABLE 3: MEAN BODY WEIGHT GAIN, F₁, LACTATION¹

MEAN BODY WEIGHT GAIN, G ± STANDARD DEV.		
DAY OF LACTATION	PYRETHRUM EXTRACT 0 PPM	PYRETHRUM EXTRACT 3000 PPM
0 - 7	16 ± 15.3	10 ± 15.4
7 - 14	1 ± 22.0	-8 ± 18.5
14 - 21	-11 ± 23.0	-5 ± 19.4
0 - 21	6 ± 18.2	-3 ± 18.5

¹ Data taken from Table 7-Maternal Body Weight Summary, F₀ females, F₁ mating

F₁ males: Mean body weights and body weight gains for weeks of age 6-16 are shown below in Table 4 for male and female F₁ animals. High dose males showed statistically significant, treatment-related reduction of body weights relative to controls throughout treatment. Weekly body weight gains of high dose animals from week of age 5 and on were comparable or at most 10% lower than controls.

F₁ females: Growth - Body weights of high dose F₁ females during growth were somewhat lower than control animals but only a few of the mean weekly weights were statistically significantly lower. While the decrease was slight it was possibly treatment-related given the decrease in F₁ males.

TABLE 4: BODY WEIGHT/WEIGHT GAIN, F₁ MALES AND FEMALES¹

WEEK OF AGE	0 PPM PYRETHRUM EXTRACT		3000 PPM PYRETHRUM EXTRACT	
	♂	♀	♂	♀
6	211±16.8 (59) ²	157±12.8 (30)	188±22.0** (53)	154±17.5 (33)
7	264±20.4 (53)	177±15.5 (20)	241±23.5** (53)	174±18.0 (20)
8	319±22.0 (55)	201±18.1 (24)	290±25.0** (49)	195±21.7 (21)
9	364±26.4 (45)	220±19.0 (19)	330±26.3** (40)	210±21.4 (15)
10	399±28.9 (35)	232±19.8 (12)	363±30.4** (33)	221±21.9 (11)
11	428±31.1 (29)	243±20.7 (11)	392±30.7** (29)	231±23.4 (10)
12	455±33.1 (27)	254±21.6 (11)	416±30.9** (24)	240±23.3 (9)
13	475±37.7 (20)	262±23.4 (8)	440±37.3** (24)	247±25.2 (7)
14	498±38.3 (23)	271±25.0 (9)	458±33.3** (18)	255±27.5 (8)
15	517±38.3 (19)	277±25.7 (6)	477±33.5** (19)	259±28.6* (4)
16	526±40.1 (9)	281±25.8 (4)	487±32.9** (10)	262±27.9* (3)

¹ Data taken from Table 9 (Summary of Body Weight Values) of study

² Mean body weight, grams ± standard deviation/ body weight gain per week, grams

* p < 0.05; ** p < 0.01

Gestation - During F_{2a} gestation, mean body weights of high dose females were decreased significantly but most weekly body weight gains were comparable to controls (Appendix 2). Body weights of high dose females during F_{2b} gestation were decreased but not statistically significantly and body weight gains were similar to controls.

Lactation - Body weights of high dose females were also lower during F_{2a} and F_{2b} lactation and during F_{2b} lactation the difference was statistically significant (Appendix 2). Weight gain was somewhat lower than controls. These differences appeared to be treatment-related.

3. Food consumption, food efficiency and compound intake

Food consumption was determined weekly for males and females during the growth periods but not when animals were cohabited during the mating periods. During gestation and lactation it was measured weekly for days PP0-7, 7-14 and 14-21. Food efficiency and compound intake were calculated using the mean daily food consumption, individual body weight and theoretical dietary concentration.

Food consumption -

During growth - There were no differences in food consumption between F_0 control and treated animals in males or females except for a few random statistically significant differences, both increases and decreases. Mean food consumption values are shown for F_1 males in Appendix 3 taken directly from the study data tables. F_1 males and females both showed some decreases (statistically significant) at the high dose level and a few at the low dose level. The decreased food consumption in F_1 animals was considered treatment-related.

During lactation - F_0 females did not show treatment-related decreases in mean food consumption during either lactation period, although a few time points with statistically significant decreases were observed. Food consumption values for F_1 females during F_{2a} and F_{2b} lactation are shown below in Table 5. F_1 females showed decreased food consumption at high dose for the F_{2a} lactation and at mid and high dose for the F_{2b} lactation. These differences were considered statistically significant and treatment-related. Decreased body weights during lactation may have been in part related to this decrease.

TABLE 5: MATERNAL FOOD CONSUMPTION, F_{2a} AND F_{2b} LACTATION¹

WEEK OF LACTATION	0 PPM			100 PPM			1000 PPM			3000 PPM		
	MEAN	SD	NO	MEAN	SD	NO	MEAN	SD	NO	MEAN	SD	NO
F _{2a} : 0-7	29.0	5.86	20	31.2	4.87	19	29.2	4.40	22	28.8	3.48	21
7-14	48.6	5.31	18	49.4	5.98	14	45.8	4.39	20	43.6**	4.08	18
14-21	63.5	9.50	21	61.5	6.61	20	59.7	8.77	24	54.4**	7.18	21
0-21	46.7	4.65	16	48.2	5.20	14	45.1	4.86	18	42.5**	3.56	18
F _{2b} : 0-7	33.6	7.06	14	31.9	5.27	13	30.5*	5.15	17	28.3*	4.33	20
7-14	51.1	5.74	14	47.5	7.40	13	43.8**	7.79	17	40.8**	8.19	19
14-21	64.0	4.95	14	59.4	8.80	14	53.8**	9.73	17	51.8**	10.88	20
0-21	49.6	5.26	14	45.8	6.62	12	42.7	7.32	17	40.2**	7.23	19

¹ Data taken from Tables 25 and 29 (Summary of Lactation Food Consumption) of study

* p < 0.05
 ** p < 0.01

Food efficiency - During growth - Food efficiency [(weekly body weight change, grams/weekly food intake, grams) X 100] is shown for control and high dose F₁ parental males and females during weeks of age 6-15 in Table 6 below. There were no significant differences in food efficiency between control and treated animals for either F₀ or F₁ animals.

TABLE 6: FOOD EFFICIENCY, F₁ MALES AND FEMALES¹

WEEK OF AGE	0 PPM PYRETHRUM		3000 PPM PYRETHRUM	
	♂	♀	♂	♀
6	37.0	24.9	36.4	28.4
7	31.0	16.9	32.9	17.6
8	29.0	18.9	31.7	17.3
9	23.5	14.7	22.8	13.1
10	18.4	9.4	18.7	9.5
11	15.4	8.7	16.1	8.6
12	14.3	8.7	13.3	7.6
13	10.5	6.1	13.2	5.8
14	12.2	6.9	10.0	6.7
15	10.4	4.9	10.4	3.6

¹ Data calculated from data in Tables 6, 9, 14, 19 and 21 (Summaries of Body Weight Values and Food Consumption Values) from study.

Compound intake (time weighted averages) during the 70 day growth periods for the males and females of both generations

combined is presented in Table 1. Compound consumption was proportional to theoretical dose level increment in each treatment group. Compound consumption was similar during gestation for parental females in each mating generation.

4. Reproductive effects

Gestation length and number of live and dead progeny were determined on the day of delivery (PP). Females that did not deliver were examined for evidence of pregnancy.

Mating performance and fertility -

The following indices were based on each breeding trial and are shown in the tables below-

Mating index - proportion of pairs showing evidence of mating/total number of pairs.

Fertility index - Proportion of pairs with evidence of mating that resulted in pregnancy/total pairs with evidence of mating.

Mating indices and fertility indices are presented in Table 7 below. No significant differences among control and treatment groups were observed. Mating indices ranged from 93% to 100% and fertility indices from 52% to 86%.

TABLE 7: MATING AND FERTILITY INDICES¹

GENERATION: MATING	PYRETHRUM EXTRACT DOSE LEVEL, PPM			
	0	100	1000	3000
F ₀ :				
F _{1a} MATING/ FERTILITY	28/28 (100%) 23/28 (82%)	27/28 (96%) 22/27 (82%)	28/28 (100%) 21/28 (75%)	28/28 (100%) 23/28 (82%)
F _{1b} MATING/ FERTILITY	27/28 (96%) 21/27 (78%)	26/27 (96%) 17/26 (61%)	26/28 (53%) 17/26 (65%)	27/27 (100%) 20/27 (74%)
F ₁ :				
F _{2a} MATING/ FERTILITY	28/28 (100%) 22/28 (79%)	28/28 (100%) 20/28 (71%)	28/28 (100%) 24/28 (86%)	28/28 (100%) 21/28 (75%)
F _{2b} MATING/ FERTILITY	27/27 (100%) 14/27 (52%)	26/28 (93%) 14/26 (54%)	27/28 (96%) 17/27 (63%)	28/28 (100%) 21/28 (75%)

¹ Data compiled from data in Appendix 1 (Individual Experimental Data-Individual Litter Data) of study.

Female fertility index - Proportion of females with evidence of mating that had at least one mating resulting in pregnancy/total females with evidence of mating.

Male fertility index - Proportion of males with evidence of mating that had at least one mating resulting in pregnancy/total males with evidence of mating.

Fertility indices for each sex did not appear to be affected by treatment at any dose tested. Results are shown in Table 8 taken from the study data tables. Male and female indices were comparable for each mating and dose level with a few, random exceptions.

TABLE 8: MALE AND FEMALE FERTILITY INDICES¹

GENERATION	PYRETHRUM DOSE LEVEL				
	0 PPM	100 PPM	1000 PPM	3000 PPM	
	proportion mated w/pregnancy/total mated (percent of total) [*]				
F _{0'} F _{1a} mating	♂	23/28 (82.1)	21/28 (75.0)	20/23 (71.4)	19/28 (67.9)
	♀	23/28 (82.1)	27/28 (78.6)	21/28 (75.0)	23/28 (82.1)
	♂	21/23 (75.0)	16/27 (59.3)	16/28 (57.1)	19/28 (67.9)
	♀	21/28 (75.0)	18/27 (60.7)	17/28 (60.7)	23/28 (82.1)
F _{1'} F _{2a} mating	♂	22/28 (78.6)	16/28 (57.1)	22/28 (78.6)	21/28 (78.6)
	♀	22/28 (78.6)	20/28 (71.4)	24/28 (85.7)	21/28 (78.6)
	♂	13/27 (48.1)	14/28 ^a (50.0)	17/28 (60.7)	20/27 (74.1) ²
	♀	14/27 (51.9)	15/28 (53.6)	18/28 (78.6)	22/28 (78.6)

¹ Data taken from Tables 31, 34, 37 and 40 of study (Summary of Reproductive Data for each mating generation).

² Does not include mating where mated male could not be determined.

There were no significant differences in copulatory intervals among treatment groups. The values for individual animals was quite variable and some males were replaced with a second male after a week if there was no evidence of mating.

Gestation parameters-

The gestation length was comparable in all treatment groups and for each generation in the study. Mean gestation length varied between 21.3 - 22.5 days (standard deviations less than 3% of means).

Liveborn index - Proportion of pregnant females delivered live progeny/total pregnant females.

Liveborn indices are presented below in Table 9. There was a slight reduction of the index in the treated F_{2b} generation;

however, since there was no dose-response and since the reduction is small, this is probably not a treatment-related effect.

TABLE 9: LIVEBORN INDICES¹

GENERATION	PYRETHRUM EXTRACT DOSE LEVEL, PPM			
	0	100	1000	3000
F ₀ :				
F _{1a} MATING	22/23 (96%)	22/22 (100%)	21/21 (100%)	23/23 (100%)
F _{1b} MATING	21/21 (100%)	17/18 (94%)	17/17 (100%)	20/20 (100%)
F ₁ :				
F _{2a} MATING	22/22 (100%)	20/20 (100%)	24/24 (100%)	21/21 (100%)
F _{2b} MATING	14/14 (100%)	13/14 (93%)	17/18 (94%)	21/22 (95%)

¹ Data calculated using data from Appendix A (Individual Experimental Data-- Individual Litter Data) for each mating of study

5. Progeny measurements

Surviving neonates were counted on days PP1, 4, 7, 14 and 21. On day PP4 the pups were sexed and litters were randomly culled to 8 pups, 4 males and 4 females when possible. Litters were weighed on days PP1, 7 and 14. Individual pup weights were obtained and pups sexed again on day PP21.

Neonatal survival No treatment-related differences in lactation survival rates or in mean litter size were observed. Data is presented in Appendix 4 taken from the study tables (Summary of Offspring Viability). The number of dead pups at birth increased somewhat for high dose F_{2b} progeny due to a single female that bore 16 stillborn pups. The study authors did not consider this miscarriage to be treatment-related.

Pup survival indices during lactation were also similar among all treatment groups with the exception of the F_{2b} high dose already mentioned. Data for F_{1b} and F_{2b} generations is presented in Appendix 5 taken directly from the study.

Neonatal body weight Neonatal body weights are provided in Appendix 6 taken from the study tables. Body weights decreased in all high dose pups by at least Day 21 of lactation and appeared to be treatment-related.

F₁ Generation: High dose F_{1a} male pups had statistically significantly lower body weight values than controls by Day 14 and females were lower by Day 21. F_{1b} high dose males and mid and high dose female pups showed significantly reduced

body weights by Day 14.

F₂ Generation: F_{2a} high dose pups all had significantly reduced body weights from Day PPO to 21. Mid dose females at Day 21 also showed significantly reduced body weights and the rest of the mid dose animals showed slightly lower values relative to controls. F_{2b} high dose pups had significantly decreased body weights by Day 14; body weights at earlier times were slightly lower than controls. Low dose pups had weights that were significantly higher than controls.

Sex distribution was not affected appreciably by administration of test compound. Ratios of males:females varied between .79 to 1.3 and variations were not dose-related. The numbers of male and female pups at birth are shown in Appendix 4 (Summary of Offspring Viability). A slight increase (statistically significant) in number of females was noted in mid and high dose F_{2a} pups relative to controls but was probably not treatment-related.

7. Sacrifice and Pathology

Progeny that died prior to scheduled sacrifice (<21 days old) were given a gross external and internal examination.

Progeny that were culled on day 4 were given a gross external and internal examination and fixed in 10% formalin for possible reexamination/histology.

E₀ - Females were sacrificed after weaning of the F_{1b} progeny, at about 36 weeks of age. Males were sacrificed following parturition of the F_{1b} litters. All were given complete gross necropsies. Reproductive tissues, including vagina, uterus, ovaries, testes, epididymis, seminal vesicles and prostate, were fixed for histologic examination. Non-reproductive tissues exhibiting gross abnormalities also were examined histologically.

E_{1a} - All were sacrificed at weaning (21 days of age) and given a gross external and internal examination.

E_{1b} - Females used for parenting (F₁) the F₂ litters were sacrificed (about 36 weeks of age) after the F_{2b} progeny were weaned. Males were sacrificed following the birth of the F_{2b} litters. All were given complete gross examination. Reproductive tissues, including vagina, uterus, ovaries, testes, epididymis, seminal vesicles and prostate, were fixed for histologic examination, and non-reproductive tissues were examined microscopically if gross abnormalities were present. Of those that were not used for breeding, 10 weanling pup/sex/litter were given a gross external and internal examination, the remainder were only given an external

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examination.

F_{2a} - Pups were given an external examination.

F_{2b} - All were sacrificed at weaning (21 days of age) and 10 of each sex from each treatment group were given a gross external and internal examination.

a. Organ weight (Parental) - Testes of males that did not induce pregnancy were weighed. No statistical analysis was performed on these values because there were so few; however, there did not appear to be any treatment effect on testes weight. One low dose F₀ and one mid dose F₁ male had significantly reduced testes weights and testis/body weight ratios.

b. Gross pathology -

Parental - No treatment-related gross lesions were observed. Pathological findings that did not appear to be related to treatment and that were found in both parental generations included renal hydronephrosis and calculi, urinary bladder calculi, thickened ear skin, broken or missing teeth and malocclusion. Four males had small testes: F₀ control, Group 3 and Group 4, and one F₁ Group 3.

Progeny - No treatment-related gross lesions were observed. The most common incidental or spontaneous lesions observed was hydronephrosis of the kidneys in F_{1b} and F_{2b} pups.

c. Microscopic pathology (Parental only) -

No treatment related microscopic lesions were noted in reproductive or nonreproductive organs and tissues. Some of the more common incidental histopathological lesions included: in the male, inflammation of the prostate, testicular atrophy, renal calculi, and hydronephrosis; in the female, hydronephrosis of the kidneys, brown pigment in uterus, and inflammation of the ear skin. The incidence of these more common findings is summarized in Table 10 below.

Several malignancies were identified at necropsy but their incidence was sporadic and did not appear to be related to treatment. A mammary adenocarcinoma was found in a control F₀ male and a lymphocytic lymphoma in a high dose F₁ male. In females, a histiocytic sarcoma of the hemolymphoreticular system was found in an F₀ control, a lymphocytic lymphoma was found in an F₁ control and a fibroadenoma of mammary tissue was found in an F₀ Group 3 animal.

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TABLE 10: MICROSCOPIC FINDINGS, F₀ PARENTAL¹

ORGAN/TISSUE	SEX	MALE				FEMALE			
	GROUP	1	2	3	4	1	2	3	4
REPRODUCTIVE									
F ₀ :									
Prostate gland	(28) ²	(0)	(0)	(28)	-	-	-	-	-
Inflammation, trace to mild	0	3	0	5	-	-	-	-	-
Testis	(28)	(0)	(1)	(28)	-	-	-	-	-
Atrophy, mild to mod.	1	0	1	1	-	-	-	-	-
Calcification, mod.	1	0	1	1	-	-	-	-	-
Uterus	-	-	-	-	(26)	(0)	(0)	(3)	-
Brown pigment	-	-	-	-	4	0	0	1	-
Calcification, mild	-	-	-	-	1	0	0	1	-
F ₁ :									
Prostate gland	(28)	(0)	(0)	(28)	-	-	-	-	-
Inflammation, trace to mild	9	0	0	7	-	-	-	-	-
Testis	(28)	(2)	(1)	(28)	-	-	-	-	-
Atrophy	2	2	0	0	-	-	-	-	-
Uterus	(28)	(1)	(1)	(28)	-	-	-	-	-
Brown pigment	3	0	0	7	-	-	-	-	-
NONREPRODUCTIVE									
F ₀ :									
Kidney	(0)	(0)	(0)	(0)	(2)	(2)	(3)	(2)	-
Hydronephrosis, mild to severe	0	0	0	0	1	2	3	1	-
Inflammation	0	0	0	0	1	2	2	1	-
Skin	(0)	(0)	(0)	(0)	(2)	(2)	(2)	(2)	-
Inflammation, ear	0	0	0	0	2	2	1	1	-
F ₁ :									
Kidney	(3)	(4)	(7)	(0)	(3)	(2)	(4)	(2)	-
Hydronephrosis, trace to moderate	1	4	7	0	3	1	4	2	-
Calculi	0	0	0	1	0	3	0	1	-
Skin	(0)	(0)	(0)	(1)	(0)	(0)	(0)	(1)	-
Inflammation, ear	0	0	0	1	0	0	0	1	-

¹ Data taken from Table 45 (Incidence of Microscopic Observations) of study
² () number animals examined

D. DISCUSSION

The NOEL for parental systemic toxicity is 100 ppm and the LEL is 1000 ppm based on F₁ parental body weight decrease (males). At 3000 ppm male F₁ animals showed significant weight loss and F₁ females slight weight loss. F_{2a} and F_{2b} females also had lowered body weights during lactation (values for F_{2b} females statistically significant). Decreased food consumption was also noted in high dose F₁ males and females and in F₁ females during F₂ lactations.

The NOEL for perinatal reproductive effects is 100 ppm and the LEL is 1000 ppm based on pup body weight decrease. At 3000 ppm, all offspring generations showed significantly reduced body weights during lactation and at birth, in the case of F_{2a} pups.

No reproductive parameters per se (fertility, mating, gestation, lactation) appeared to be affected by administration of pyrethrum extract under the conditions of this study.

This study appears to have been properly conducted and is satisfactory for regulatory purposes. One deficiency noted was that some of the females showing evidence of mating but not bearing young were not specified as gravid or nongravid in the Data Tables (Appendix A, Individual Litter Data, F_{1a}, F_{2a} matings). This was not enough to alter the conclusions of the study and the study is classified as core-guideline.

APPENDIX 1

008639

Table 1. Summary of Body Weight Values (g) - F₀ Females

Week of Study	0 ppm (Control)			100 ppm			1,000 ppm			3,000 ppm		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
0	145	8.9	28	146	9.1	28	142	8.5	28	148	9.0	28
1	170	11.7	28	171	13.3	28	167	8.7	28	171	10.5	28
2	186	12.2	28	189	14.0	28	180	12.2	28	187	13.2	28
3	207	15.9	28	209	16.3	28	202	16.0	28	205	14.9	28
4	217	17.9	28	220	18.6	28	215	18.0	28	215	16.8	28
5	228	17.8	28	234	21.8	28	225	18.5	28	227	17.2	28
6	235	19.7	28	239	21.2	28	233	19.7	28	237	18.2	28
7	246	19.7	28	247	23.5	28	240	22.4	28	245	19.6	28
8	252	21.4	28	255	23.5	28	246	23.4	28	251	20.3	28
9	259	22.1	28	261	24.4	28	250	26.8	28	257	21.9	28
10	260	23.0	28	263	25.0	28	254	27.3	28	260	22.3	28
11	269	23.2	28	271	27.9	28	264	28.7	28	265	24.2	28
12 ^a	275	35.9	9	265	36.1	11	265	29.9	13	275	24.4	13
13 ^a	278	-	1	300	74.2	2	297	13.3	5	321	10.7	3
14 ^a	-	-	-	375	-	1	310	-	1	-	-	-
15 ^a	-	-	-	360	-	1	-	-	-	-	-	-
16 ^a	285	40.2	4	361	-	1	278	33.1	5	253	-	1
17 ^a	-	-	-	-	-	-	-	-	-	-	-	-
18 ^a	294	22.8	15	298	27.1	15	297	20.4	14	287	23.3	14
19 ^a	285	26.2	27	282	28.9	27	276	30.1	26	273	25.1	25
20	297	26.5	28	296	28.5	27	288	29.7	28	279	24.5	27
21	302	25.5	28	305	32.6	27	294	30.4	28	285	24.0	27
22	309	27.1	28	313	36.1	27	301	33.0	28	288	29.0	27
23 ^b	323	30.2	13	329	48.4	10	310	46.1	10	294	29.0	15
24 ^b	358	45.8	4	337	66.1	5	349	27.8	5	298	8.9	3
25 ^b	352	15.9	3	364	66.0	4	392	21.2	2	303	-	1
26 ^b	348	6.4	2	403	52.0	3	376	16.3	2	-	-	-
27 ^b	339	-	1	427	4.2	2	369	14.8	2	-	-	-
28	350	-	1	446	-	1	378	15.6	2	-	-	-
29	354	-	1	421	-	1	381	14.8	2	-	-	-

Values of the treated groups were not significantly different from those of the Control; $p > 0.05$

S.D. - Standard deviation

N - Number of animals used in the calculation

- - Not applicable

^a P_{1a} gestation/lactation periods^b P_{1b} gestation/lactation periods

556-005

APPENDIX 2

008679

TABLE 10. Summary of Gestation Body Weight Values - F1 Females, F2a Mating

Parameters Measured	DAY OF GESTATION	0 PPM (CONTROL)			100 PPM			1000 PPM			3000 PPM	
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.
Body Weight	0	279	23.5	22	302	23.0	20	273	32.4	13	267*	29.8
grams	6	280	22.6	22	323	24.5	20	295	41.1	23	287*	30.5
	15	314	22.4	22	350	24.0	20	326	30.9	23	317	32.0
	20	398	28.8	22	414	27.7	20	395	35.0	23	383	38.3

556-005

S.D. - Standard Deviation *Significantly different from the Control group; p<0.05
N - Number of Animals

TABLE 12. Summary of Gestation Body Weight Values - F1 Females, F2b Mating

Parameters Measured	DAY OF GESTATION	0 PPM (CONTROL)			100 PPM			1000 PPM			3000 PPM	
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.
Body Weight	0	322	33.9	13	331	31.1	14	305	34.5	16	287	33.7
grams	6	345	32.0	13	356	30.2	14	323	34.8	16	325*	36.2
	15	375	27.3	13	383	32.6	14	366	40.7	16	398**	41.3
	20	442	33.5	13	442	38.6	14	428	51.8	16	411	48.3

556-005

S.D. - Standard Deviation *Significantly different from the Control group; p<0.05
N - Number of Animals

TABLE 13. Summary of Lactation Body Weight Values - F1 Females, F2b Mating

Parameters Measured	DAY OF LACTATION	0 PPM (CONTROL)			100 PPM			1000 PPM			3000 PPM	
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.
Body Weight	0	343	32.0	14	367	32.5	14	337	45.3	17	321	38.1
grams	7	355	24.0	14	366	28.9	14	342	39.3	17	326*	34.4
	14	358	28.1	14	371	27.4	14	346	35.9	17	326**	32.8
	21	352	21.1	14	350	22.6	14	332	24.4	17	325**	30.9

556-005

S.D. - Standard Deviation *Significantly different from the Control group; p<0.05 **Significantly different from the control group; p<0.01
N - Number of Animals

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APPENDIX 3

378639

Table 11

Summary of Food Consumption Values - F1 Males

Parameter Measured	Wk UP Alt	0 PPM (LIMITHU)			100 PPM			1000 PPM			2000 PPM		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Food Consumption	5	19.0	2.01	20	19.0	2.06	20	18.1	2.36	20	16.7**	2.70	20
g/animal/day	6	22.8	2.00	20	22.8	1.55	20	21.5*	2.01	20	20.6**	2.83	20
	7	24.4	2.04	20	24.7	2.06	20	23.3	1.80	20	23.0**	2.75	20
	8	27.1	2.15	20	27.2	2.57	20	25.1**	2.18	20	24.4**	2.70	20
	9	27.4	2.60	20	27.3	3.15	27	25.7	2.45	20	25.1**	2.70	20
	10	27.2	2.13	20	27.7	1.71	27	25.7*	2.60	20	25.2**	2.75	20
	11	26.9	2.37	20	27.1	2.23	27	25.5	2.42	20	25.7	2.70	20
	12	27.0	2.79	20	27.3	2.42	27	26.1	2.72	20	25.8	2.70	20
	13	27.2	3.21	20	27.8	2.10	27	25.7	2.72	20	25.9	2.70	20
	14	26.9	2.45	20	27.1	2.07	27	25.1*	2.62	20	25.7	2.72	20
	15	26.0	2.49	20	26.3	4.03	27	24.0*	3.90	20	25.3	2.72	20
	16	28.4	4.76	20	27.8	3.16	27	26.3	2.91	27	27.4	2.70	20
	17	26.5	3.01	27	28.7	6.19	27	26.6	3.65	24	26.1	2.70	25
	18	27.2	2.56	26	26.8	2.94	22	27.6	3.81	24	26.6	2.70	23
	19 ^a												
	20 ^b												
	21				29.0	0.81	2	26.0	2.11	3	24.1	2.70	2
	22	27.8	1.72	2	29.2	2.29	5	25.1	1.15	3	25.5	2.75	10
	23	27.1	3.23	20	27.7	2.95	27	25.8	3.23	26	24.6**	2.70	26
	24	24.7	6.54	20	27.5	3.67	27	25.2	2.71	27	27.6	2.70	27
	25	26.4	3.29	20	28.0	3.05	27	25.3	2.81	27	25.8	2.70	20
	26	26.2	2.49	20	27.3	2.81	25	25.0	2.71	27	25.3	2.70	27
	27	26.7	2.63	20	28.1	2.80	27	25.8	3.45	27	24.6*	2.70	20
	28	26.6	3.67	20	27.4	3.06	27	24.7	2.23	24	25.5	2.70	26
	29	25.8	3.27	26	26.7	2.83	21	25.1	2.95	24	24.2	2.70	22
	30 ^a												
	31 ^a												
	32				30.7	1.21	2	25.8	0.59	3	24.2	2.70	2
	33	26.3	2.61	8	29.0	2.25	7	23.4	5.85	8	25.0	2.70	11
	34	25.5	2.92	27	27.3*	2.00	26	24.4	5.37	26	25.5	2.70	25
	35	27.4	3.98	20	26.7	3.73	26	25.4*	2.40	27	25.5*	2.70	25
	36	26.9	2.96	20	27.6	3.05	26	25.6	3.51	27	26.4	2.70	25
	37	27.0	4.39	20	27.4	3.67	25	25.6	3.05	22	26.1	2.70	22
	38	26.8	3.18	20	27.0	2.80	18	26.3	3.63	18	26.9	2.70	16

550-005

S.D. - Standard Deviation
N - Number of Animals

*Significantly different from the control group; p<0.05 **Significantly different from the con
^aIndividual food consumption not measured during the mating periods

APPENDIX 4

TABLE 32. Summary of Offspring Viability - F_{1a} Pups

Dosage Level (ppm)	Total Litter Size		No. Dead Pups at Lactation Day 0				No. Live Pups at Lactation Day 0			
	Mean	S.D.	Male		Female		Male		Female	
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
0 (Control):	13.0	2.90	0.2	0.65	0.0	0.00	6.0	2.23	6.9	2.23
100:	12.5	1.71	0.2	0.39	0.2	0.69	6.5	2.20	5.7	2.17
1,000:	13.0	1.75	0.1	0.36	0.0	0.00	7.3	1.65	5.6	1.83
3,000:	13.3	2.36	0.2	0.65	0.1	0.42	6.3	1.92	6.7	2.12

TABLE 33. Summary of Offspring Viability - F_{1b} Pups

Dosage Level (ppm)	Total Litter Size		No. Dead Pups at Lactation Day 0				No. Live Pups at Lactation Day 0			
	Mean	S.D.	Male		Female		Male		Female	
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
0 (Control):	13.0	3.29	0.0	0.22	0.1	0.36	5.9	2.55	6.9	2.49
100:	13.4	2.21	0.2	0.39	0.2	0.44	6.2	2.11	6.8	1.82
1,000:	13.5	3.12	0.4	0.61	0.2	0.53	6.9	2.59	6.1	2.68
3,000:	12.4	4.03	0.3	0.57	0.1	0.31	5.8	2.78	6.2	2.86

TABLE 41. Summary of Offspring Viability - F_{2b} Pups

Dosage Level (ppm)	Total Litter Size		No. Dead Pups at Lactation Day 0				No. Live Pups at Lactation Day 0			
	Mean	S.D.	Male		Female		Male		Female	
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
0 ppm (Control):	14.3	2.46	0.1	0.36	0.2	0.43	6.8	2.08	7.1	2.31
100 ppm	11.4	3.77	0.1	0.27	0.1	0.27	6.1	2.21	5.1	2.36
1,000 ppm	12.6	4.90	0.2	0.56	0.0	0.00	7.0	3.32	5.4	2.45
3,000 ppm	13.3	3.93	0.4	1.54	0.5	1.99	6.3	2.94	6.0	2.56

TABLE 40. Summary of Offspring Viability - F_{2a} Pups

Dosage Level (ppm)	Total Litter Size		No. Dead Pups at Lactation Day 0				No. Live Pups at Lactation Day 0			
	Mean	S.D.	Male		Female		Male		Female	
			Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
0 ppm (Control):	12.9	3.39	0.2	0.39	0.3	0.57	6.8	2.20	5.6	1.74
100 ppm	13.8	2.86	0.0	0.00	0.2	0.37	6.7	2.01	7.0	2.16
1,000 ppm	14.5	2.40	0.1	0.34	0.1	0.45	6.9	1.87	7.4*	2.26
3,000 ppm	14.0	2.11	0.0	0.22	0.1	0.30	6.1	2.10	7.7**	2.08

S.D. - Standard deviation

556-005

No. - Number

*Significantly different from the Control group; p<0.05

**Significantly different from the Control group; p<0.01

APPENDIX 5

208639

TABLE 39. Cont.

Summary of Offspring Viability - F_{1b} Pups

Dosage Level (ppm)	Pup Survival Index (Lactation Days)											
	0		4		7		14		21		28	
	No. Live Pups at Day 0	%	No. Live Pups at Day 4 BR	%	No. Live Pups at Day 7	%	No. Live Pups at Day 14	%	No. Live Pups at Day 21	%	No. Live Pups at Day 28	
0 (Control):	269/275	98.5	265/269	98.5	162/162	100	162/162	100	162/162	100	162/162	100
100:	221/228	96.9	218/221	98.6	154/155	99.3	134/134	100	134/134	100	132/134	98.5
1,000:	221/230	96.1	215/221	97.3	131/132	99.2	131/131	100	131/131	100	131/131	100
3,000:	240/248	96.8	234/240	97.5	149/149	100	149/149	100	148/149	99.3	148/148	100

556-005

BR - Before reduction
AR - After reduction
S.D. - Standard deviation
No. - Number

TABLE 41. Cont.

Summary of Offspring Viability - F_{2b} Pups

Dosage Level (ppm)	Pup Survival Index (Lactation Days)									
	0		4		7		14		21	
	No. Live Pups at Day 0	%	No. Live Pups at Day 4 BR	%	No. Live Pups at Day 7	%	No. Live Pups at Day 14	%	No. Live Pups at Day 21	%
0 ppm (Control):	195/200	97.5	188/195	96.4	110/110	100	110/110	100	110/110	100
100 ppm	157/159	98.7	155/157	98.7	104/105	99.0	103/104	99.0	103/103	100
1,000 ppm	211/215	98.1	208/211	98.6	122/122	100	122/122	100	121/122	99.2
3,000 ppm	260/280	92.9	254/260	97.7	151/151	100	151/151	100	151/151	100

BR - Before reduction
AR - After reduction
S.D. - Standard deviation
No. - Number

APPENDIX 6

008639

TABLE 55. Summary of Offspring Growth - F₁ Pups

Dosage Level (ppm)	Group Mean Body Weight (grams) of Live Pups during Lactation (Lactation Days)																			
	0				1 BR				1				13							
	Male		Female		Male		Female		Male		Female		Male		Female					
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.				
0 (Control):	6.2	0.63	5.9	0.61	3.9	1.14	9.4	1.30	16.2	1.56	15.6	1.73	31.8	2.62	30.9	2.97	49.0	4.70	48.0	4.29
100:	6.5	0.59	5.9	0.66	10.6	1.00	9.9	0.80	17.2	1.32	16.1	1.09	32.7	4.26	31.1	3.59	51.6	7.53	48.7	5.82
1,000:	6.3	0.47	5.9	0.47	10.1	0.87	9.7	0.99	16.5	1.31	15.9	1.52	31.5	2.76	30.6	3.04	48.3	5.28	49.9	5.08
3,000:	5.8*	0.77	5.5	0.82	9.5	1.37	9.1	1.59	15.7	1.72	15.2	1.84	29.8	2.69	28.4*	3.54	42.8**	6.27	41.8**	6.82
			13		15				47		47		7		12		1		1	

S.D. - Standard deviation
BR - Before reduction

*Significantly different from Control group; p<0.05
**Significantly different from Control group; p<0.01

TABLE 56. Summary of Offspring Growth - F₁ Pups

Dosage Level (ppm)	Group Mean Body Weight (grams) of Live Pups During Lactation (Lactation Days)											
	0				4 BR				7			
	Male		Female		Male		Female		Male		Female	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
0 (Control):	6.5	0.74	6.1	0.66	10.1	1.21	9.6	1.37	16.5	1.63	16.1	1.85
100:	6.4	0.62	5.9	0.53	10.3	1.23	9.9	0.94	16.8	1.76	16.3	1.57
1,000:	6.2	0.83	5.7	0.81	10.0	1.73	9.6	1.44	16.3	2.29	15.3	1.86
3,000:	6.2	0.70	6.1	0.93	9.8	1.36	9.5	1.43	15.7	1.88	15.3	2.54

Values of the treated groups were not significantly different from those of the Control group; p>0.05

S.D. - Standard deviation
BR - Before reduction

TABLE 56. Cont. Summary of Offspring Growth - F₁ Pups

Dosage Level (ppm)	Group Mean Body Weight (grams) of Live Pups During Lactation (Lactation Days/Days of Age)											
	14				21				28			
	Male		Female		Male		Female		Male		Female	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
0 (Control):	33.1	2.9	32.1	2.72	52.9	5.86	50.7	5.36	93.0	8.39	86.7	7.05
100:	33.8	3.5	32.9	2.89	53.6	4.80	51.7	4.22	92.0	8.94	86.0	7.41
1,000:	32.0	2.9	30.3*	2.33	51.0	4.24	47.2*	3.51	89.0	6.22	79.9*	5.89
3,000:	30.2*	3.4	29.3*	5.03	46.1**	7.22	45.1*	8.07	82.4**	11.53	77.2*	11.89

S.D. - Standard deviation
BR - Before reduction

*Significantly different from Control group; p<0.05
**Significantly different from Control group; p<0.01

308639

Summary of Offspring Growth - F_{2b} Pups

Group Mean Body Weight (grams) of Live Offspring During Lactation (Lactation Days/Day of Age)

Dosage level	0		4BR		7		14		21											
	Male Mean	Female S.D.																		
0 ppm (Control):	6.5	0.70	6.1	0.73	10.3	1.54	9.7	2.03	16.8	2.14	16.0	1.96	32.8	5.37	31.6	5.18	54.0	4.92	52.8	3.89
100 ppm	6.6	0.67	6.1	0.66	10.7	1.64	10.2	1.68	17.4	2.05	16.8	2.25	34.5	5.21	33.2	3.41	56.4	5.09	34.1	5.08
1,000 ppm	6.1*	0.32	5.8	0.44	9.6	1.16	9.1	1.24	15.8	1.55	15.1	1.70	31.1	2.65	29.9	2.77	50.8	4.52	48.4*	4.56
3,000 ppm	5.7**	0.49	5.2**	0.37	9.0**	1.25	8.3**	1.03	14.4**	1.91	13.6**	1.74	27.9**	3.30	25.6**	2.79	43.7**	4.77	41.1**	3.90

556-005 Values of the treated groups were not significantly different from those of the Control; p>0.05
 BR - Before reduction
 AR - After reduction
 S.D. - Standard deviation
 *Significantly different from Control group; p<0.05
 **Significantly different from Control group; p<0.01

TABLE 42. Summary of Offspring Growth - F_{2b} Pups

Group Mean Body Weight (grams) of Live Offspring During Lactation (Lactation Days/Day of Age)

Dosage level	0		4BR		7		14		21											
	Male Mean	Female S.D.																		
0 ppm (Control):	6.3	0.47	5.8	0.30	9.7	1.05	9.0	1.03	15.9	1.84	15.0	1.70	33.1	2.48	31.5	2.40	52.2	4.80	49.7	3.34
100 ppm	7.1**	0.70	6.6**	0.60	11.5*	1.85	10.9*	1.97	18.5**	2.22	17.4**	2.75	36.3*	3.58	35.0*	4.04	57.5*	5.05	34.9*	3.95
1,000 ppm	6.2	0.64	5.8	0.77	9.9	1.74	9.4	1.77	15.9	2.44	15.3	2.28	31.1	5.11	30.6	5.27	48.9	9.95	47.7	3.16
3,000 ppm	6.0	0.77	5.5	0.77	9.3	1.60	8.5	1.64	15.0	1.64	14.2	1.53	28.5**	2.97	26.8**	2.55	43.4**	4.76	41.1**	4.50

556-005 Values of the treated groups were not significantly different from those of the Control; p>0.05
 BR - Before reduction
 AR - After reduction
 S.D. - Standard deviation
 *Significantly different from Control group; p<0.05
 **Significantly different from Control group; p<0.01