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DATA EVALUATION REPORT

STUDY TYPE: Reproductive toxicity

EPA IDENTIFICATION NUMBERS

TOX CHEM. Number:

MRID Number: 420959-01

TEST MATERIAL: Tetramethylthiuram disulfide

SYNONYM: Thiram

SPONSOR: Thiram Task Force II

STUDY NUMBER: 399-104

TESTING FACILITY: International Research and Development Corporation, Mattawan, MI

TITLE OF REPORT: Two-Generation Reproduction Study in Rats

AUTHOR: R.G. York

REPORT ISSUED: October 16, 1991

CONCLUSIONS: In a two-generation reproduction study, Sprague-Dawley rats were fed thiram in the diet at dosage levels of 0, 30, 60, or 180 ppm (during premating approximately 0, 2.0, 4.0, and 12.2 mg/kg/day, respectively, for males and 0, 2.4, 4.8, and 14.3 mg/kg/day, respectively, for females). Parental toxicity was observed at 180 and 60 ppm in females of both generations and was manifested as significantly decreased body weight/weight gain and food consumption. Because the analyses for stability of the test compound in the diet showed only a 65% recovery on many occasions, it is recommended that the actual dosage levels be considered at 0, 20, 40, and 117 ppm when determining the NOEL and LOEL for this compound. Thus, the NOEL for parental toxicity was 20 ppm (for males 1.3 mg/kg/day; for females 1.5 mg/kg/day); the LOEL was 40 ppm (for males 2.6 mg/kg/day; for females 3.1 mg/kg/day).

Fertility indices (mating, fertility, and gestation), length of gestation, and pup viability were not affected by the test compound. However, pup growth was significantly decreased during lactation at 180 ppm in the F_{1a} litters and at all dosage levels in the F_2 litters. Consequently, the LOEL for reproductive toxicity was 20 ppm (1.4 mg/kg/day, sexes combined); the NOEL could not be determined.

CLASSIFICATION: Core Supplementary Data. This study does not meet the minimum requirements set forth under Guideline Series 83-4 for a two-generation reproductive toxicity study in rats as a NOEL was not observed in F_2 litters.

A. MATERIALS

Test Compound

Purity:	97.5%
Description:	White powder
Storage:	Room temperature
Shelf-life:	Stable for the duration of the study
Lot No.:	117
Received:	June 23, 1989
Contaminants:	None reported

Vehicle: None used; the test material was administered in the diet.

Test Animals

Species:	Rat
Strain:	Charles River (Crl:CD[R] VAF/Plus[R])
Source:	Charles River Laboratories, Inc., Portage, MI
Age:	F_0 males--63 days, study day 0
	F_0 females--63 days, study day 0
Weight:	F_0 males--268-310 g, study day 0
	F_0 females--176-205 g, study day 0

B. STUDY DESIGN

This study was designed to assess the potential of thiram to cause reproductive toxicity when administered continuously in the diet for two successive generations.

Environmental Conditions: The temperature was 73° ± 2.6°F (mean ± S.D.) and the humidity was 50% ± 12.4%. The light/dark cycle was 12/12 hours. The number of air changes per hour was not reported.

Mating: After 14 days of acclimatization followed by 81 days of dietary treatment, the F_0 females were mated with males from the same group in a ratio of 1:1 until evidence of mating (vaginal plug) was obtained or for a maximum period of 21 days. The day on which mating was confirmed was designated day 0 of gestation. A 16-day rest period was allowed after weaning of the first litter and before mating for the second litter; a 13-day rest period was allowed after weaning of the second litter and before mating for the third litter . Females were mated with different males in the second and third matings. The F_1 animals were mated in a similar fashion following 84 days on the test diet and the rest period between litters was 17 days. Sibling matings were avoided.

<u>Group Arrangement</u>: Animals were randomly distributed amongst 4 groups based on body weight stratification as follows:

Test Group	Dietary Level (ppm)	Number Assigned per Group F_0 Males	F_0 Females	F_1 Males	F_1 Females
Control	0	26	26	26	26
Low dose	30	26	26	26	26
Mid-dose	60	26	26	26	26
High-dose	180	26	26	26	26

<u>Dosage Administered</u>: The test material was administered continuously in the diet (Purina Certified Rodent Chow #5002) for two consecutive generations. Diets were prepared weekly and stored frozen until dispersed into daily aliquots. A premix was first prepared for each group by mixing the test material with a small portion of the feed for 5 minutes in a Hobart blender. More feed was then added to achieve the desired concentration and the final mix was blended in a twin-shell blender for 10 minutes. Homogeneity analyses (all dosage levels) of the test material in the diet were conducted prior to study initiation and once during the study. Stability of the test material in the diet was evaluated for all dosage groups after 12 hours in room temperature; after 7 days in frozen storage followed by 12 hours in room temperature; after 12 days in frozen storage followed by 12 hours in room temperature; and on week 1 diets after 12 hours in room temperature. Concentration analyses of all dosage levels were conducted weekly for the first month and every fourth week, thereafter.

Dosage levels were selected by the sponsor and based on results from previously conducted studies. No details regarding these previous studies were provided in this report.

<u>Observations</u>: Observations for mortality, moribundity, and overt signs of toxicity were conducted twice a day. A more detailed clinical examination was performed weekly. Body weight was recorded weekly for all males throughout the study; it was recorded weekly during the premating and rest periods for all females, on gestation days 0, 7, 14, and 20 (sperm-positive females), and on lactation days 0, 4, 7, 14, and 21 (females delivering live litters). Food consumption for males was measured daily and calculated weekly except during mating; for females, it was measured daily and calculated weekly during the premating and rest periods and measured and calculated daily during the gestation and lactation periods.

The following data were recorded for each litter.

- Number of stillborn pups on lactation day 0
- Number of live pups, pup body weight, and pup clinical observations on lactation days 0, 4, 7, 14, and 21
- Gross pup abnormalities on lactation days 0, 4, 7, 14, and 21
- Survival and behavioral abnormalities in nesting and nursing twice daily

On lactation day 4, pups were randomly culled to 4/sex/litter whenever possible; culled pups were examined externally and discarded. However, due to poor delivery results in all groups following the F_{1c} mating, not all F_{1c} litters were culled. Pups found dead or moribund were necropsied and stored in 10% neutral buffered formalin. Following weaning, F_{1a} and F_{1b} pups were sacrificed and discarded, with the exception of pups with gross anomalies which were preserved in 10% neutral buffered formalin. Following weaning of the third litters, 26 F_{1c} pups/dosage level/sex were randomly selected as F_1 parental animals; the remaining weanlings were euthanized, necropsied, and discarded. F_2 pups were handled in a similar manner as the F_1 pups and were also given a more thorough examination of the reproductive organs.

Following weaning of the last litters, parental F_0 and F_1 animals were sacrificed and necropsied. Males failing to sire a litter were evaluated for presence of sperm in the epididymis; sperm-positive females that did not deliver within 26 days were evaluated for pregnancy status by staining the uteri with 10% ammonium sulfide to reveal early embryo death. The following tissues from all groups were preserved in fixative and examined histologically at the control and high-dosage levels:

- Gross lesions
- Seminal vesicles
- Prostate
- Uterus
- Ovaries
- Coagulating gland
- Tissue masses
- Testes
- Epididymides
- Vagina
- Pituitary
- Cervix

Testicular weights were recorded for any male failing to sire a litter (in the F_0 generation, 3, 1, 5, and 1 males at 0, 30, 60, and 180 ppm, respectively; in the F_1 generation, 1 and 2 males at 0 and 30 ppm, respectively).

Statistical Analysis: The following analyses were conducted.

- Parental and pup body weights, maternal weight gain, food consumption, and number of live born pups--ANOVA followed by Bartlett's test for homogeneity of variances and Dunnett's test for multiple comparisons between groups (equal variances) or pairwise comparisons with a Bonferoni correction factor (unequal variances)
- Pup survival indices--Mann-Whitney U-test
- Fertility indices (mating, conception, and gestation)--Chi-square test (with Yate's correction) and/or Fisher's exact test

Compliance:

- A signed Statement of No Data Confidentiality Claim, dated November 4, 1991, was provided.

- A signed Statement of Compliance with EPA GLPs, dated November 4, 1991, was provided.

- A signed Quality Assurance Statement, dated October 14, 1991, was provided.

C. RESULTS

1. Test Material Analysis: Concentrations of the test material in the diet ranged from 82% to 107% of target. Homogeneity analyses revealed concentrations from 79% to 100% of target; stability analyses of the test material in the diet following storage at room temperature for 12 hrs, ranged from 65% to 93% of target.

2. Parental Toxicity

Mortality: No compound-related mortalities were observed.

In the F_0 generation, 1 male at 180 ppm and 1 female at 30 ppm died during weeks 20 and 26, respectively. The cause of death for the male was carcinoma of the kidney. Clinical signs and necropsy did not reveal a cause of death for the female.

In the F_1 generation, 1 female in the control group and 1 female at 180 ppm died at 6 and 32 weeks of age, respectively. Clinical signs and necropsies did not reveal a cause of death for either animal.

Clinical Observations: No compound-related clinical signs were observed. Hair loss, malocclusion, and material around nose and/or eye were frequently observed in all dosage groups.

Body Weight: Compound-related decreased body weight and/or body weight gain were observed at 180 and 60 ppm in females of both generations. Summaries of body weight and/or body weight gain from selected time intervals are presented in Tables 1, 2, and 3. Detailed results are presented in the text. Body weight gain was only reported for the gestation and lactation periods in females.

In the F_0 generation among males (Table 1), body weight in treated animals was never significantly different from that in controls at any time during the study. Among females, body weight was significantly decreased at 180 ppm (10%) and 60 ppm (5%) from week 0 throughout the premating period and during the first rest period (data not shown). During the second rest period, it was significantly decreased at 180 ppm (12%). Body weight during the gestation periods (data not shown) was significantly decreased at 180 ppm (10%) and 60 ppm (5%) on days 0, 7, 14, and 20 following the F_{1a} mating; at 180 ppm (11%) on days 0, 7, 14, and 20 following the F_{1b} mating; and at 180 ppm (10%) on day 7 following the F_{1c} mating.

Body weight gain during the gestation periods (Table 2) was significantly decreased at 180 ppm (15%) on days 14-20 and 0-20 following the F_{1a} mating and at 60 ppm (24%) on days 7-14 following the F_{1c} mating. Body weight during the lactation periods (data not shown) was significantly decreased at 180 ppm (11%) on days 0, 4, 7, 14, and 21 following the F_{1a} mating and at 180 ppm (12%) on days 0 and 4 following the F_{1b} mating. Body weight changes were not noted during lactation (Table 3). These effects on body weight/body weight gain in females at 180 and 60 ppm were all considered to be compound related.

In the F_1 generation among males (Table 1), body weight was significantly decreased below control at 180 ppm (8%) on weeks 4-8 and week 10 of age during premating. Among females, body weight was significantly decreased at 180 ppm (6%) from week 0-11 and week 13 of age (data not shown). Body weight during the gestation periods (data not shown) was significantly decreased at 180 ppm (9%) on days 7, 14, and 20 following the F_{2a} mating and at 180 ppm (8%) on days 0 and 20 following the F_{2b} mating. Body weight gain during the gestation periods (Table 2) was significantly decreased at 180 ppm (24%), at 60 ppm (28%), and at 30 ppm (22%) on days 14-20 and 0-20 following the F_{2a} mating and at 180 ppm (19%) and at 60 ppm (21%) on days 14-20 following the F_{2b} mating. Body weight during the lactation periods (data not shown) was significantly decreased at 180 ppm (8%) on days 0, 4, and 7 following the F_{2a} mating and at 180 ppm (9%) on day 4 following the F_{2b} mating. Body weight gain during lactation (Table 3) decreased significantly at 30 ppm following the F_{2a} mating. It increased significantly at 180 ppm on days 7-14, 14-21, and 0-21 and at 60 ppm on days 0-21 following the F_{1a} mating and at 180 ppm on days 4-7, 14-21, and 0-21 and at 60 ppm on days 4-7 and 0-21 following the F_{2b} mating. The decreased body weight/body weight gain in females at 180 and 60 ppm were all considered to be compound related. The effects observed in males for a few weeks during premating may have been treatment related; however, they were not biologically relevant.

<u>Food Consumption</u>: A compound-related decrease in food consumption was observed at 180 and 60 ppm in females of both generations. Summaries of food consumption data (g/day) from selected intervals are presented in Tables 4, 5, and 6; detailed results are presented in the text.

In the F_0 generation among males (Table 4), incidental but significant decreases were noted in food consumption at 180 ppm on weeks 1, 4, and 5 and at 60 ppm on weeks 1 and 5 during the premating period. Among females, significant decreases were observed at 180 ppm (11%) on weeks 1-4, 7-9, 11, and 20-21 and at 60 ppm (8%) on week 2 during the premating (Table 4) and/or rest periods (data not shown). During the gestation periods (Table 5), significant decreases were observed at 180 ppm (11%) during the entire gestation and at 60 ppm (9%) on days 14-20 and 0-20 following the F_{1a} mating and at 180 ppm (17%) and 60 ppm (14%) on days 0-7 and 0-20 following the F_{1b} mating. During the lactation periods (Table 6), significant decreases were observed at 180 ppm on days 4-7, 7-14, 14-21, and 0-21 following the F_{1a} mating. The decreased food intake observed at 180 and 60 ppm in females was considered to be treatment treatment.

In the F_1 generation, among males (Table 4), incidental but significant changes were observed in food consumption at 180 ppm (5% decrease) on weeks 8 and 9 of age and at 60 ppm (9% increase) on weeks 6 and 14 of age during the premating period. Likewise, among females during premating (Table 4), incidental but significant changes were observed at 180 ppm (7% decrease on week 11 of age and at 60 ppm (26% increase) on week 4 of age. During the gestation periods (Table 5), significant decreases were observed at 180 ppm (12%) during the entire gestation; at 60 ppm (15%) on days 14-20 and 0-20; and at 30 ppm (12%) on days 14-20 following the F_{2a} mating and at 180 ppm (12%) and 60 ppm (14%) on days 14-20 following the F_{2b} mating. During the lactation periods (Table 6), significant decreases were observed at 180 ppm (14%) on days 0-4, 4-7, 7-14, and 0-21; at 60 ppm (22%) on days 0-4; and at 30 ppm (22%) on days 0-4. 4-7, 7-14, and 0-21 following the F_{2a} mating and at 180 ppm (19%) on days 0-4 and 0-21; at 60 ppm (29%) on days 0-4; and at 30 ppm (22%) on days 0-4 and 0-21 following the F_{2b} mating. The decreased food intake observed in females during the gestation and lactation periods was considered to be a compound-related effect.

Test Material Intake: In the F_0 generation, mean test material intake during premating for males was 0, 1.62, 3.42, and 10.12 mg/kg/day at 0, 30, 60, and 180 ppm, respectively; and for females at the same doses it was 0, 2.13, 4.26, and 12.60 mg/kg/day, respectively. For females during the gestation periods, test material intake averaged 0, 1.85, 3.71, and 11.30 mg/kg/day at 0, 30, 60, and 180 ppm, respectively.

In the F_1 generation, mean test material intake during premating for males was 0, 2.30, 4.65, and 14.23 mg/kg/day at 0, 30, 60, and 180 ppm, respectively; and for females at the same doses it was 0, 2.60, 5.24, and 16.02 mg/kg/day, respectively. For females during the gestation period, test material intake averaged 0, 1.83, 3.46, and 11.06 mg/kg/day at 0, 30, 60, and 180 ppm, respectively.

Gross and Microscopic Pathology: No compound-related gross or microscopic findings were observed for any sex and generation.

3. Reproductive Toxicity: The effects of dietary administration of the test material on reproductive parameters are summarized in Tables 7-11. Fertility indices (mating, fertility, and gestation), length of gestation, and pup survival were not affected by the test compound. However, pup body weight was significantly decreased at 180 ppm in F_1 litters and at all treatment levels in F_2 litters. Detailed results are reported below.

In the F_1 offspring after the first mating (Table 7), the viability index decreased at 180 ppm. In fact, all dosage groups were outside the normal range, but since this was not observed in any other group, it was not considered to be a treatment-related effect. Pup body weight was significantly decreased (85%) at 180 ppm on lactation days 0, 4, and 7 for both sexes combined and on day 21 for females only. This was considered to be a compound related effect.

In the F_1 offspring after the second mating (Table 8), male and female fertility indices were significantly increased at 180 ppm due to unusually low fertility rates in the control groups (see Reviewers' Discussion for further comment). Pup body weight was decreased (20%) starting on day 7 at all dosage levels during the entire lactation. Weight decreases were significant for the following days and dosage levels: day 7 at 180 and 30 ppm for both sexes combined; day 14 at 180 ppm for both sexes combined; and day 21 at 180 and 30 ppm for both sexes separated and at 60 ppm for males only. These weight decreases were probably compound related. However, few litters were available for evaluation after this mating, and therefore, less emphasis should be placed upon effects observed in these litters.

In the F_1 offspring after the third mating (Table 9), male and female fertility indices were significantly increased at 180 ppm due to unusually low fertility rates in the control groups (see Reviewers' Discussion for further comment). Pup body weight was slightly (10%) decreased throughout lactation at 180 ppm, which may have been due to the test compound. However, few litters were available for evaluation after this mating as well which may have masked a true effect.

In the F_2 offspring after the first mating (Table 10), a slight decrease was observed at 30 ppm in the number of pups per litter and consequently in the viability index. Since this decrease was not observed in a dosage-related manner, it was considered normal variation. Pup body weight was consistently decreased at all dosage levels during lactation (significant at 180 ppm [5%-15%] and 30 ppm [7%-11%]) and was believed to be compound-related.

In the F_2 offspring after the second mating (Table 11), a slight decrease was again noted in the number of pups per litter at 30 ppm (and in the viability index) which was again considered to be normal variation. Pup body weight (males and females separated) was significantly decreased due to the test compound at all dosage levels (7%-19%) on day 21 and at 180 and 60 ppm on day 14 (sexes combined; data not shown).

No compound-related clinical observations and gross findings were noted in pups from any litter and generation.

C. <u>REVIEWERS' DISCUSSION/CONCLUSIONS</u>

1. <u>Test Material Analyses</u>: Concentrations and homogeneity of the test compound in the diet were within ± 21% of target values. However, the test compound did not appear to be stable in the diet over time regardless of storage conditions; recovery was frequently 65% including all dosage levels. Therefore, the reviewers suggest that the actual dosage levels be observed at 65% of their target (i.e., 20, 40 and 117 ppm instead of 30, 60 and 180 ppm, respectively).

2. Parental Toxicity: Parental toxicity was observed at 180 and 60 ppm in females of both generations. It was manifested as significantly decreased body weight/body weight gain and food consumption. During lactation in the second generation, second mating, food consumption and body weight gain appeared to be affected at all dosage levels; this was not observed in previous litters. Maternal food consumption during lactation (especially during the latter part of this period) is not a reliable parameter because of the initiation of food intake in pups. Therefore, limited emphasis has been placed on this effect, particularly at the lowest dosage levels, since it was not consistently observed. Mortality, clinical observations, and gross and microscopic findings were not affected by the test compound.

   Based on 65% recovery of the test material in the diet and decreased body weight and food consumption at the high- and mid-dosage levels, the parental NOEL and LOEL were 20 and 40 ppm, respectively.

3. Reproductive Toxicity: Reproductive toxicity was observed at 180 ppm in the first generation (F_{1a} litter) and at all dosage levels in the second generation. It was manifested as decreased pup body weight during most of the lactation period, although it was not always dose-related or statistically significant. The F_{1b} and F_{1c} pup body weights were less affected but the number of litters evaluated was unusually low and may have masked an effect. The F_{2a} and F_{2b} pup body weights demonstrated consistent effects with a sufficient number of litters to evaluate at all dosage levels. Therefore, this body weight decrease was believed to be a treatment-related effect.

   The unusually low fertility and reduced birth rates at all dosage levels including the controls following 2nd and 3rd matings of F_0 parents, were outside the historical control range. The Agency has received reports of fertility problems involving Charles River rats with generally good results for the first mating followed by a reduction in fertility indices in subsequent matings. Paradoxically, thiram at the highest dosage level may have actually inhibited this effect. These low values may also indicate a problem with general disturbance in the environment in the animal quarters during mating since this effect was not observed in the second generation. This is not believed to be an effect of the test compound since it occurred in the control groups as well.

   Based on 65% recovery of the test material in the diet and decreased pup body weight at all treatment levels in the second generation litters, the LOEL for reproductive toxicity was 20 ppm; the NOEL was not determined.

4. Reporting Deficiencies: Food consumption data would be more informative, were it to be reported as mg/kg/day rather than as g/animal/day.

   No protocol was submitted.

A more detailed discussion regarding the low fertility indices in the F_0 second and third matings should have been included and explaining the environmental conditions that may have caused this effect.

D. CLASSIFICATION: CORE Supplementary Data. This study does not meet the minimum requirements set forth under Guideline Series 83-4 for a two-generation reproductive toxicity study in rats as a NOEL for reproductive toxicity was not determined.

Parental toxicity NOEL = 20 ppm
(for males 1.3 mg/kg/day, for females 1.5 mg/kg/day)

Parental toxicity LOEL = 40 ppm
(for males 2.6 mg/kg/day, for females 3.1 mg/kg/day)

Reproductive toxicity NOEL = Not determined

Reproductive toxicity LOEL = 20 ppm
(1.4 mg/kg/day, sexes combined)

E. RISK ASSESSMENT: Not Applicable

TABLE 1. Mean Body Weight (g ± S.D.) During the Premating Period for Rats Fed Thiram for Two Successive Generations[a]

Study Week:	Dietary Level (ppm) 0	30	60	180
F_0 Males				
0	291 ± 11.9	285 ± 10.8	289 ± 10.4	291 ± 10.6
3	364 ± 29.0	351 ± 18.0	360 ± 17.1	353 ± 21.4
7	441 ± 39.1	429 ± 28.3	437 ± 23.4	431 ± 31.6
11	469 ± 43.4	453 ± 33.2	469 ± 29.4	465 ± 34.1
F_0 Females				
0	193 ± 6.9	189 ± 7.4	188 ± 7.6*	187 ± 7.2*
3	221 ± 9.2	217 ± 12.5	210 ± 9.5**	201 ± 9.7**
7	249 ± 14.3	244 ± 17.7	235 ± 12.7**	222 ± 12.9**
11	262 ± 17.1	258 ± 21.8	249 ± 15.9*	237 ± 13.5**
F_1 Males				
0/4[b]	82 ± 15.9	80 ± 8.4	84 ± 9.1	75 ± 6.9
3/7	236 ± 31.3	233 ± 20.8	238 ± 21.7	214 ± 15.7*
7/11	377 ± 41.2	372 ± 35.2	385 ± 38.0	357 ± 22.3
12/16	450 ± 48.2	451 ± 36.5	468 ± 43.1	443 ± 40.6
F_1 Females				
0/4	78 ± 9.9	77 ± 10.9	78 ± 5.6	70 ± 7.3*
3/7	161 ± 15.4	165 ± 12.9	165 ± 12.7	150 ± 10.4**
7/11	217 ± 21.6	227 ± 16.2	224 ± 16.3	204 ± 14.3*
12/16	250 ± 26.2	260 ± 18.8	262 ± 16.8	239 ± 16.8

[a]Data were extracted from Study No. 399-104, Tables 6 and 13.

[b]Week of study/week of age

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

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

TABLE 2. Mean Maternal Body Weight Gain (g ± S.D.) During Gestation for Rats Fed Thiram for Two Successive Generations[a]

	Dietary Level (ppm)			
Gestation Days:	0	30	60	180
F_0 Generation - F_{1a} Litters				
0 - 7	28 ± 8.6	30 ± 6.9	27 ± 9.1	24 ± 6.4
7 - 14	20 ± 3.6	18 ± 4.7	20 ± 8.4	20 ± 6.5
14 - 20	66 ± 17.3	63 ± 8.9	55 ± 9.7	54 ± 7.9*
0 - 20	113 ± 21.8	111 ± 10.6	102 ± 15.3	98 ± 11.0*
F_0 Generation - F_{1b} Litters				
0 - 7	31 ± 7.5	25 ± 6.0	24 ± 5.5	25 ± 8.6
7 - 14	20 ± 7.0	20 ± 4.1	18 ± 3.7	18 ± 6.2
14 - 20	54 ± 16.1	46 ± 15.4	33 ± 12.0	40 ± 19.3
0 - 20	105 ± 25.8	93 ± 21.9	75 ± 16.2	83 ± 21.5
F_0 Generation - F_{1c} Litters				
0 - 7	28 ± 10.2	22 ± 4.0	27 ± 9.2	22 ± 11.0
7 - 14	25 ± 4.0	21 ± 5.2	19 ± 2.8*	23 ± 4.6
14 - 20	67 ± 17.1	48 ± 17.2	56 ± 8.4	60 ± 9.0
0 - 20	120 ± 27.7	91 ± 20.5*	102 ± 10.3	106 ± 15.2
F_1 Generation - F_{2a} Litters				
0 - 7	26 ± 8.2	23 ± 5.7	23 ± 6.8	23 ± 7.0
7 - 14	25 ± 12.4	25 ± 4.4	17 ± 7.4	21 ± 6.4
14 - 20	71 ± 25.2	53 ± 6.2*	50 ± 16.2**	50 ± 8.7**
0 - 20	122 ± 20.3	100 ± 8.4**	90 ± 19.8**	94 ± 16.1**
F_1 Generation - F_{2b} Litters				
0 - 7	24 ± 13.7	23 ± 6.1	17 ± 18.3	23 ± 7.1
7 - 14	23 ± 8.9	21 ± 4.1	23 ± 10.3	20 ± 4.8
14 - 20	65 ± 18.2	60 ± 9.1	52 ± 11.7**	51 ± 12.8**
0 - 20	112 ± 22.8	105 ± 10.6	92 ± 18.7	94 ± 14.0

[a]Data were extracted from Study No. 399-104, Tables 7, 9, 11, 14, and 16.

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

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

TABLE 3. Mean Maternal Body Weight Gain (g ± S.D.) During Lactation for Rats Fed Thiram for Two Successive Generations[a]

Lactation Days:	Dietary Level (ppm) 0	30	60	180
F_0 Generation - F_{1a} Litters				
0 - 4	-4 ± 22.0	3 ± 12.6	0 ± 12.2	3 ± 12.4
4 - 7	12 ± 23.0	7 ± 11.0	14 ± 11.8	11 ± 8.8
7 - 14	18 ± 17.0	12 ± 14.4	16 ± 9.4	6 ± 21.1
14 - 21	4 ± 8.3	7 ± 10.1	5 ± 9.8	1 ± 25.5
0 - 21	30 ± 19.4	30 ± 15.9	36 ± 12.2	20 ± 20.7
F_0 Generation - F_{1b} Litters				
0 - 4	3 ± 7.9	-2 ± 34.4	-4 ± 14.8	-2 ± 25.1
4 - 7	6 ± 9.9	-1 ± 16.3	0 ± 7.8	17 ± 18.0
7 - 14	6 ± 20.4	8 ± 24.7	3 ± 13.1	13 ± 13.3
14 - 21	-6 ± 18.8	2 ± 14.2	-1 ± 12.0	-4 ± 11.8
0 - 21	9 ± 15.0	7 ± 26.6	-3 ± 26.3	24 ± 11.7
F_0 Generation - F_{1c} Litters				
0 - 4	3 ± 25.0	1 ± 13.1	3 ± 15.0	4 ± 14.7
4 - 7	5 ± 5.2	5 ± 4.4	10 ± 5.1	8 ± 8.4
7 - 14	6 ± 20.6	-7 ± 12.7	-1 ± 12.2	11 ± 10.8
14 - 21	-11 ± 20.3	-14 ± 14.0	-14 ± 8.9	-2 ± 10.6
0 - 21	3 ± 9.7	-15 ± 21.7	-2 ± 10.2	21 ± 18.6
F_1 Generation - F_{2a} Litters				
0 - 4	5 ± 12.3	-4 ± 8.5*	7 ± 9.8	3 ± 9.8
4 - 7	7 ± 8.4	7 ± 6.3	12 ± 9.5	11 ± 7.9
7 - 14	13 ± 8.3	7 ± 9.0	14 ± 7.9	19 ± 7.0*
14 - 21	-13 ± 10.0	-7 ± 12.9	-8 ± 8.2	-5 ± 7.9**
0 - 21	10 ± 14.6	3 ± 18.1	25 ± 15.3**	28 ± 10.5**
F_1 Generation - F_{2b} Litters				
0 - 4	2 ± 15.8	-3 ± 9.2	4 ± 10.2	-3 ± 8.8
4 - 7	4 ± 6.3	5 ± 7.4	11 ± 10.0*	11 ± 7.1*
7 - 14	14 ± 10.4	10 ± 12.2	14 ± 10.9	16 ± 8.6
14 - 21	-15 ± 12.8	-15 ± 22.2	-4 ± 14.7	1 ± 9.6**
0 - 21	5 ± 22.9	-4 ± 26.1	25 ± 19.3*	25 ± 20.3*

[a]Data were extracted from Study No. 399-104, Tables 8, 10, 12, 15, and 17.

*Significantly different from control (p≤0.05)

**Significantly different from control (p≤0.01)

TABLE 4. Mean Food Consumption (g/day ± S.D.) During the Premating Period for Rats Fed Thiram for Two Successive Generations[a]

Study Week:	Dietary Level (ppm) 0	30	60	180
F_0 Males				
1	23.0 ± 2.2	22.1 ± 1.7	21.6 ± 1.9*	19.2 ± 2.1**
4	24.2 ± 2.5	23.8 ± 2.4	23.4 ± 1.8	22.0 ± 2.2**
7	23.1 ± 3.6	22.4 ± 2.0	22.7 ± 1.4	22.4 ± 1.8
11	24.5 ± 2.4	25.1 ± 5.1	24.9 ± 3.3	23.9 ± 2.0
F_0 Females				
1	14.8 ± 1.1	15.0 ± 1.1	14.0 ± 1.3	11.8 ± 1.6**
4	16.8 ± 1.5	16.7 ± 1.7	16.5 ± 1.6	15.5 ± 1.1**
7	15.4 ± 1.5	15.7 ± 1.9	15.4 ± 1.6	14.0 ± 1.3**
11	17.8 ± 1.4	18.2 ± 2.5	18.0 ± 1.7	16.4 ± 1.1**
F_1 Males				
1/4[b]	9.4 ± 3.0	9.5 ± 1.8	10.7 ± 2.0	10.2 ± 3.9
4/7	21.1 ± 2.2	21.3 ± 1.6	21.6 ± 1.8	20.1 ± 1.7
7/11	24.0 ± 2.4	24.1 ± 3.8	25.1 ± 2.0	23.0 ± 1.9
12/16	23.0 ± 2.6	23.3 ± 2.5	24.1 ± 2.9	22.5 ± 3.2
F_1 Females				
1/4	8.9 ± 1.9	9.8 ± 4.7	11.2 ± 3.3*	9.5 ± 3.6
4/7	14.7 ± 2.1	16.3 ± 1.4*	15.6 ± 1.0	15.2 ± 1.8
7/11	16.9 ± 1.8	18.2 ± 1.2**	17.3 ± 1.3	15.7 ± 1.3*
12/16	16.7 ± 1.9	17.5 ± 1.7	17.0 ± 1.2	16.3 ± 1.2

[a]Data were extracted from Study No. 399-104, Tables 18 and 25.

[b]Week of study/week of age

*Significantly different from control (p≤0.05)

**Significantly different from control (p≤0.01)

Table 5. Mean Food Consumption (g/day ± S.D.) During Gestation for Rats Fed Thiram for Two Successive Generations[a]

Gestation Days:	Dietary Level (ppm) 0	30	60	180
F_0 Generation - F_{1a} Litters				
0 - 7	22.7 ± 2.0	22.1 ± 1.6	21.3 ± 3.5	20.1 ± 2.3**
7 - 14	23.3 ± 2.8	22.5 ± 1.8	21.9 ± 2.4	21.2 ± 1.9**
14 - 20	23.2 ± 3.2	22.0 ± 2.7	20.6 ± 1.8**	19.7 ± 2.1**
0 - 20	23.0 ± 2.2	22.2 ± 1.3	21.3 ± 2.0**	20.4 ± 1.8**
F_0 Generation - F_{1b} Litters				
0 - 7	22.1 ± 2.2	20.7 ± 2.0	19.5 ± 2.1*	18.3 ± 1.5**
7 - 14	22.0 ± 4.6	19.3 ± 1.8	18.5 ± 2.1	17.6 ± 1.7
14 - 20	24.0 ± 4.1	21.1 ± 1.7	19.5 ± 1.7	19.6 ± 1.6
0 - 20	22.6 ± 3.2	20.3 ± 1.8	19.2 ± 1.6**	18.5 ± 1.4**
F_0 Generation - F_{1c} Litters				
0 - 7	24.3 ± 4.0	21.9 ± 1.5	22.7 ± 2.3	21.0 ± 2.2
7 - 14	22.7 ± 4.0	21.5 ± 1.9	21.6 ± 2.4	20.6 ± 2.0
14 - 20	23.5 ± 4.7	21.5 ± 1.9	19.5 ± 1.0	20.5 ± 2.1
0 - 20	23.6 ± 3.8	21.6 ± 1.5	21.4 ± 1.6	20.7 ± 1.8
F_1 Generation - F_{2a} Litters				
0 - 7	19.2 ± 2.7	19.2 ± 2.1	18.1 ± 1.5	17.2 ± 1.6*
7 - 14	20.8 ± 3.4	20.2 ± 1.8	19.0 ± 1.6	18.3 ± 1.9*
14 - 20	22.8 ± 4.0	20.1 ± 1.6*	18.4 ± 3.4**	19.1 ± 2.3**
0 - 20	20.8 ± 3.0	19.8 ± 1.5	18.5 ± 1.4**	18.2 ± 1.6**
F_1 Generation - F_{2b} Litters				
0 - 7	21.0 ± 3.9	21.3 ± 2.4	19.5 ± 5.1	19.8 ± 1.4
7 - 14	22.7 ± 3.7	22.1 ± 1.7	21.6 ± 1.9	21.4 ± 1.9
14 - 20	23.2 ± 2.9	21.4 ± 1.8	19.9 ± 1.3**	20.5 ± 2.4*
0 - 20	22.2 ± 3.2	21.6 ± 1.5	20.4 ± 2.4	20.6 ± 1.5

[a]Data were extracted from Study No. 399-104, Tables 19, 21, 23, 26, and 28.

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

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

TABLE 6. Mean Food Consumption (g/day ± S.D.) During Lactation for Rats Fed Thiram for Two Successive Generations[a]

Lactation Days:	Dietary Level (ppm) 0	30	60	180
F_0 Generation - F_{1a} Litters				
0 - 4	20.8 ± 5.7	22.4 ± 4.9	20.3 ± 5.4	19.3 ± 6.1**
4 - 7	34.4 ± 7.7	35.5 ± 7.6	32.6 ± 4.9	27.2 ± 5.5**
7 - 14	43.9 ± 10.1	41.5 ± 9.0	41.3 ± 8.1	32.6 ± 10.1**
14 - 21	55.6 ± 12.8	56.3 ± 13.7	54.5 ± 12.6	40.5 ± 16.2**
0 - 21	41.0 ± 7.3	40.9 ± 7.8	38.5 ± 6.5	31.7 ± 9.5**
F_0 Generation - F_{1b} Litters				
0 - 4	23.9 ± 5.1	20.8 ± 9.9	17.1 ± 5.1	20.7 ± 8.1
4 - 7	33.1 ± 9.6	29.8 ± 15.9	24.0 ± 8.5	32.6 ± 10.1
7 - 14	39.8 ± 12.3	33.7 ± 10.8	30.5 ± 10.5	41.1 ± 7.1
14 - 21	48.3 ± 18.9	39.6 ± 14.4	37.0 ± 15.2	49.5 ± 9.0
0 - 21	37.6 ± 11.1	32.8 ± 11.1	29.0 ± 10.3	37.9 ± 6.6
F_0 Generation - F_{1c} Litters				
0 - 4	20.8 ± 9.9	24.1 ± 6.6	18.9 ± 3.8	20.9 ± 6.7
4 - 7	34.8 ± 12.8	35.8 ± 14.0	34.5 ± 4.1	31.1 ± 7.9
7 - 14	48.2 ± 8.8	38.7 ± 11.1	44.0 ± 3.7	42.9 ± 8.5
14 - 21	59.5 ± 12.1	47.3 ± 17.0	55.6 ± 5.5	51.9 ± 10.4
0 - 21	45.0 ± 10.2	38.3 ± 10.3	41.6 ± 3.7	40.2 ± 8.6
F_1 Generation - F_{2a} Litters				
0 - 4	25.4 ± 5.6	16.8 ± 6.1**	19.8 ± 5.9**	19.0 ± 4.6**
4 - 7	36.4 ± 5.0	29.6 ± 5.9**	33.4 ± 4.7	31.5 ± 4.5**
7 - 14	47.6 ± 5.5	39.1 ± 9.0**	44.3 ± 6.4	43.5 ± 4.0*
14 - 21	54.3 ± 6.0	46.9 ± 11.8	50.9 ± 9.5	54.2 ± 9.8*
0 - 21	44.0 ± 4.9	35.8 ± 8.6	40.2 ± 6.5	40.6 ± 4.3*
F_1 Generation - F_{2b} Litters				
0 - 4	25.9 ± 6.1	18.7 ± 5.9**	18.3 ± 4.9**	20.0 ± 4.8**
4 - 7	33.3 ± 6.7	29.7 ± 6.7	31.7 ± 6.3	33.7 ± 8.7
7 - 14	46.2 ± 10.3	38.7 ± 7.8	42.9 ± 7.0	40.1 ± 5.2*
14 - 21	57.1 ± 11.6	48.2 ± 10.4	53.5 ± 10.4	50.5 ± 7.0*
0 - 21	44.0 ± 8.8	36.6 ± 7.5*	39.9 ± 6.5	37.2 ± 8.1*

[a] Data were extracted from Study No. 399-104, Tables 20, 22, 24, 27, and 29.

*Significantly different from control (p≤0.05)

**Significantly different from control (p≤0.01)

TABLE 7. Summary of Effects of Dietary Administration of Thiram on F_{1a} Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Level (ppm) 0	30	60	180
No. matings (F_0 parents)	26	26	25	26
Mating index (%), males[b]	92.3	100	100	100
females	92.3	100	100	100
Fertility index (%), males[c]	84.6	96.2	100	100
females	84.6	96.2	84.0	88.5
Gestation index (%)[d]	100	100	100	100
Gestation length (days)	22.2	22.0	22.0	21.8
Total No. stillbirths	6	7	2	7
Total No. live litters day 0	22	25	21	23
Total No. live pups				
Day 0	257	303	247	278
Day 4 precull	223	269	206	196
Day 21	150	170	146	119
Mean No. live pups/litter				
Day 0	11.7 (22)[e]	12.1 (25)	11.8 (21)	12.1 (23)
Day 4 precull[f]	10.1 (22)	10.8 (25)	9.8 (21)	9.8 (20)
Day 21[f]	7.1 (21)	7.1 (24)	7.0 (21)	6.3 (19)
Live birth index (%)[g]	97.7	97.7	99.2	97.5
Viability index (%)[h]	86.8	88.8	83.4	70.5
Lactation index (%)[i]	89.8	91.4	96.7	83.8
Mean pup body weight (g)				
Day 0	6.1	6.0	5.8	5.4**
7	11.4	10.9	11.0	9.1*
21, males	35.1	35.7	33.4	31.4**
females	34.6	33.7	32.6	29.5**
Sex ratio (% males, day 21)[f]	50.0	53.5	52.1	55.5

[a]Data were extracted from Study No. 399-104, Tables 42-44 and individual animal data from Appendix J.

[b]Mating index: No. females (or males) mated expressed as % of total No. paired females (or males)

[c]Fertility index: No. gravid females (or fertile males) expressed as % of No. paired females (or males)

[d]Gestation index: No. females delivering a live litter expressed as % of No. pregnant females

[e]Number of litters included in calculation.

[f]Calculated by the reviewers using individual animal data

[g]Live birth index: Percentage of pups surviving one day

[h]Viability index: Percentage of pups surviving four days (precull)

[i]Lactation index: Percentage of pups surviving 21 days based on No. pups on day 4 postcull

*Significantly different from control 1 ($p \leq 0.05$)

**Significantly different from control 1 ($p \leq 0.01$)

TABLE 8. Summary of Effects of Dietary Administration of Thiram on $F_{1,b}$ Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Level (ppm) 0	30	60	180
No. matings (F_0 parents)	26	25	25	26
Mating index (%), males[b]	61.5	60.0	76.0	76.0
females	61.5	60.0	76.0	76.9
Fertility index (%), males[c]	23.1	32.0	36.0	64.0**
females	23.1	32.0	36.0	65.4**
Gestation index (%)[d]	100	100	88.9	88.2
Gestation length (days)	23.0	22.4	22.6	22.4
Total No. stillbirths	2	2	1	1
Total No. live litters day 0	6	8	8	15
Total No. live pups				
Day 0	46	55	39	125
Day 4 precull	45	50	37	124
Day 21	33	34	35	101
Mean No. live pups/litter				
Day 0	7.7 (6)[e]	6.9 (8)	4.9 (8)	8.3 (15)
Day 4 precull[f]	7.5 (6)	6.3 (8)	4.6 (8)	8.3 (15)
Day 21[f]	5.5 (6)	4.9 (7)	5.0 (7)	6.7 (15)
Live birth index (%)[g]	95.8	96.5	97.5	99.2
Viability index (%)[h]	97.8	90.9	94.9	99.2
Lactation index (%)[i]	100	79.1	100	96.2
Mean pup body weight (g)				
Day 0	6.9	6.2*	7.0	6.4*
7	17.6	13.4**	15.8	13.7*
21, males	51.2	41.7**	43.1*	41.5**
females	48.5	40.8*	38.1	40.6**
Sex ratio (% males, day 21)[f]	42.4	52.9	48.6	50.5

[a]Data were extracted from Study No. 399-104, Tables 46-48 and individual animal data from Appendix J.

[b]Mating index: No. females (or males) mated expressed as % of total No. paired females (or males)

[c]Fertility index: No. gravid females (or fertile males) expressed as % of No. paired females (or males)

[d]Gestation index: No. females delivering a live litter expressed as % of No. pregnant females

[e]Number of litters included in calculation.

[f]Calculated by the reviewers using individual animal data

[g]Live birth index: Percentage of pups surviving one day

[h]Viability index: Percentage of pups surviving four days (precull)

[i]Lactation index: Percentage of pups surviving 21 days based on No. pups on day 4 postcull

*Significantly different from control 1 ($p \leq 0.05$)

**Significantly different from control 1 ($p \leq 0.01$)

TABLE 9. Summary of Effects of Dietary Administration of Thiram on $F_{1,c}$ Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Level (ppm) 0	30	60	180
No. matings (F_0 parents)	21	18	16	21
Mating index (%), males[b]	76.2	88.9	87.5	90.5
females	76.2	88.9	87.5	90.5
Fertility index (%), males[c]	33.3	44.4	43.8	76.2*
females	33.3	44.4	43.8	76.2*
Gestation index (%)[d]	100	87.5	100	100
Gestation length (days)	22.3	22.4	22.0	21.9
Total No. stillbirths	1	2	0	20
Total No. live litters day 0	7	8	7	16
Total No. live pups				
Day 0	82	65	81	182
Day 4 precull	78	65	80	177
Day 21	62	53	56	125
Mean No. live pups/litter				
Day 0	11.7 (7)[e]	8.1 (8)	11.6 (7)	11.4 (16)
Day 4 precull[f]	11.1 (7)	9.3 (7)	11.4 (7)	11.8 (15)
Day 21[f]	8.9 (7)	7.7 (7)	8.0 (7)	8.3 (15)
Live birth index (%)[g]	98.8	97.0	100	90.1
Viability index (%)[h]	95.1	100	98.8	97.3
Lactation index (%)[i]	100	98.1	100	97.7
Mean pup body weight (g)				
Day 0	5.8	6.4	5.9	5.6
7	14.3	15.4	14.7	13.4
21, males	49.0	48.3	48.3	44.4
females	46.9	46.9	46.0	43.0
Sex ratio (% males, day 21)[f]	45.2	56.6	51.8	56.0

[a]Data were extracted from Study No. 399-104, Tables 50-52 and individual animal data from Appendix J.

[b]Mating index: No. females (or males) mated expressed as % of total No. paired females (or males)

[c]Fertility index: No. gravid females (or fertile males) expressed as % of No. paired females (or males)

[d]Gestation index: No. females delivering a live litter expressed as % of No. pregnant females

[e]Number of litters included in calculation

[f]Calculated by the reviewers using individual animal data

[g]Live birth index: Percentage of pups surviving one day

[h]Viability index: Percentage of pups surviving four days (precull)

[i]Lactation index: Percentage of pups surviving 21 days based on No. pups on day 4 postcull

*Significantly different from control 1 ($p \leq 0.05$)

TABLE 10. Summary of Effects of Dietary Administration of Thiram on $F_{2,a}$ Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Level (ppm) 0	30	60	180
No. matings (F_1 parents)	25	23	26	26
Mating index (%), males[b]	92.0	91.3	100	100
females	92.0	91.3	100	100
Fertility index (%), males[c]	88.0	69.6	84.6	100
females	88.0	69.6	84.6	100
Gestation index (%)[d]	100	100	100	100
Gestation length (days)	22.0	21.9	22.2	21.7
Total No. stillbirths	2	3	5	5
Total No. live litters day 0	22	16	22	26
Total No. live pups				
Day 0	298	206	263	304
Day 4 precull	283	169	248	288
Day 21	172	111	166	206
Mean No. live pups/litter				
Day 0	13.5 (22)[e]	12.9 (16)	12.0* (22)	11.7** (26)
Day 4 precull[f]	12.9 (22)	12.1 (14)	11.8 (21)	11.1 (26)
Day 21[f]	7.8 (22)	7.9 (14)	7.9 (21)	7.9 (26)
Live birth index (%)[g]	99.3	98.6	98.1	98.4
Viability index (%)[h]	95.0	82.0*	94.3	94.7
Lactation index (%)[i]	100	100	98.8	99.0
Mean pup body weight (g)				
Day 0	5.9	5.5*	5.8	5.6*
7	15.0	13.3**	14.3	12.6**
21, males	47.0	42.2*	45.6	40.2*
females	45.0	40.5*	43.5	38.6*
Sex ratio (% males, day 21)[f]	54.1	51.4	50.6	46.6

[a]Data were extracted from Study No. 399-104, Tables 54-56 and individual animal data from Appendix J.

[b]Mating index: No. females (or males) mated expressed as % of total No. paired females (or males)

[c]Fertility index: No. gravid females (or fertile males) expressed as % of No. paired females (or males)

[d]Gestation index: No. females delivering a live litter expressed as % of No. pregnant females

[e]Number of litters included in calculation

[f]Calculated by the reviewers using individual animal data

[g]Live birth index: Percentage of pups surviving one day

[h]Viability index: Percentage of pups surviving four days (precull)

[i]Lactation index: Percentage of pups surviving 21 days based on No. pups on day 4 postcull

*Significantly different from control 1 ($p \le 0.05$)

**Significantly different from control 1 ($p \le 0.01$)

TABLE 11. Summary of Effects of Dietary Administration of Thiram on $F_{2,b}$ Reproductive Parameters, Offspring Survival, and Pup Body Weight[a]

Parameter	Dietary Level (ppm) 0	30	60	180
No. matings (F_1 parents)	25	23	26	26
Mating index (%), males[b]	100	87.0	100	100
females	100	87.0	100	100
Fertility index (%), males[c]	76.0	73.9	80.8	73.1
females	76.0	73.9	80.8	73.1
Gestation index (%)[d]	100	100	95.2	100
Gestation length (days)	22.3	22.0	22.1	21.8
Total No. stillbirths	8	18	13	5
Total No. live litters day 0	19	17	20	19
Total No. live pups				
Day 0	224	204	242	211
Day 4 precull	220	172	226	194
Day 21	138	117	149	135
Mean No. live pups/litter				
Day 0	11.8 (19)[e]	12.0 (17)	12.1 (20)	11.1 (19)
Day 4 precull[f]	11.6 (19)	10.1 (17)	11.9 (19)	10.8 (18)
Day 21[f]	7.7 (18)	6.9 (17)	7.8 (19)	7.5 (18)
Live birth index (%)[g]	96.6	91.9	94.9	97.7
Viability index (%)[h]	98.2	84.3	93.4	91.9
Lactation index (%)[i]	97.9	98.3	98.7	99.3
Mean pup body weight (g)				
Day 0	5.9	5.4	5.6	5.5
7	14.6	12.5	13.5	13.5
21, males	51.2	43.5**	47.1*	41.7**
females	49.4	41.6**	44.8**	40.8**
Sex ratio (% males, day 21)[f]	52.2	48.7	47.7	48.1

[a]Data were extracted from Study No. 399-104, Tables 54-56 and individual animal data from Appendix J.
[b]Mating index: No. females (or males) mated expressed as % of total No. paired females (or males)

[c]Fertility index: No. gravid females (or fertile males) expressed as % of No. paired females (or males)

[d]Gestation index: No. females delivering a live litter expressed as % of No. pregnant females

[e]Number of litters included in calculation

[e]Calculated by the reviewers using individual animal data

[f]Live birth index: Percentage of pups surviving one day

[g]Viability index: Percentage of pups surviving four days (precull)

[h]Lactation index: Percentage of pups surviving 21 days based on No. pups on day 4 postcull

*Significantly different from control 1 ($p \leq 0.05$)

**Significantly different from control 1 ($p \leq 0.01$)