2-13-92

[83-4. Cypermethrin-S (1991)]

Reviewed by: John Doherty, PhD John Doherty 2/13/92 009347
Section IV, Toxicology Branch I (H7509C)
Secondary reviewer: Marion Copley, DVM
Section IV, Toxicology Branch I (H7509C) Marion Copley 2/13/92

DATA EVALUATION REPORT

STUDY TYPE: 83-4. Multi generation reproduction study - rats.

MRID NO.: 419682-04 (3 volumes) TOX CHEM. NO.: 271DE
PC No.: 129064

TEST MATERIAL: FMC 56701 technical from lot number E-6539-78. Stated as being 89.6% pure.

STUDY NUMBER(S): Laboratory No.: 106-007, Sponsors No.: A89-2959.

SPONSOR: FMC Corporation.

TESTING FACILITY: Argus Research Laboratories, Inc., Horsham, Pa.

TITLE OF REPORT: "Multigeneration study with FMC 56701 Technical Administered oral via Diet to Crl:CD^{R}BR Rats"

AUTHOR(S): Alan M. Hoberman, Ph.D., D.A.B.T.

REPORT ISSUED: February 11, 1991. Study dates of in life phase: October 24, 1989 (initiation of dosing) to August 24, 1990 (final sacrifices).

CONCLUSIONS:

NOEL/LEL = 100/375 ppm. At 375 ppm: decreased parental weight most noticeable during lactation; increased relative brain weight in males and females; threshold for clinical signs; decreased pup weight gain during lactation. At 750 ppm: pup and parental mortality and more definite clinical signs.

Dose levels tested: 0, 7.5, 25, 100 and 375 and 750 (one generation only) ppm. Approximately 0, 0.5, 1.8, 7, 27 and 45 mg/kg/day.)

Classification: CORE-GUIDELINE. The study satisfies the requirement for an 83-4 multi generation reproduction study.

Quality Assurance Statement: Signed by Luann Seaman, February 2, 1991.
Good Laboratory Practice Statement: Provided.

REVIEW

Experimental Constants.

TEST MATERIAL. FMC 56701 Technical from Lot E-6539-78. Described as a dark brown viscous fluid. Stated as being 89.6% pure[1].

TEST ANIMALS. Charles River Crl:CD^{R}(SD)BR rats were obtained from the Charles River Laboratories, Inc. Portage, Michigan. The rats were reported as being 44 days of age on receipt and the males weighted 138 to 188 gms and the females weighted 104 to 141 gms. The rats were approximately 8 weeks old at initiation of dosing after an acclimation period.

Basic Study Design.

Six groups of 30 male and 30 female rats were selected and dosed with either 0 (control), 7.5, 25, 100, 375 or 750 ppm[1] of cypermethrin-S to be the P1 parental group.

The rats were assigned to dose groups based on physical appearance and body weight assisted by a computer generated (weight ordered) randomization. The P1 parental group was dosed for 83 days and then mated 1:1 within each group. The time of copulation was assessed by the presence of spermatozoa in smears of the vaginal contents or presence of a copulatory plug. The dams were allowed to deliver and day of delivery was assigned day 1 of lactation/postpartum. On day 4 postpartum, the F1 litters were culled to four males and four females when possible. The litters remained with the dams for 28 days and then were placed on the diets containing cypermethrin-S.

Selection of the F1 pups to be the P2 parental group was started on postpartum day 21 and was done by the assistance of a table of random units. The P2 group consisted of 40 male and 40 female rats for the control, 7.5, 25, 100 and 375 ppm dose groups. The 750 ppm dose group consisted of 27 males and 30 females. Because there were not enough male rats in the high dose group it was eventually discontinued before mating. After 95 days on the test diets, 30 rats were mated 1:1 to produce the F2 generation.

---

[1]The test material was 89.6% pure cypermethrin isomer and the diets were not adjusted for 100% purity. Therefore the dosages are in terms of ppm of mg/kg/day of technical FMC 56701, not as cypermethrin isomers.

Thus, there are 4 blocks of data as follows:

P1 parental group
F1 pup group - which becomes the P2 group
P2 parental group
F2 pup group.

Stability, Homogeneity and Concentration in the Diets.

The test diets were prepared by first mixing the test material with Wesson Oil and combining with Certified Purina Rodent Chow #5002M. Test diets were reportedly prepared every one or two weeks and stored at room temperature. The description and results of the analytical tests for stability, homogeneity and concentration were presented in Appendix H of the study report. The analytical work was done at the Lancaster Laboratories, Lancaster, Pa.

1. **Stability.** The results of a single experiment are reported in which each of the dose levels containing cypermethrin-S was sampled in triplicate on days 0, 14, 21, 28 and 35. The data presented supported the conclusion that the compound was stable at room temperature (it was not specifically stated that the samples were stored at room temperature for this analytical study but this is assumed since the prepared diets were stored at room temperature) over this period and that the each test diet preparation deviated over time as follows: 7.5 ppm 4%, 25 and 100 ppm 2%, 375 ppm 2% and 750 ppm 0%.

2. **Homogeneity.** Samples from the top, middle and bottom of the sample mixture were assessed in triplicate for the target concentration of cypermethrin-S. Appendix H summary maintains that the Relative Standard Deviation (RSD) for the sampling was 10%, 3%, 3%, 2% and 3% for the 7.5, 25, 100, 375 and 750 ppm dose levels. Meaning that there was good homogeneity for the sample preparations.

Inspection of Table III of this Appendix indicated that the achieved concentrations were 30-40% for 7.5 and 25 ppm diets, 20 - 26% for the 100 ppm diet, 14 - 18% for the 375 ppm diet and 6-12% for the 750 ppm diet. Meaning that at lower dose levels for these preparations of the diet the achieved concentration was much below the target.

3. **Concentration.** The results of the analysis of some 23 diet preparations were presented. In general, survey of the means for the date indicated that the actual concentrations were from -16 to +11% of the target doses. The low dose group had the largest variations being -13 to +11% of the target 7.5 ppm. For one interval at 12/27/89, the control and 7.5 ppm samples were apparently mixed since there was no cypermethrin-S in the spiked diet but it was present in the controls. A retest at a later time found that the reverse was true. In conclusion, the data

3

indicate that the target concentrations were achieved with reasonable success.

4. **Achieved dosage.** Food consumption and body weight data were compared to determine the dose level achieved in mg/kg/day. Table 1 illustrates the achieved dosage.

Table 1. Achieved dosage of cypermethrin-S.

Cypermethrin-S Mg/Kg/Day/Standard Deviation

Dose Level (ppm)		Premating[1] P1	Premating[1] P2	Gestation[2] P1	Gestation[2] P2	Lactation[3] P1	Lactation[3] P2
7.5	M	0.4/0.0	0.5/0.0				
	F	0.6/0.0	0.6/0.0	0.5/0.0	0.5/0.1	0.9/0.1	0.9/0.1
25	M	1.5/0.1	1.8/0.1				
	F	1.9/0.1	2.1/0.1	1.6/0.1	1.7/0.1	2.9/0.5	2.9/0.4
100	M	5.9/0.2	7.2/0.3				
	F	7.4/0.5	8.6/0.7	6.4/0.4	6.8/0.7	11.8/1.7	12.1/1.8
375	M	22.1/1.0	27.8/1.4				
	F	27.6/1.2	32.9/1.9	24.2/1.8	25.3/2.0	40.7/6.0	45.7/5.5
750	M	43.4/1.5	--				
	F	53.0/2.2	--	47.8/2.2	--	67.5/6.5	--

1. Data are for days 1-83 for P1 and 1-85 for P2.
2. Data are for days 0-20.
3. Data are for days 1-14. [Note after day 14, the pups begin to consume treated feed and the amount consumed by the dams is obscured].

4

Statistics. The following statistical tests were used.

Test	Parameters Assessed
Bartlett's Test for Homogeneity of Variance and Analysis of Variance	Body weight and gain (parental and maternal) Mean litter weights Food consumption Organ weight (absolute and relative) Sex ratio Mortality and survival
Dunnett's Test	If ANOVA was significant this test was used to identify the statistical significance of the individual groups.
Bartlett's test	If ANOVA not appropriate.
Kruskal-Wallis Test	If Bartlett's test significant and 75% or less ties were present.
Fisher's Exact Test	If Bartlett's test significant and 75% or more ties were present.
Dunn's Method of Multiple comparisons	When K-W Test was significant this test was used to identify the significance of the individual groups.
Variance test for homogeniety of the Binomial Distribution	Parental, maternal and pup incidence data.

Results

A. Parental Generations (P1 and P2).

1. Mortality. P1 Group. Two compound related deaths were present among the females in the high dose (750 ppm) dose group. These rats died during the lactation period (on days 18 or 21) when they were consuming the highest level of diet and test material. One control male died of apparent urinary tract pathology.

P2 Group. [The 750 ppm dose group is no longer included because of deaths of the pups]. No compound related deaths were noted in either males or females for the dose groups 0, 7.5, 25, 100 or 375 ppm.

2. Clinical Signs. P1 Group. Three of the males dosed with 750 ppm were reported as having soft/liquid stools. One or both of the two female rats in the high dose group which died were reported as displaying signs of emaciation, ataxia and

hypersensitivity to sound as well as chromodacryorrhea or chromorrhinorrhea during the period preceding death.

P2 Group. [Review limited to comments on animals in the groups dosed with 0, 7.5, 25, 100 and 375 ppm and the postweaning period.]

One male (8 incidents) and female (6 incidents) in the high (375 ppm) dose group were reported to have "hypersensitivity to sound" out of >5000 possible incidents. Since this symptom is consistent with type II pyrethroid toxicity and it was not observed in the lower dose groups, the 375 ppm dose group is considered to be near the threshold for this effect. Both males (548 incidents for 17 rats) and females (118 incidents for 5 rats) were reported as having "lesion c", a lesion about the region of the head whereas[2] all other groups had < 23 (females) or 22 (males) of this condition. Other conditions in the groups dosed with 375 ppm that appeared to be compound related were alopecia in females during premating.

3. Body Weight and Gain and Food Consumption.

Males. P1 Group. Over the period of days 1 - 83 the control, 7.5, 25, 100, 375 and 750 ppm dose groups gained 245.2, 247.4, 253.4, 249.6, 246.6 and 180.8 (-26.3% less than controls) gms respectively. Body weight gain for the P1 high dose (750 ppm) group males was significantly affected as early as day 8 of dosing. The other groups were considered equivalent to the control.

P2 Group. The high dose group (now 375 ppm) was 11.8% lower in weight at weaning (79.4 $\pm$ 10.0 gms, $p < 0.01$) than the control (90.0 $\pm$ 9.0 gms). The weight gain, however was only slightly (-5.1%) decreased from day 1 (postweaning) to day 106 since the rats gained 471.3, 459.5, 470.3, 465.6 and 447.2 gms for the control, 7.5, 25, 100 and 375 ppm dose groups respectively. An affect on weight gain in this high dose group is considered by TB-I to be obscured by the initial lower body weights of the pups after weaning.

Females. Table 2 illustrates the effects on body weight gain during premating, lactation and gestation for both the P1 and P2 female groups.

---

[2]This lesion was not fully described but is considered to be a superficial condition of the skin of less than 2 cm in diameter.

6

Table 2. Body weight gain (gm) during premating, gestation and lactation.

		Premating[1,3]	Gestation	Lactation[2]
0	P1	94.3	92.9	316.8/21
	P2	210.5	107.1	337.4/30
7.5	P1	94.3	108.1	311.6/22
	P2	209.8	107.2	338.8/26
25	P1	90.2	103.2	313.2/13
	P2	205.4	108.5	333.3/31
100	P1	89.7 (-4.9%)	102.3	305.3/20
	P2	212.3 (+0.9%)	111.8	337.7/25
375	P1	85.3 (-9.5%)	101.3	287.4/27** (-9.3%)
	P2	200.9 (-4.6%)	109.5	308.2/23** (-8.7%)
750	P1	62.1** (-34.1%)	94.5*	232.4/26**(-26.6%)
	P2	--	--	--

* $p < 0.05$, ** $p < 0.01$, study report statistics for body weight when mean weight of test group is compared with mean weight of control. Note: Statistics are not on weight gain.
1. Data are the difference between the mean value at start of interval and mean value at end of interval for the premating and gestation periods.
2. Data are mean weight/standard deviation for the day 16 during lactation. The number in () is the percent difference between the control and dose group.
3. For premating the P1 rats were about 175 gms at day 1 but the P2 rats were 72 to 81 gms (just after weaning). The standard deviations were < 10% of the mean for the P1 rats and but they were occasionally > 10% for the P2 rats.

Premating. Table 2 shows a pronounced effect on weight gain (-34.1%) during premating is noted for the 750 ppm P1 group. There were no statistical differences in body weight at any interval in the groups dosed with 375 ppm or lower for weight gain during premating. Although nearly a 10% decrease in weight gain is evident in the 375 ppm dose group for the P1 generation, this is reduced to only a 5% decrease in the P2 generation. The P2 generation rats were smaller in weight for the 375 ppm group (mean 72.8 $\pm$ 9.3 gms, -10.1%, $p < 0.01$) than the controls (81.0 $\pm$ 9.4 gms) and remained statistically significant for the first 7

weeks. The study report, however, maintains that the 375 ppm dose group was an effect level for weight effects in females but not males during premating. This is consistent with the more severe (-34%) decrease observed at 750 ppm for the P1 generation.

Gestation. The study report maintains that there was no effect on body weight or weight gain for either P1 or P2 parental groups during gestation.

Lactation. The group dosed with 375 ppm had a slight but statistical significantly decreased body weight gain at day 16 as indicated in Table 2 above and other days (7-21 for P1 and 4-21 for P2) during lactation. This is also consistent with the more severe (-26%) decrease observed at 750 ppm for the P1 generation.

Food Consumption. P1 Group: Consistent with the body weight decrease, there was a corresponding decrease in food consumption in male and female groups dosed with 750 ppm. There was a transient decrease in food consumption for days 1-8 for males (-8%, $p < 0.05$) and females (-12%, $p < 0.01$) in the groups dosed with 375 ppm. Other occasional decreases in food consumption were not considered toxicologically significant.

CONCLUSION (body weight, gain and food consumption): NOEL/LEL 100/375 ppm). The most significant effect at 375 ppm is in females during lactation.

4. Reproductive Performance/Mating Behavior. The study report maintains that there were no adverse effects on the mating behavior of either males or females with regard to mating performance, fertility, days in cohabitation, number of mated rats, number of pregnant rats or males showing copulation for either the P1 or P2 groups. Tabulated data support this conclusion. The following discussed the individual performance/fertility endpoints.

Males (there were 29 to 30 males per dose group).

-Days in cohabitation. P1 Group: The control was 3.0 $\pm$ 2.5, the high dose was 3.0 $\pm$ 1.2 days. P2 Group: The control and high dose group were 2.5 $\pm$ 1.5. The other groups were similar.

-Mating Index. P1 Group: Ranged from 89.6 in the control to 100% in the 25, 100 and 375 ppm groups, the high dose was 96.7%. P2 Group: Ranged from 86.7 in the control to 100% with the high dose being 93.3%

-Fertility Index. P1 Group: Ranged from 84.6 in the control to 96.7% and the high dose was 89.6%. P2 Group: Ranged from 66.7% in the 7.5 ppm dose group to 82.1 in the high dose

8

group with control being 76.9%.

Females (there were 30 females per dose group).

-Days in cohabitation. P1 Group: The control group was 4.1 ± 4.4 days and the high dose was 3.4 ± 2.6 days. P2 Group: The control was 4.5 ± 5.3 days and the high dose group was 3.0 ± 2.8 days. The other groups were less than the control.

-Mating Index. P1 Group: All groups were 100% except for the control which was 96.7%. Ranged from 96.7% for the three highest dose groups to 100% for the control and low dose group.

-Fertility Index. Ranged from 86.2% in the control to 96.7% and the high dose group was 90.0%. Ranged from 66.7% in the low dose group to 82.8% in the high dose group and the control was 80.0%.

4. Organ Weights. No organ weight data were presented for the P1 group for either sex.

Males. For the P2 Group, data for the terminal weight and ratios (to body and brain) were presented for the left and right epididymis and testis, prostate, seminal vesicle (with and without fluid), pituitary and brain.

Females. For the P2 Group, data were presented for the terminal weight and ratios for the pituitary, brain, ovary (left and right) and uterus. The means were based on 39 to 40 animals for each sex.

Brain. The relative brain weight for the males (+7.9%) and females (+7.8%) in the 375 ppm dose group were elevated ($p < 0.01$ for both sexes). Relative brain weights were very close to the control value for all other dose groups.

CONCLUSION (organ weights): NOEL/LEL = 100/375 ppm. Increase in brain weight in both sexes.

[Note: The increase in relative brain weight cannot be dismissed easily as being related to a change in body weight because for other than during lactation period in females there was very little evidence for a weight effect in adults. The larger brain might possibly result from the smaller body weight at birth and during lactation.]

B. Gestation and Pup Data (F1 and F2)

1. Gestation and Birth Data.

The study report asserts that there were no effects on natural delivery of the pups in either generation. The following discusses the parameters involved in gestation and delivery.

-Gestation Length. F1 Group: The range was from 22.8 ± 0.6 to 23.0 ± 0.8 days. F2 Group: The range was from 23.0 ± 0.2 to 23.2 ± 0.6 and no effect of the test material was evident in either group.

-Gestation Index. (Number of pregnant vs. number delivering a litter). There were only three groups in the combined F1 and F2 groups which did not have 100% index. These were the control for F1 Group (1 rat did not deliver), the 7.5 ppm F2 group (2 rats did not deliver) and the high (375 ppm) F2 group (one rat did not deliver). These data are not considered by TB-I to indicate an effect of the test material.

-Delivered litters. F1 Group: Ranged from 24 (control group) to 29 and the high dose group had 27. F2 Group: Ranged from 18 (7.5 ppm group) to 24 in the control group and the high dose group had 23.

-Number of pups live pups born. F1 Group: Ranged from 289 in the control group to 353 and the high dose group (750 ppm) had 332. F2 Group: Ranged from 222 in the 7.5 ppm dose group to 302 in the control and the high dose group had 298.

-Number of Stillborns. F1 Group: There were 4 in the control and the high dose group (750 ppm) had 0. F2 Group: Ranged from 1 (in the 100 ppm dose group) to 7 (in the 7.5 ppm dose group) and the control had 5 and the high (375 ppm) dose group had 3.

-Sex Ratio. The percent males for F1 Group range was from 47.8 ± 15.4 to 52.7 ± 15.4 (control group) and the high dose group was 52.4 ± 11.9. For the F2 Group the range was 47.0 ± 15.1 for the 25 ppm dose group to 55.3 ± 13.2 for the 7.5 ppm dose group and the high dose group was 49.4 ± 16.9. Thus there was no effect on sex ratio.

2. Viability and Lactation Indexes. There was poor survival in the high dose group (750 ppm) for the F1 group especially during lactation. The viability (survival to day 4) and lactation (survival from day 4 to day 21 or day 28) are illustrated in Table 3.

Table 3. Viability and Lactation Indices.

Dose Group (ppm)	Viability Index (%) F1	Viability Index (%) F2	Lactation Index (%) F1	Lactation Index (%) F2
Control	99.3	97.6	100.0	99.5
7.5	97.4** (9)	99.1	100.0	100.0
25	99.4	99.2	99.5	100.0
100	98.6	98.2	100.0	98.9
375	100.0	97.5	99.5	99.4
750	97.0** (10)	--	30.2** (132)	--

** $p < 0.01$ study report statistics. The number in () is the number of animals dying.

Table 3 shows that the group dosed with 750 ppm has an increase in deaths but the lower dose groups are not affected. The viability index for the low dose group was statistically significant but since no dose response was evident, TB-I does not consider the finding to be related to the test material. There is thus no definite effect demonstrated on the viability index, but the lactation index is clearly affected at 750 ppm.

3. Pup Weight gain During Lactation. The study report maintains that the pups in the 375 (F1 and F2 Groups) and 750 (F1 Group only) ppm animals had decreased weight gain. Table 4 illustrates these data.

Table 4. Pup weight gain during lactation.

Dose Level (ppm)	F1[1] Day 1 - Day 21	F2 Day 1 - Day 21
Control	6.1/0.7 - 47.1/4.7 = 41.0	6.2/0.8 - 50.4/4.4 = 44.2
7.5	6.1/0.6 - 46.1/3.9 = 40.0	6.2/0.5 - 50.3/3.6 = 44.1
25	6.1/0.6 - 46.2/4.5 = 40.1	6.2/0.6 - 49.7/5.4 = 43.5
100	6.1/0.5 - 47.4/3.3 = 41.3	6.3/0.4 - 50.2/3.6 = 43.9
375	6.0/0.6 - 41.5/5.1 = 35.5** (-13.4%)	6.1/0.6 - 45.4/5.8 = 39.3** (11.1%)
750	5.8/0.5 - 20.4/4.7 = 14.6** (-64.4%)	No data

** $p < 0.01$ study report statistics for comparison of group mean weight with control group.
1. Data are in grams and are the mean weight of the pups at day indicated/standard deviation of the mean.

Statistical differences for weight gain for the 750 ppm dose group were evident as early as day 4. They were evident for the 375 ppm diose group as early as day 7 in the F1 Group and day 14 for the F2 Group.

4. Deaths among pups. In the F1 high dose group, 132 pups out of 332 pups died during lactation. After weaning additional pups died such that the experiment at this dose level had to be discontinued. Compound related deaths were not apparent in the other groups.

5. Symptoms in pups. Symptoms in the pups were reported in the high dose (750 ppm) F1 group only and these included pale appearance, cold to touch, not nursing, weak and/or dehydrated appearance.

C. **Pathology (P1 and F1)** [Note: The histopathology report is in Appendix L of the study report and was the responsibility of W. Ray Brown, D.V.M., Ph.D.].

1. Histopathology was limited to animals in the control and high dose (750 ppm) for the P1 group and including selected animals with gross lesions in the other dose groups. The pathology report indicated that the following organs were examined.

12

For males:
-coagulating gland
-epididymis
-prostate
-seminal vesicle
-testis
-preputial gland*

For females:
-cervix
-ovaries
-uterus
-vagina
-mammary gland

For Both:
-pituitary -urinary bladder* -stomach* -lungs*
-kidney* -ureter* -liver*

*These organs were only occasionally examined. The other organs were examined for all available animals in the P1 Group (generally 30 of each sex) and F1 Group (generally 40 of each sex).

No definite compound related lesions were noted for the animals dosed with 375 ppm and below. There were noted three incidents of atrophy of the testis in the F1 group high dose group (375 ppm) vs. only 1 incident in the control. This is not considered a sufficient response to determine that the effect was a result of cypermethrin-S dosing.

The high dose P1 group (750 ppm) had more incidents (5) of "purulent exudate" from the vagina and acute vaginitis (4) than the control (1 or 0). This may be related to the test material inducing stress on the animal.

2. Organ weight. Organ weight data were presented for the P2 group males and females. The brian, epididymis (left and right), testis (left and right), ovary (left and right), prostate, seminal vesicles (with and without fluid), pituitary and uterus were reported as being weighed. Table 5 below shows that brain weight relative to body weight was increased.

Table 5. Relative brain weight in male and female rats for the P2 group.

Dose Level	Males	Females
Control	0.38/.05	0.64/.06
7.5 ppm	0.39/.05	0.64/.08
25 ppm	0.38/.04	0.64/.08
100 ppm	0.38/.03	0.64/.10
375 ppm	0.41/.04** (7.9%)	0.69/.07** (7.8%)

** $p < 0.01$, Study report statistics.

13

TB-I considers this increase to be related to dosing in the high dose group. The consistent effect between sexes helps to justify the conclusion. It might be possible that the weight difference in the pups at birth and during lactation contribute to accounting for this difference in the adults.

C. Discussion. Comparison of TB-I conclusions with the study report conclusions.

Study Report Conclusion	TB-I Conclusion
Parental Effects - body weight, survival, clinical signs, pathology and organ weights. NOEL/LEL = 100/375 ppm. 375 ppm: decreased body weight gain (especially in females during lactation) and threshold for clinical signs. 750 ppm: mortality especially in pups and adult females.	Concurs. Weight effect is apparently threshold in adults and most noticeable during lactation. Relative brain weight in both males (7.9%) and females (7.8%) increased.
Parental Effects - reproductive performance/mating behavior. No effects evident. NOEL > 750 ppm.	Concurs
Pup Effects NOEL/LEL = 100/375 ppm. 375 ppm decreased weight gain during lactation, threshold for clinical signs. 750 ppm: Pup mortality during lactation (decreased lactation index) and clinical signs.	Concurs

CONCLUSION. This study is classified as GUIDELINE and supports the following "one Liner":

NOEL/LEL = 100/375 ppm. At 375 ppm: decreased parental weight most noticeable during lactation; increased relative brain weight in males and females; threshold for clinical signs; decreased pup weight gain during lactation. At 750 ppm: pup and parental mortality and more definite clinical signs.

Dose levels tested: Approximately 0, 0.5, 1.8, 7, 27 and 45 mg/kg/day.