(072560)

(1-15-03)

DATA EVALUATION RECORD

Experimental Additive Number 9823-37

Study Type: Reproduction and Fertility Effects (Rat)

Prepared for

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U.S. Environmental Protection Agency
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Contract Number: 68-W-01-036
Work Assignment No.: 0248.2000.002.02 TAF 2-2-13
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Antimicrobials Division (7510C)

DATA EVALUATION RECORD

STUDY TYPE: Reproduction and Fertility Effects - Rat; OPPTS 870.3800

DP BARCODE: D286393
SUBMISSION CODE: S623914
P.C. CODE: 072560

TEST MATERIAL (PURITY): Experimental Additive Number 9823-37 (purity not provided)

SYNONYMS: not provided

CITATION: Wood, E. (2002). Experimental Additive Number 9823-37: Dietary Two Generation Reproduction Study in the Rat. Milliken Chemical, Division of Milliken & Company (Spartanburg, SC). Report No. 656/082, September 13, 2002. MRID 457694-02. Unpublished.

SPONSOR: SafePharm Laboratories, Ltd.
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EXECUTIVE SUMMARY: In a two-generation reproduction study (MRID 457694-02), Experimental Additive Number 9823-37 was administered via diet to male and female Crl:CD® IGS BR rats at dose levels of 0, 1000, 5000, or 20,000 ppm. Animals were exposed to the test article for 75 (F_0 animals) or 76 (F_1 animals) days prior to mating. For both generations, treatment continued through the mating period until termination and included gestation and lactation periods for females. There was clear evidence of parental effects in 20,000-ppm animals, including significantly decreased body weights (F_1 males and females), significantly decreased body weight during gestation and lactation (F_1 females), and significantly decreased mean food consumption (F_1 males and females). Additionally, 20,000-ppm F_1 dams exhibited a significant decrease in the number born and in live litter size on Day 1 *post partum* as well as a nonsignificant decrease in litter size on Day 4 *post partum* and a nonsignificant decrease in the mean number of implantation sites. Other treatment-related observations for both generations included darkened or discolored pancreas (20,000- and 5000-ppm males and females), darkened mesenteric lymph nodes (20,000- and 5000-ppm males and females), and darkened thymus (20,000-ppm females and 5000-ppm F_0 females only). These pigmentation alterations were reportedly caused from the silver salt found in the test material and were of no toxicological significance. **Therefore, the NOAEL for parental toxicity is 5000 ppm, and the LOAEL for parental toxicity is 20,000 ppm (based on decreased body weights, during maturation, decreased body weights during gestation and lactation, decreased food consumption, decreased number born, and decreased live litter size).** There was clear evidence of offspring effects in 20,000-ppm animals including significant decrease in litter weight (F_1 dose group) and significant decrease in pup weight (F_1 and F_2 dose group). **Therefore, the offspring toxicity NOAEL is 5000 ppm and the offspring toxicity LOAEL is 20,000 ppm (based on decreased pup and litter weights).**

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This reproductive toxicity study in the rat is classified acceptable. Minor study design and/or reporting deficiencies (see Section F) are not considered to have affected the study findings.

COMPLIANCE: A signed and dated Compliance Statement is included in the study (p. 3). According to this statement, the study was conducted according to Good Laboratory Practice (GLP) guidelines of the Organization for Economic Cooperation and Development (revised 1997, ENV/MC/CHEM [98]17) and Directives 87/18EEC (as amended by Directive 1999/11/EC) and 88/320/EEC; therefore, the study is acceptable under the GLPs of US Environmental Protection Agency (40 CFR Part 160 and 792), US Food and Drug Administration (21 CFR Part 58), Japanese Ministry of Agriculture, Forest and Fisheries (11 NohSan No. 6283, October 1999), Japanese Ministry of Health and Welfare (Notification No 313), and Japanese Ministry of International Trade and Industry (Chemical Substance Control Law, Kanpogyo No. 39 Environmental Agency, Kikyoku No. 85). A signed and dated Quality Assurance Statement is included in the study (p. 9). According to the statement, the study protocol, draft, and final report were audited. Further inspections were performed on the following: animal and test material preparation, dosing procedures, parental and litter observations, pairing, mating, smearing, sperm assessment, *post mortem* evaluation, and chemical analysis. Inspections were documented, and findings were reported promptly to management. A Statement of No Data Confidentiality Claims also is included (p. 2), as well as a Flagging Statement (p. 4).

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Experimental Additive Number 9823-37
   Description: white powder
   Supplier: not provided
   Batch #: 7100510
   Purity: not provided; reportedly the responsibility of the Sponsor
   CAS #: not provided
   Storage Conditions: at ambient temperature and humidity in the dark
   Stability: not provided; reportedly the responsibility of the Sponsor

2. Vehicle: administered as a dietary admixture

3. Test Animals: rat
   Strain: Sprague-Dawley Crl:CD® IGS BR
   Source: Charles River (UK) Limited (Margate, Kent)
   Age on arrival: not provided
   Weight on arrival: not provided[1]
   Age at mating: not provided
   Weight at mating: not provided
   Housing: Prior to mating, housed 4/cage in polypropylene cages with stainless steel grid tops and bottoms that were suspended above paper-lined polypropylene trays. After mating, males were returned to group housing, and females were individually housed in

[1] Weight at start of treatment was 150-232 g (F_0 males) and 137-183 g (F_0 females).

polycarbonate cages with solid bottoms and stainless steel tops. Mated females were provided softwood chips as bedding during gestation and lactation.
Acclimation period: 14 days
Diet: powdered diet VRF1-C (supplied by Charles River [UK] Limited, Margate, Kent) available *ad libitum*; reportedly contained no contaminants known to interfere with study
Water: tap water available from polypropylene bottles *ad libitum*; reportedly contained no contaminants known to interfere with study
Environmental conditions:[2]
Temperature: 21±2°C (target range)
Humidity: 55±15% (target range)
Air changes: 15/hour
Photoperiod: 12 hours dark/12 hours light

B. PROCEDURES AND STUDY DESIGN

1. In Life Dates
Start: February 20, 2001
End: October 25, 2001

2. Animal Assignment
Healthy F_0 males and females were randomized into 4 treatment groups (as shown in Table 1) through a randomization procedure designed to minimize variations in body weights. Offspring from the F_0 animals were designated F_1, and at Day 4 *post partum*, litters were standardized to 4/sex where possible using random number tables. For litters with unequal sex distribution, the litters were still standardized to a total of 8 pups; however, the number of males and females were unequal. Litters with 8 or less total pups at Day 4 *post partum* were not standardized. F_1 pups were weaned on Day 21 *post partum* and treatment groups (totaling 24 animals/sex/group) were formed. The F_1 males and females were reared to maturity and mated to produce the F_2 generation.

TABLE 1. Animal Assignment

Test Group	Dose (ppm)	Number Assigned per Group			
		F_0 Males	F_0 Females	F_1 Males	F_1 Females
1	0 (control)	1-28	113-140	225-248	321-344
2	1000	29-56	141-168	249-272	345-368
3	5000	57-84	169-196	273-296	369-392
4	20,000	85-112	197-224	279-320, 417	393-416

[2] Occasional, minor variations in temperature and humidity reportedly occurred; these changes were not considered to have affected the integrity of the study.

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3. Dose Selection Rationale
The dose selection was based on a previous 90-day repeat dose study in rats (Safepharm Laboratories Project Number 656/043). No details of this study were provided.

4. Dosage Preparation and Analysis
Treated diets were prepared weekly, with each dose level prepared as a separate mixture. For each dose level; the appropriate amount of test material was weighed and added to a pre-weighed sample of diet, which was then mixed using a Hobart QE200 mixer. The pre-mix was then transferred to a Hobart H800 mixer and mixed again after additional diet was added as needed to achieve the correct final dietary concentration.

Each formulation was sampled once per week during the first four weeks and approximately once every month until study completion. Samples were analyzed for achieved concentration via atomic absorption spectroscopy. Homogeneity was evaluated by analyzing dietary admixtures from the middle and two opposite sides of the sample flasks in triplicate. Stability was evaluated by determining the initial concentration and comparing it to the concentration after the compound was store for 14 days in the dark at room temperature.

Results

Homogeneity Analysis: Homogeneity results are presented in Table 2 below. The values appear consistent; however, our reviewers could not definitively evaluate homogeneity because the coefficient of variation was not provided.

TABLE 2. Admixture Analysis

Nominal Concentration (ppm)	Sampling Location	Concentration Found (ppm)			
		1	2	3	Mean
1000	Side	809	742	824	792
	Middle	826	818	826	823
	Side	849	829	874	851
5000	Side	4492	4681	5011	4728
	Middle	4492	4653	4738	4628
	Side	4626	4571	4803	4667
20,000	Side	25441	26712	27530	26561
	Middle	25591	26138	27257	26329
	Side	26448	29297	27204	27650

[a]Data extracted from Appendix 35, p. 742.

Stability Analysis: The samples were stable over a 14-day period (see results presented in Table 3 below).

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TABLE 3. Stability Analysis[a]

Nominal Concentration (ppm)	Concentration Found Initially (ppm)	Concentration Found After Storage for 14 Days	
		(ppm)	(expressed as % of initial)
1000	893	822	92
5000	4669	4674	100
20,000	23022	26846	117

[a]Data extracted from Appendix 35, p. 743.

Concentration Analysis: Table 4 (see Appendix I of this DER) summarizes the concentration analysis results. The analytical data indicate that test article concentrations were within ±16% of the nominal target concentrations (range 84-110%). Although this range falls outside that which is normally accepted (±10%), our reviewers do not believe this adversely affected the study results.

5. Dosage Administration

All doses were administered through treated diets. F_0 males and females were exposed to the test article for 75 days prior to mating. Treatment continued through the mating period until termination and included gestation and lactation periods for females. F_1 males and females were exposed to the test article for 76 days prior to mating. As with the F_0 animals, treatment continued through the mating period until termination and included gestation and lactation periods for females. Chemical intake was calculated weekly during the maturation periods of the F_0 and F_1 generations as follows:

$$\text{Chemical intake} = \frac{\text{Dose Level (ppm) X Group Mean Food Consumption (g/animal/day)}}{\text{Group Mean Body weight for Week}}$$

6. Mating

F_0 and F_1 females were mated with designated males from the same group until evidence of mating was obtained (ejected copulation plug, copulation plug in the vagina, or presence of sperm in vaginal smear) or for a maximum of 21 days. It was not reported whether sibling matings were avoided.

7. Culling

On day 4 *post-partum*, F_0 and F_1 litters with >8 pups were standardized to four/sex/litter.

C. OBSERVATIONS

1. Parental Animals

Signs of clinical toxicity were recorded daily. Mortality and morbidity were assessed twice daily during the working week and once daily on weekends and public holidays. Body weights were recorded weekly during the maturation and mating periods. After mating, males were weighed weekly until termination; females that showed evidence of mating were weighed on gestation days (gd) 1, 4, 7, 14, and 21. Body weights for females delivering live litters were recorded on Days 1, 4, 7, 14 and 21 *post partum*. Food consumption for each cage was recorded weekly during the maturation periods for males and females and during the post-mating period for males only. Food consumption for females showing evidence of

mating was recorded on gd 1 to 7, 7 to 14, and 14 to 21. Food consumption for females with live litters was recorded on Days 1 to 7, 7 to 14, and 14 to 21 *post partum*.

The estrous stage of all F_0 and F_1 females was determined by examining daily vaginal lavage samples (three weeks prior to mating); samples were stained with Giemsa. Examinations continued until there was positive evidence of mating. Additionally, during the work week, females were observed at 8:30, 12:30, and 4:30 hours each day at or around the day of expected parturition so that date of mating, date and time of observed parturition, and date and time of observed completion of parturition could be recorded. Similar observations were recorded during the weekends at the hours of 8:30 and 12:30.

All abnormalities were preserved for possible future study. Animals found dead during the course of the study were examined macroscopically. Animals that survived until scheduled necropsy (including non-fertile animals) were anesthetized with CO_2 followed by cervical dislocation. Animals were then were examined macroscopically for internal and external abnormalities. The italicized organs and tissues listed below were preserved in fixative; bolded organs listed below were weighed. Preserved tissues from high-dose and control animals, target organs from low- and mid-dose animals, and significantly abnormal tissues from decedents were subjected to histopathology examination by Precision Histology International Limited. Organs and tissues were dehydrated in alcohol and embedded in paraffin wax. Sections cut at approximately 5 µm thickness were stained with hematoxylin and eosin. Prepared sections were then evaluated microscopically by a pathologist. For F_1 females, uteri were stained with 10% ammonium polysulphide solution, and the number of implantation sites were recorded prior to preservation.

- ***Adrenals***
- **Brain**
- **Epididymides (*right epididymis*)**
- **Kidneys**
- **Left cauda epididymis**
- **Liver**
- ***Ovaries***
- *Pancreas and mesenteric lymph nodes (target organs)*[3]
- ***Pituitary gland***
- ***Prostate***
- ***Seminal vesicles (with coagulating gland)***
- *Significant lesions*
- **Spleen**
- **Testes (*right testis*)**
- **Thymus**
- ***Uterus* (*with cervix and oviducts*)**
- *Vagina*

At the time of scheduled necropsy, F_0 and F_1 males were evaluated for sperm concentration, motility, and morphology. Descriptions of the sperm motility characteristics and morphology

[3] The pancrease and mesentric lymph nodes were note preserved for a small number of F_0 females from each dose group due to technical error. These females are identified in Appendix 31of the study report.

assessments are provided in Table 5 below. Sperm samples were collected by removing the left testis and epididymis. The tunica albuginea was removed from the testis, and the testicular tissue was frozen until needed. Thawed testicular tissue was homogenized in appropriate saline/detergent mixture and was stained with a DNA-specific fluorescent stain. A sub-sample of the homogenate was analyzed to determine the number of homogenization-resistant spermatids. A sample of luminal fluid collected following the incision of the distal region of the epididymis was transferred to a buffer solution for assessment of sperm motility and morphology. A minimum of 200 individual sperm were analyzed; the number of motile, progressively motile, and non-motile sperm were assessed via an automated semen analyzer. The characteristics of the motile sperm were determined via a computer-assisted sperm analyzer. A morphometric analysis of sampled sperm was performed using the RAT Metrix program after a DNA-specific fluorescent stain was used on a sample of semen, and a sub-sample was placed on a glass slide with a cover slip. The cauda epididymis was separated from the body of the epididymis, weighed, and frozen until needed. When thawed, the cauda epididymis was re-weighed, homogenized in the appropriate saline/detergent mixture, and samples were stained with a DNA-specific fluorescent stain.

TABLE 5. Sperm Motility Characteristics and Morphology Assessments

Sperm Motility Characteristics	Sperm Morphology Assessments
Concentration - based on the number of motile and non-motile cells identified	Chord length - the straight line distance measured from the base of the head to the tip of the hook
Motility - the ratio of recorded motile cells to the total concentration	Arc length - the length measured along the curve of the sperm head from the base to the tip of the hook
Progressive Velocity (VSL) - the straight line distance between the beginning and end of the tract divided by time elapsed	Area - the total head area viewed under fluorescent illumination
Tackspeed (VSL) - the total distance between each Center of Brightness of the sperm head (CB) position for a given cell during image acquisition	Linearity - ratio of Chord length to Arc length
Path Velocity (VAP) - the smoothed averaged position of the CB and gives an average cell path velocity	
Straightness (Str) - the departure of a cell path from a straight line	
Linearity (LIN) - the departure of a cell track from a straight line	
Amplitude of lateral head displacement (ALH) - the mean width of the head oscillation as the cell swims	

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Sperm Motility Characteristics	Sperm Morphology Assessments
Beat cross frequency (BCF) - the frequency with which the cell track crosses the cell path in either direction.	

The number of oocytes also was evaluated by collecting the ovaries of 10 selected control and high-dose F_1 females. Slides (5/female) were prepared by serial sectioning of the tissue and selection of every tenth section for mounting on a glass slide. Slides were stained with hematoxylin and eosin, and sections of ovary from selected females were examined microscopically. Selected ovary sections also were examined for visible oocytes, which were identified and classified as small follicles (S), medium follicles (G), and large follicles (A).[4]

2. Offspring

The following data were recorded for each litter. Additionally, the subsequent date and time of Day 1 *post partum* litter observations were standardized as shown in Tables 6 and 7.

- Pup viability (alive, dead) at completion of parturition
- Number of offspring (up to weaning) on Days 1, 4, 7, 14, and 21 *post partum*
- Individual pup body weight on Days 1, 4, 7, 14, and 21 *post partum*
- Sex determination on Days 1 and 21 *post partum*
- Clinical condition of pups (measured daily)
- Individual pup surface righting reflex (ability to turn over to a normal resting position when placed on their back on a flat surface) on Day 1 *post partum*
- Individual pup mid-air righting reflex (ability to turn body to a normal upright position, in mid-air, when dropped from a standard height above a bed of saw dust) on Day 17 *post partum*
- Individual pup startle reflex (assessment of auditory function by reaction to short auditory stimulus) on Day 21 *post partum*
- Individual pup pupil reflex (assessment to light shone in each eye) on Day 21 *post partum*

All live pups were monitored for the following developmental endpoints:

- detachment of pinna (as noted by the separation of the edges and subsequent unfolding of both pinnae);
- tooth eruption (as noted by the eruption of the upper incisors through gum);
- eye opening (as noted by the separation of the upper and lower eyelids of both eyes).

All F_1 pups selected to be F_1 mating adults also were monitored for sexual development. For females, sexual development was recorded as the day of vaginal opening. For males, sexual development was recorded at the day of separation of the prepuce from the *glans penis*.

[4] Small follicles were defined as the range from a single oocyte to an oocyte with an associated layer of granulosa cells. Medium follicles were defined as the range from oocytes with more than a single layer of granulosa cells to oocytes with multiple layers of granulosa cells. Large follicles were defined as the range from oocytes with microcavitation representing the early follicular antrum to Graafian follicles.

TABLE 6. Day 1 Observations - Weekdays

Littering complete	8:30 hours	12:30 hours	16:30 hours
Day 1 litter observations performed	16:30 hours same day	8:30 hours next day	12:30 hours next day

TABLE 7. Day 1 Observations - Weekends/Public Holidays

Littering started	Overnight	12:30 hours
Littering complete	8:30 hours	16:30 hours same day assumed
Day 1 litter observation performed	12:30 hours same day	12:30 hours next day

All F_1 pups not selected to be F_1 mating adults and all F_2 pups alive at weaning were anesthetized with CO_2 followed by cervical dislocation. Pups were then examined macroscopically for internal and external abnormalities; pups that died or were sacrificed *in extremis* were similarly examined macroscopically, both internally and externally. From one male and one female pup per litter (randomly selected), the brain, spleen, and thymus were weighed.

D. DATA ANALYSIS

1. Statistical Analyses

Table 8 summarizes the parameters evaluated and the method used to determine their statistical significance. Statistical analysis was not performed on body weight gain.

TABLE 8. Statistical Analyses

Parameter	**Statistical Method**
Adult male body weight; adult female body weight during maturation; gestation and lactation periods; adult male food consumption; adult female food consumption during maturation; gestation; and lactation; litter size; litter weight; individual pup body weight; pup landmarks of physical development; adult absolute organ weights; sperm motility; morphological characteristics; and homogenization-resistant spermatid counts; sexual development of F_1 pups	• Levene's test followed by one-way analysis of variance to establish homogeneity • Dunnett's T3 Multiple Comparison Method for unequal variances • Dunnett's Multiple Comparison Method for equal variances

Parameter	Statistical Method
Adult pre-coital intervals; female gestation lengths; pup reflexological responses; litter sex ratios; and adult organ weights relative to body weight	• Kruskal-Wallis Nonparametric Rank Sum test on individual values • Mann-Whitney "U" test for pairwise comparison of control values vs. treated group values where significant differences were observed
Pregnancy and parturition indices	• Chi-squared analysis
Histopathology findings	• Histopathology computer program LABCAT version HP4.33

2. Indices

The following indices were calculated:

- Mating index (percentage of animals that mated) was calculated for both males and females in each dose group and was defined as: [number of animals mated/number of animals paired] X 100.
- Pregnancy index (percentage of pregnancies) was calculated for females in each dose group and was defined as: [number of pregnant females/number of animals mated] X 100.
- Parturition index (percentage of pregnant females with live pups) was calculated for each group and was defined as: [number of females delivering live pups/number of pregnant females] X 100.
- Live birth index was calculated as: [number of pups alive on Day 1/number of pups born] X 100.
- Viability index 1 was calculated as: [number of pups alive on Day 4 before culling/number of pups alive on Day 1] X 100.
- Viability index 2 was calculated as: [number of pups alive on Day 7/number of pups alive on Day 4 after culling] X 100.
- Viability index 3 was calculated as: [number of pups alive on Day 14/number of pups alive on Day 7] X 100.
- Viability index 4 was calculated as: [number of pups alive on Day 21/number of pups alive on Day 14] X 100.
- Viability index 5 was calculated as: [number of viable pups at weaning/number of pups on day 4 after culling].
- Sex ratio was calculated as: [number of male pups/number of pups of determined sex] X 100.

3. Historical Control Data

Historical control data for pre-coital intervals and offspring thymus weights are provided in Appendix 39 of the study report. No other historical control data are provided.

II. RESULTS

A. PARENTAL TOXICITY

All summary tables for parental toxicity are presented in Appendix I of this report.

1. Mortality and Clinical Observations

In F_0 animals, there were no treatment-related deaths that occurred during the study; however, one 1000-ppm female (number 165) was sacrificed *in extremis* during pregnancy due to possible dystocia. According to the study authors, there were no previous signs of clinical toxicity observed. Additionally, 2 control females (number 120 and 126) were found dead prior to necropsy. Dam number 120 showed the following clinical signs of toxicity: swollen hind limb, hunched posture, piloerection, staining around the snout, dehydration, and increase respiration. Dam number 126 died without any signs of clinical toxicity. The examination performed *post mortem* showed a fetus present in the vaginal lumen and other dead offspring *in utero* indicating possible dystocia. *Post mortem* macroscopic and microscopic findings for the F_0 generation are discussed further in Section 8, Gross Pathology, and Section 9, Histopathology. There were no significant, treatment-related signs of clinical toxicity in any other F_0 animals. At 20,000 ppm, there was a slight increase in the incidence of fur loss in males and females; however, this observation was not considered treatment-related since the location, time of appearance, and duration are not consistent.

In F_1 animals, two 20,000-ppm males (number 313 and its replacement, number 417) were found dead prior to study termination; however, there were no clinical signs of toxicity observed, and both animals were found cannibalized. Another 20,000-ppm male (number 308), showing full-body convulsions, was found dead prior to study termination. One high-dose male (number 305) was sacrificed *in extremis*, and the following clinical abnormalities were observed: tip of tail necrotic, tip of tail missing, swollen and cut lip, hunched posture, piloerection, emaciation, pallor of the extremities, and bleeding from mouth. Two high-dose females (numbers 398 and 401) also were sacrificed *in extremis*. Dam 398 was sacrificed due to suspected dystocia which was confirmed via *post mortem* evaluation, which revealed the presence of offspring *in utero*. Dam 401 showed signs of ataxia, hunched posture, emaciation, and dehydration. Macroscopic and microscopic findings for the F_1 generation are further discussed in Section 8, Gross Pathology, and Section 9, Histopathology. There were no significant, treatment-related signs of clinical toxicity in any other F_1 animals.

2. Body Weight

Male and female body weight and body weight change data are summarized in Tables 9-18 of the Appendix of this report. In F_0 animals, there were no significant changes in mean body weight or in mean body weight gain throughout the recorded periods for all treatment groups.

In 20,000-ppm F_1 males, body weight was consistently lower than the control group throughout the study; the difference was statistically-significant during study weeks 21 through 24 and 26 through 34. At 1000 and 5000 ppm, male body weights were generally comparable to controls; a significant increase in mean body weight for the 1000-ppm dose group during week 34 was not considered biologically significant. As with the males, high-dose F_1 females exhibited a consistently lower body weight than the control group throughout the study, with a significant decrease during study weeks 19 and 20. According to the study author, the significant decrease observed during the first week of observation (week 19) may

have been the result of lower mean offspring weights at Day 21 of weaning. Our reviewers agree that these two observations may be related; however, there is no evidence of a cause/effect relationship. High-dose F_1 females also exhibited consistently lower body weights during gestation and lactation than controls, with significant reductions observed during gd 4, 7, and 14 and lactation days 1, 4, 7, 14, and 21. There were no significant changes in mean body weight observed in females administered 1000- or 5000-ppm test material. There were no significant changes in mean body weight gain for either F_1 males or females.

3. Food Consumption

Male and female food consumption data are summarized in Tables 19-24 of the Appendix of this report. In F_0 animals, there were no significant changes in mean food consumption throughout the recorded periods for all treatment groups.

In 20,000-ppm F_1 males, food consumption was consistently lower than the control group throughout the study; the difference was statistically-significant during study weeks 22, 31, 33, and 34. At 1000 and 5000 ppm, there were no significant, treatment-related differences in F_1 male food consumption value; a significant increase in food consumption for the 1000-ppm males at week 26 was not considered biologically significant. High-dose F_1 females exhibited a significant increase in food consumption during study weeks 22 and 23 which was not considered biologically significant. High-dose F_1 females exhibited decreased food consumption during gestation and lactation, with reductions reaching significance on Days 1-7 and 7-14 *post coitum* and Days 1-7 *post partum*. There were no significant, treatment-related changes in F_1 female food consumption values at 1000 or 5000 ppm.

Male and female food conversion ratio data are summarized in Tables 25-26 of the Appendix of this report.. In F_0 and F_1 male and female animals, food conversion ratios were comparable among treated and control animals at all measurements.

Male and female test material intake data are summarized in Tables 27-28 of the Appendix of this report. F_1 animals had an overall higher test material intake than F_0 animals. This increase occurred because F_1 animal dosing was initiated at an earlier age, which according to the study author, was a more pronounced growth phase and resulted in a increase in food consumption in relation to body weight.

4. Estrous Cycling Evaluation

There were no treatment-related effects on estrous cycling for F_0 and F_1 females at any dose level. There were no significant differences in the populations of the various stages of oocyte development for selected 20,000-ppm females when compared to controls; consequently, the extension of the evaluation was considered unnecessary.

5. Mating, Fertility, and Reproduction

Data on mating fertility, and reproduction are summarized in Tables 29-30 of the Appendix of this report. There were no treatment-related effects observed in the mating and fertility indices and gestation length for both generations. According to the study report, the majority of F_0 mating pairs showed evidence of mating within the first four days of pairing. In F_1 animals, there reportedly was a small increase in the proportion of 20,000-ppm animals with

a pre-coital interval of 5 or more days; however, this increase did not affect the overall fertility rate of this group.

The mean number of implantation sites was not provided for F_0 animals, and there were no significant differences between the number born when treatment groups were compared to the control group. In F_1 dams, there were no treatment-related effects observed on the mean number of implantation sites at any dose level; however, a slight, nonsignificant decrease in the mean number of implantation sites at 20,000 ppm was observed. Additionally at 20,000 ppm, there was a significant decrease in the number born and in the litter size at Day 1 *post partum* and a nonsignificant decrease in litter size on Day 4 *post partum*. There were no treatment-related effects in litter size observed in the 1000- or 5000-ppm dose groups.

6. Sperm Analysis

Data from the sperm analysis are summarized in Tables 31-32 of the Appendix of this report. There were no treatment-related effects on any sperm parameters at necropsy for F_0 or F_1 males, including motility, morphology, and testicular and epididymal sperm count. Statistically-significant differences in sperm motility (decreased lateral amplitude and increased straightness) observed in 20,000-ppm F_0 males were not considered treatment-related by the study author (reason not provided). Additionally, statistically-significant differences in sperm morphology (head area) observed in 5000- and 20,000-ppm F_1 males were not considered treatment-related by the study author due to the lack of a dose response. Our reviewers agree that these statistically-significant changes appear to be incidental.

7. Organ Weight

Organ weight data are summarized in Tables 33-35 of the Appendix of this report. In F_0 males, there were significant changes in absolute or relative organ weight observed at all dose levels. At 20,000 ppm, significant decreases in absolute mean thymus and seminal vesicles and coagulating gland (SVCG) weights were observed. Additionally at 20,000 ppm, a significant increase in relative mean spleen weight was observed. At 5000 ppm, males also exhibited an increase in relative mean spleen weight and a decrease in absolute SVCG weight. At 1000 ppm, a significant decrease was observed in only the absolute mean right epididymis weight. In F_0 females, a significant decrease in absolute mean brain weight at 5000 ppm was the only alteration in organ weight observed. According to the study author, none of these organ weight changes in F_0 males or females were toxicologically significant due to the lack of corresponding histopathological changes.

In F_1 males, there were significant changes in absolute or relative organ weight observed at all dose levels. At 20,000 ppm, significant decreases in mean adrenals, absolute kidneys, prostate, SVCG, and right testis weights were observed. Additionally, significant increases in relative mean brain, left and right epididymis, and left testis, and a significant decrease in relative mean prostate weight were observed at 20,000 ppm. At 5000 ppm, a significant increase in absolute and relative mean thymus weight was observed, as well as a significant decrease in relative kidney weight and a significant increase in absolute mean left epididymis weight. At 1000 ppm, F_1 males exhibited a significant decrease in relative mean brain weight. In 20,000-ppm F_1 females, a significant decrease in absolute and relative mean uterine weight was observed. According to the study author, none of these organ weight changes in F_1 males or females were toxicologically significant due to the lack of corresponding histopathological changes.

8. Gross Pathology

Gross pathological findings are summarized in Tables 36-37 of the Appendix of this report. In F_0 animals, one 1000-ppm female (number 165) was sacrificed *in extremis* during pregnancy due to possible dystocia and an additional 2 control females (numbers 120 and 126) were found dead prior to necropsy. At *post mortem*, dam number 165 showed external pallor, blood from the vagina, one dead offspring *in utero*, and slightly thickened gastric mucosa in the stomach. Dam number 120 showed adrenal and splenic enlargement with possible bile stain mucus of the intestines and red foci on the surface of the lungs. Dam number 126 died without any signs of clinical toxicity; however, the examination performed at *post mortem* showed a fetus present in the vaginal lumen and other dead offspring *in utero* indicating possible dystocia.

In F_1 animals, two 20,000-ppm males (number 313 and its replacement, number 417) were found dead prior to study termination; however, both animals were found without macroscopic abnormalities. Another 20,000-ppm male (number 308), also was found dead prior to study termination, and macroscopic findings included a darkened pancreas. One high-dose male was sacrificed *in extremis* (number 305), and macroscopic findings included the following: small and flaccid prostate, small seminal vesicles and coagulating gland, darkened pancreas, darkened mesenteric lymph nodes, gaseous and distended cecum, and darkened fluid contents in the intestines. Two high-dose females (numbers 398 and 401) also were sacrificed *in extremis*. Dam 398 was sacrificed due to suspected dystocia, which was confirmed when the *post mortem* examination revealed the presence of offspring *in utero*. Additionally, macroscopic findings included minimal blood staining around the vagina and darkened (green) pancreas and mesenteric lymph nodes. Dam 401 showed the following macroscopic findings: staining around the anus and mouth, darkened pancreas, slightly thickened non-glandular region of the stomach, slightly distended duodenum with discolored contents, and liquified contents and bile-stained cecum.

The majority of 20,000-ppm F_0 and F_1 animals surviving to terminal sacrifice exhibited a darkened or discolored pancreas. There also was an increased incidence of darkened mesenteric lymph nodes in F_0 females and F_1 males and females, with the F_1 generation exhibiting a greater incidence. Both of these effects were considered to be treatment-related. A low incidence of darkening of the thymus also occurred in 20,000-ppm F_1 females, which may have been treatment-related according to the study author. Our reviewers note that 20,000-ppm F_0 females also exhibited a low incidence of thymus darkening and believe that this effect is treatment-related.

At 5000 ppm, there again were increases in the incidences of darkened or discolored pancreas and darkened mesenteric lymph nodes that affected both the F_0 and F_1 generation; however, these incidence rates were less than those observed at 20,000 ppm. Our reviewers further note that the incidence of darkened mesenteric lymph nodes is greater in 5000-ppm females than males. According to the study author, there also were isolated occurrences of darkened thymus, which were considered treatment-related. Our reviewers agree; however we also note that the incidents only occurred in F_0 females at this dose.

At 1000 ppm, there were no significant, treatment-related effects observed in males or females of either generation. Although treatment-related macroscopic alterations were observed at 5000 and 20,000 ppm, the study author did not consider them to have

toxicological significance due to the lack of associated histopathological changes. Our reviewers disagree based on the histopathology findings (see Section 9). All other macroscopic findings were considered incidental by the study author because the frequency and nature of the findings were unrelated to the dose level.

9. Histopathology

Histopathology finding are summarized in Tables 38-39 of the Appendix of this report. At 20,000 and 5000 ppm, pigmented macrophages largely in sinuses of the mesenteric lymph nodes and diffuse pigmented macrophages of the pancreas were found in both F_0 and F_1 males and females and were considered treatment-related. According to the study report, discussion with the Sponsor's Monitoring Scientist confirmed that these alterations were caused from the silver salt found in the test material and were of no toxicological significance. Our reviewers cannot evaluate the validity of the statement because no further details or supporting information are provided. At 1000 ppm, there were no significant histopathology findings.

B. OFFSPRING TOXICITY

All summary tables for offspring toxicity are presented in Appendix I of this report.

1. Mortality, Viability, and Clinical Observations

Data on offspring mortality and viability are summarized in Tables 29-30 of the Appendix of this report. There were no significant effects on the live birth index or viability indices for any F_1 and F_2 offspring at any dose level. There were no significant differences observed in the sex ratio for F_1 offspring. In F_2 offspring, there was a significant decrease in the percent of males per litter at Day 1 *post partum* in the 1000-ppm dose group; the study author did not consider this decrease treatment-related.

There were no significant findings with regard to the mean landmarks of offspring development (pinna unfolding, tooth eruption, and eye opening) for F_1 or F_2 pups. Additionally, there were no treatment-related alterations in offspring reflexological responses for either F_1 or F_2 pups. At 20,000 ppm, there was a statistically-significant ($p<0.01$) increase in the proportion of F_1 pups successfully completing the surface righting reflex; however, the study author did not consider this treatment-related.[5]

2. Body Weights

Pup and litter weights are summarized in Tables 29-30 of this report. At 20,000 ppm, F_1 pup weights were generally comparable to the controls; however, a statistically-significant decrease in mean pup and litter weight was observed on Day 21 *post partum*. According to the study author, these decreases may be treatment-related since pups would have been exposed to the test material. A statistically-significant increase in mean litter weight observed on Day 4 *post partum* was considered unremarkable by the study author. At 5000 and 1000 ppm, F_1 pup and litter weights were generally comparable to the controls. The statistically-significant decrease in mean pup weight observed at 5000 ppm on Day 1 *post*

[5] Table 24, page 119, appears to be incorrectly labeled. The table title reads "Group Summary Offspring Reflexological Responses a) F_0-F_1 Generation." Our reviewers believe that these data are actually for the F_1-F_2 generation.

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partum was considered by the study author to be nontreatment-related. Due to the absence of a dose-response relationship, our reviewers agree.

At 20,000 ppm, F_2 pup weight was significantly reduced at Day 21 *post partum*; litter weight also was decreased but did not reach statistical significance. According to the study author, this decrease may be treatment-related since pups would have been exposed to the test material. Although not discussed by the study author, 20,000-ppm pups also exhibited a reduction in mean litter weight on Day 1 *post partum*; our reviewers do not believe that this reduction is treatment-related since litter weights were comparable to controls for the remainder of the study. At 5000 and 1000 ppm, F_2 litter and pup weights were generally comparable to controls; although a slight decrease at 5000 ppm in mean pup weight was observed on Day 21 *post partum*, this value did not reach statistical significance.

3. Sexual Maturation
There were no significant, treatment-related effects on the age of sexual maturation for any F_1 male or female at any dose level.

4. Organ Weights
Organ weight data are summarized in Table 40 of this report. In F_1 and F_2 offspring, brain and spleen weights were comparable to controls at all dose levels. At 20,000 ppm, significant, treatment-related decreases in mean thymus weights were observed in F_1 and F_2 males and females. At 5000 ppm, a significant decrease in mean thymus weight was observed in F_1 males and F_2 females. The study author noted that these decreases at 5000-ppm do not fall outside of historical control data and are not considered unusual. Our reviewers agree with the study author's assessment with respect to female thymus weight; however, F_1 male 5000-ppm thymus weight is below the mean historical values provided (only when standard deviations were taken into account did F_1 male 5000-ppm thymus weight fall within the historical control values). Nevertheless, this finding was not supported by any macroscopic alteration of the thymus.

5. Gross Pathology
There were no significant, treatment-related macroscopic findings for offspring that died during the course of lactation or for those that were examined at termination.

III. DISCUSSION

A. INVESTIGATOR'S CONCLUSIONS

1. Parental Toxicity
The study author concluded that there was clear evidence that exposure to Experimental Additive Number 9823-37 via diet had parental effects at doses of 20,000 and 5000 ppm in F_0 and F_1 animals. According to the authors, doses of 20,000 ppm caused significantly decreased body weights (F_1 males and females), significantly decreased body weight during gestation and lactation (F_1 females), and significantly decreased mean food consumption (F_1 males and females). Additionally, F_1 animals exhibited an overall higher test material intake than F_0 animals, which according to the study author, was the result of an earlier dosing initiation of F_1 animals. There were no treatment-related changes in the mating and fertility indices and gestation length for either generation; however, in 20,000-ppm F_1 dams there was

a significant decrease in the number born and in litter size on Day 1 *post partum* as well as a nonsignificant decrease in litter size on Day 4 *post partum* and a nonsignificant decrease in the mean number of implantation sites. According to the Discussion Section of the study report, the study author stated that this decrease is correlated to the slight toxicity observed in F_1 adults.

In F_0 males, statistically-significant decreases in absolute mean organ weight were observed for the thymus (20,000 ppm), SVCG (20,000 and 5000 ppm), and right epididymis (1000 ppm); statistically-significant increases in relative mean organ weight were observed for the spleen (20,000 and 5000 ppm). In F_0 females, a statistically-significant decrease in absolute mean brain weight at 5000 ppm was the only alteration in organ weight observed. F_1 males and females also exhibited the following alterations in organ weights: increased absolute mean adrenals (20,000-ppm males), thymus (5000-ppm males), and left epididymis (5000-ppm males) weights; increased relative mean brain (20,000-ppm males), thymus (5000-ppm males), left and right epididymis (20,000-ppm males), and left testis (20,000 ppm males) weights; decreased absolute mean kidneys (20,000-ppm males), prostate (20,000-ppm males), right testis (20,000-ppm males), and uterine (20,000-ppm females) weights; and decreased relative mean brain (1000-ppm males), kidneys (5000-ppm males), prostate (20,000-ppm males), SVCG (20,000 ppm males), and uterine (20,000-ppm females) weights. According to the study author, decreased absolute SVCG weights (20,000-ppm F_0 and F_1 males), decreased absolute and relative prostate weights (20,000-ppm F_1 males), and decreased absolute and relative uterine weights (20,000-ppm females) were not conclusively related to treatment because there was a lack of corresponding histological findings. The remaining significant alterations in organ weights also were not considered treatment-related due to the lack of corresponding histological changes. Gross pathology results showed that the majority of 20,000- and 5000-ppm F_0 and F_1 animals exhibited treatment-related darkened or discolored pancreas, as well as treatment-related darkened mesenteric lymph nodes. Additionally, according to the study author, 20,000-ppm F_1 females and 5000-ppm animals (generation and sex not specified by study author) exhibited an increase in the incidence of thymus darkening. This finding was considered treatment-related by the study author. At 20,000 and 5000 ppm, histologic examinations confirmed gross pathology findings, showing pigmented macrophages largely in the sinuses of the mesenteric lymph nodes and diffuse pigmented macrophages of the pancreas in both generations. These microscopic effects were considered treatment-related. According to the study report, discussions with the Sponsor's Monitoring Scientist confirmed that these alterations were caused from the silver salt found in the test material and were of no toxicological significance. Based on these findings, the study authors stated that the parental NOAEL was 5000 ppm (p.54).

2. Offspring Toxicity

The study authors concluded that there was clear evidence that the offspring of animals exposed to 20,000-ppm Experimental Additive Number 9823-37 exhibited toxicological effects. At 20,000 ppm, a statistically-significant decrease in F_1 mean litter weight and F_1 and F_2 mean pup weights were observed on Day 21 *post partum*. According to the study author, this decrease may be treatment-related since pups would have been exposed to the test material via diet. At 20,000 ppm, a significant decreases in mean thymus were observed in both generations (males and females). These reductions were considered treatment-related by the study author due to the pronounced effect. At 5000 ppm, a significant decrease in mean thymus weight was observed in F_1 males and F_2 females. The study author noted that

these decreases at 5000-ppm did not fall outside of historical control data and are not considered unusual. The authors stated that the offspring toxicity NOAEL was 5000 ppm (p. 54).

B. REVIEWERS' DISCUSSION

1. Parental Toxicity

Our reviewers agree that there was clear evidence that exposure to Experimental Additive Number 9823-37 via diet had parental effects at doses of 20,000 and 5000 ppm in F_0 and F_1 animals, including significantly decreased body weights during maturation (20,000-ppm F_1 males and females), significantly decreased body weight during gestation and lactation (20,000-ppm in F_1 females), and significantly decreased mean food consumption (20,000-ppm F_1 males and females). Our reviewers agree that there were no treatment-related changes in the mating and fertility indices and gestation length for either generation; however, in 20,000-ppm F_1 dams there was a significant decrease in the number born and in litter size on Day 1 *post partum* as well as a nonsignificant decrease in litter size on Day 4 *post partum* and a nonsignificant decrease in the mean number of implantation sites. Our reviewers agree that decreased absolute seminal vesicles and coagulating gland weights (20,000-ppm F_0 and F_1 males), decreased absolute and relative prostate weights (20,000-ppm F_1 males), and decrease absolute and relative uterine weights (20,000-ppm females) are of questionable significance due to the lack of corresponding histological findings. Our reviewers concur that the remaining significant alterations in organ weights also are not considered treatment-related due to the lack of corresponding histological changes. Our reviewers also observe that gross pathology results showed that the majority of 20,000- and 5000-ppm F_0 and F_1 animals exhibited a treatment-related darkened or discolored pancreas, as well as treatment-related darkened mesenteric lymph nodes. Our reviewers also observe a treatment-related increased incidence in thymus darkening in 20,000-ppm F_0 and F_1 females, as well as in 5000-ppm F_0 females. This differs slightly with the study author's assessment that 20,000-ppm F_1 females and 5000-ppm animals (generation and sex not specified by study author) exhibited an increase in the incidence of thymus darkening. Gross pathology findings were confirmed with histological results that showed treatment-related pigmented macrophages largely in sinuses of the mesenteric lymph nodes and diffuse pigmented macrophages of the pancreas in both F_0 and F_1 males and females. Our reviewers cannot fully assess the conclusions of the Sponsor's Monitoring Scientist, who indicated that these alterations were caused from the silver salt found in the test material and were of no toxicological significance. In general, however, our reviewers do not consider pigmentation changes an adverse effect. Based on the findings, our reviewers conclude that the NOAEL for parental effects from exposure to Experimental Additive Number 9823-37 is 5000 ppm, and the LOAEL is 20,000 ppm (based on decreased body weights during maturation, decreased body weights during gestation and lactation, decreased food consumption, decreased number born, and decreased live litter size).

2. Offspring Toxicity

Overall, our reviewers agree with the study author's conclusions regarding treatment-related effects on litters and pups. Like the study authors, our reviewers believe that there is clear evidence that the offspring of animals exposed to 20,000 ppm Experimental Additive Number 9823-37 exhibited toxicological effects. At 20,000 ppm, a statistically-significant decrease in F_1 mean litter weight and F_1 and F_2 mean pup weights were observed on Day 21

post partum. Although not discussed by the study author, 20,000-ppm pups also exhibited a reduction in mean pup weight on Day 1 *post partum*; our reviewers do not believe that this reduction is treatment-related since pup weights were comparable to controls for the remainder of the study. At 20,000 ppm, significant decreases in mean thymus weights were observed in both generations (males and females). Our reviewers agree that this effect was treatment-related; however, it is unclear if it is toxicologically significant due to the lack of corresponding macroscopic alterations. At 5000 ppm, a significant decrease in mean thymus weight was observed in F_1 males and F_2 females. Decreases at 5000-ppm did not fall outside of historical control data for F_2 females; however, the mean F_1 male 5000-ppm thymus weight is below the mean historical values provided (only when standard deviations were taken into account did F_1 male 5000-ppm thymus weight fall within the historical control values). Therefore, our reviewers consider the effect at 5000 ppm to be questionable. Based on the findings, our reviewers conclude that the NOAEL for litter and pup effects from exposure to Experimental Additive Number 9823-37 is 5000 ppm, and the LOAEL is 20,000 ppm (based on decreased body weights).

C. STUDY DEFICIENCIES

Some minor study design and reporting deficiencies identified by our reviewers are:

- The age of animals on arrival was not provided.
- The age and weight of the animals at mating was not provided.
- It was not reported whether sibling matings were avoided.
- The mean number of implantation sites was not provided for F_0 animals.
- Several mean values were calculated with a small number of total animals as the denominator. These values may have inaccurately reflected the outcome for the group as a whole.

These deficiencies are not considered by our reviewers to have affected the study outcome or interpretation of the study findings.

APPENDIX I

TABLE 4. Concentration Analysis[a]

Week	Nominal Concentration (ppm)	Sampling Location	Concentration Found		Mean	
			(ppm)	(expressed as % of nominal)	(ppm)	(expressed as % of nominal)
1	1000	Side Middle Side	872 862 862	87 86 86	865	87
	5000	Side Middle Side	4708 5334 5219	94 107 104	5087	102
	20,000	Side Middle Side	19790 15854 17621	99 79 88	17755	89
2	1000	Side Middle Side	886 884 881	89 88 88	884	88
	5000	Side Middle Side	4304 4321 4304	86 86 86	4310	86
	20,000	Side Middle Side	17975 18474 18511	90 92 93	18320	92
3	1000	Side Middle Side	917 912 964	92 91 96	931	93
	5000	Side Middle Side	4783 5515 5694	96 110 114	5331	107
	20,000	Side Middle Side	20900 20144 20104	105 101 101	20383	102

Week	Nominal Concentration (ppm)	Sampling Location	Concentration Found		Mean	
			(ppm)	(expressed as % of nominal)	(ppm)	(expressed as % of nominal)
4	1000	Side Middle Side	1020 985 962	102 99 96	989	99
	5000	Side Middle Side	5358 5271 4910	107 105 98	5180	104
	20,000	Side Middle Side	21836 22963 21354	109 115 107	22051	110
8	1000	Side Middle Side	1025 1107 1131	103 111 113	1088	109
	5000	Side Middle Side	4389 4586 4686	88 92 94	4554	91
	20,000	Side Middle Side	29681 20341 21915	148 102 110	21128	106
12	1000	Side Middle Side	890 876 907	89 88 91	891	89
	5000	Side Middle Side	5042 4884 4864	101 98 97	4930	99
	20,000	Side Middle Side	19946 19790 19717	100 99 99	19818	99

Week	Nominal Concentration (ppm)	Sampling Location	Concentration Found		Mean	
			(ppm)	(expressed as % of nominal)	(ppm)	(expressed as % of nominal)
17	1000	Side Middle Side	909 903 896	91 90 90	903	90
	5000	Side Middle Side	5160 5253 5263	103 105 105	5226	105
	20,000	Side Middle Side	20635 20718 21887	103 104 109	21080	105
21	1000	Side Middle Side	875 847 997	87 85 100	906	91
	5000	Side Middle Side	4513 4526 4526	90 91 91	4521	90
	20,000	Side Middle Side	19176 19839 19842	96 99 99	19619	98
26	1000	Side Middle Side	936 974 1002	94 97 100	971	97
	5000	Side Middle Side	5110 5349 5275	102 107 106	5245	105
	20,000	Side Middle Side	21872 21828 21828	109 109 109	21843	109

Week	Nominal Concentration (ppm)	Sampling Location	Concentration Found		Mean	
			(ppm)	(expressed as % of nominal)	(ppm)	(expressed as % of nominal)
30	1000	Side Middle Side	1006 998 929	101 100 93	978	98
	5000	Side Middle Side	4686 4771 4297	94 95 86	4585	92
	20,000	Side Middle Side	16189 18030 16221	81 90 81	16814	84
35	1000	Side Middle Side	881 902 813	88 90 81	866	87
	5000	Side Middle Side	4815 4699 4389	96 94 88	4635	93
	20,000	Side Middle Side	20005 20083 19811	100 100 99	19966	100

[a]Data extracted from Appendix 35, p. 743-746.

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TABLE 9. F_0 Male Mean Body Weight (g)[a]

Group (Concentration - ppm)		Week of Measurement												
		1	2	3	4	5	6	7	8	9	10	11	15	16
Group 1 (Control)	MEAN	198	265	317	366	410	446	470	494	513	532	545	589	604
	S.D.	17.1	19.7	29.4	30.6	34.0	38.3	41.4	45.4	50.6	52.1	53.3	56.7	59.9
	N	28	28	28	28	28	28	28	28	28	28	28	28	28
Group 2 (1000 ppm)	MEAN	202	268	310	358	404	444	466	488	514	533	549	588	609
	S.D.	15.2	20.5	34.0	34.7	33.7	36.5	38.5	41.7	42.0	46.7	49.4	59.0	63.8
	N	28	28	28	28	28	28	28	28	28	28	28	28	28
Group 3 (5000 ppm)	MEAN	205	265	320	365	405	436	460	480	498	519	529	570	583
	S.D.	13.5	22.7	27.4	28.5	30.1	33.6	37.2	41.3	43.6	45.0	47.6	49.5	52.0
	N	28	28	28	28	28	28	28	28	28	28	28	28	28
Group 4 (20,000 ppm)	MEAN	199	263	303	350	398	430	461	479	500	514	531	568	580
	S.D.	14.4	16.0	29.7	29.0	28.4	31.8	31.3	35.5	39.8	37.8	39.2	46.2	50.6
	N	28	28	28	28	28	28	28	28	28	28	28	28	28

[a]Data extracted from Table 4, p. 78.

TABLE 10. F_0 Female Mean Body Weight (g) Before Pairing[a]

Group (Concentration - ppm)		Week of Measurement										
		1	2	3	4	5	6	7	8	9	10	11
Group 1 (Control)	MEAN	159	186	208	227	244	256	264	272	281	287	290
	S.D.	10.5	12.3	18.4	17.1	18.0	20.0	20.4	22.6	21.9	22.7	23.3
	N	28	28	28	28	28	28	28	28	28	28	28
Group 2 (1000 ppm)	MEAN	160	188	212	230	246	257	268	277	285	290	294
	S.D.	10.8	12.3	14.3	16.6	19.0	18.8	20.5	21.9	21.3	23.4	22.6
	N	28	28	28	28	28	28	28	28	28	28	28
Group 3 (5000 ppm)	MEAN	160	189	211	228	243	254	264	273	281	289	293
	S.D.	8.4	8.8	10.5	12.0	12.3	13.3	12.6	15.0	14.2	13.2	15.9
	N	28	28	28	28	28	28	28	28	28	28	28
Group 4 (20,000 ppm)	MEAN	161	191	211	229	243	259	268	277	283	290	294
	S.D.	9.1	11.5	13.6	14.4	16.3	18.4	18.4	19.0	17.9	18.0	18.5
	N	28	28	28	28	28	28	28	28	28	28	28

[a]Data extracted from Table 5, p. 80.

TABLE 11. F_0 Female Mean Body Weight (g) During Gestation and Lactation[a]

Group (Concentration - ppm)		Day *Post Coitum*					Day *Post Partum*				
		1	4	7	14	21	1	4	7	14	21
Group 1 (Control)	MEAN	304	322	334	366	457	337	354	356	354	360
	S.D.	24.0	25.4	24.9	23.0	26.8	26.5	26.9	28.9	40.8	19.0
	N	27	27	27	27	27	26	26	25	26	25
Group 2 (1000 ppm)	MEAN	310	326	336	370	460	334	352	353	362	350
	S.D.	21.9	24.2	26.3	30.6	40.7	30.1	33.9	27.4	30.8	31.6
	N	27	27	27	37	26	26	26	25	26	26
Group 3 (5000 ppm)	MEAN	305	321	334	367	457	324	348	352	354	353
	S.D.	16.4	15.0	17.6	20.6	31.3	33.5	22.5	27.6	36.4	22.7
	N	28	28	28	28	27	28	28	28	27	27
Group 4 (20,000 ppm)	MEAN	306	323	333	366	449	327	346	355	362	355
	S.D.	23.8	23.4	23.6	23.6	37.9	27.3	22.7	22.4	22.8	21.0
	N	27	27	27	27	27	27	27	27	27	27

[a]Data extracted from Tables 16 and 17, pp. 102 and 104, respectively

TABLE 12. F_0 Male Mean Body Weight Gain (g)[a]

Group (Concentration - ppm)		Week of Measurement									
		1-2	1-3	1-4	1-5	1-6	1-7	1-8	1-9	1-10	1-11
Group 1 (Control)	MEAN	67.3	119.4	168.1	211.6	247.6	271.9	296.1	315.3	334.0	347.3
	S.D.	7.79	15.89	19.99	25.03	30.31	34.07	37.11	44.28	44.83	45.51
	N	28	28	28	28	28	28	28	28	28	28
Group 2 (1000 ppm)	MEAN	66.6	108.3	156.4	202.6	242.9	264.0	286.3	312.1	331.0	347.1
	S.D.	12.83	26.60	26.12	23.4	25.64	27.26	30.88	32.59	36.57	39.68
	N	28	28	28	28	28	28	28	28	28	28
Group 3 (5000 ppm)	MEAN	59.5	114.5	160.0	199.3	231.1	254.4	275.1	292.6	313.4	323.9
	S.D.	14.50	19.63	20.24	21.67	27.01	29.50	32.85	37.45	39.09	40.57
	N	28	28	28	28	28	28	28	28	28	28
Group 4 (20,000 ppm)	MEAN	63.7	104.0	151.2	198.7	230.7	261.4	280.2	300.4	314.4	331.4
	S.D.	8.83	24.32	22.56	20.67	25.21	27.23	30.20	34.21	33.18	35.37
	N	28	28	28	28	28	28	28	28	28	28

[a]Data extracted from Table 38, p. 164.

TABLE 13. F_0 Female Mean Body Weight Gain (g)[a]

Group (Concentration - ppm)		Week of Measurement									
		1-2	1-3	1-4	1-5	1-6	1-7	1-8	1-9	1-10	1-11
Group 1 (Control)	MEAN	27.6	49.6	68.5	84.7	97.4	105.4	113.0	121.9	128.0	131.4
	S.D.	4.12	13.64	10.34	11.36	13.15	14.60	16.33	15.75	16.80	17.44
	N	28	28	28	28	28	28	28	28	28	28
Group 2 (1000 ppm)	MEAN	28.2	52.3	70.5	86.0	97.5	108.0	117.1	125.4	130.0	134.5
	S.D.	4.63	7.82	9.28	12.81	14.56	15.34	16.11	16.95	19.07	17.90
	N	28	28	28	28	28	28	28	28	28	28
Group 3 (5000 ppm)	MEAN	29.1	51.5	68.2	83.2	94.4	103.7	113.5	120.9	129.2	132.9
	S.D.	2.86	5.85	6.83	8.52	11.86	10.59	11.75	11.64	11.28	14.28
	N	28	28	28	28	28	28	28	28	28	28
Group 4 (20,000 ppm)	MEAN	30.4	50.4	67.9	82.8	98.5	107.0	116.0	122.6	129.0	133.7
	S.D.	5.83	9.87	10.50	12.05	13.99	15.00	15.69	15.12	15.10	15.49
	N	28	28	28	28	28	28	28	28	28	28

[a]Data extracted from Table 39, p. 166.

TABLE 14. F_1 Male Mean Body Weight (g)[a]

Group (Concentration - ppm)		Week of Measurement													
		19	20	21	22	23	24	25	26	27	28	31	32	33	34
Group 1 (Control)	MEAN	74	125	188	248	306	358	394	429	455	479	530	532	548	547
	S.D.	16.4	21.0	26.0	29.6	34.6	40.3	43.4	48.1	54.1	57.2	59.9	63.3	64.3	68.0
	N	24	24	24	24	24	24	24	24	24	24	24	24	24	24
Group 2 (1000 ppm)	MEAN	72	120	183	245	309	366	406	436	470	502	565	570	582	591*
	S.D.	10.7	14.1	19.2	25.9	29.5	34.9	39.8	44.8	49.6	54.5	64.3	67.5	69.4	71.6
	N	24	24	24	24	24	24	24	24	24	24	24	24	24	24
Group 3 (5000 ppm)	MEAN	77	126	188	250	312	367	406	430	460	489	549	555	568	579
	S.D.	11.9	14.7	23.0	18.1	21.3	25.0	29.4	32.0	35.2	38.0	50.6	52.8	56.2	58.7
	N	24	24	24	24	24	24	24	24	24	34	24	24	24	24
Group 4 (20,000 ppm)	MEAN	66	112	167**	221**	284*	334*	371	399*	422*	440*	466***	468**	474***	486***
	S.D.	9.7	13.6	16.7	23.0	29.9	26.1	27.6	33.7	38.5	43.6	36.8	40.3	48.2	49.9
	N	24	24	24	23	23	23	23	23	23	23	22	22	22	21

[a]Data extracted from Table 4, p. 79.
*Significantly different from control, $p<0.05$.
**Significantly different from control, $p<0.01$.
***Significantly different from control, $p<0.001$.

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TABLE 15. F_1 Female Mean Body Weight (g) Before Pairing[a]

Group (Concentration - ppm)		Week of Measurement									
		19	20	21	22	23	24	25	26	27	28
Group 1 (Control)	MEAN	76	115	155	182	207	227	247	259	268	280
	S.D.	14.0	18.2	19.7	22.5	24.2	25.6	26.2	29.3	28.9	30.1
	N	24	24	24	24	24	24	24	24	24	24
Group 2 (1000 ppm)	MEAN	72	109	147	174	198	220	241	252	265	278
	S.D.	8.6	12.2	12.0	13.7	16.0	18.3	23.2	23.9	25.1	26.2
	N	24	24	24	24	24	24	24	24	24	24
Group 3 (5000 ppm)	MEAN	71	116	149	177	203	226	249	257	268	281
	S.D.	9.7	17.9	13.6	15.7	20.2	24.7	29.4	20.8	21.5	24.3
	N	24	24	24	24	24	24	24	23	23	23
Group 4 (20,000 ppm)	MEAN	64*	101**	138**	170	199	220	241	253	261	269
	S.D.	9.2	11.8	14.6	16.3	18.6	21.4	24.3	24.9	23.4	23.1
	N	24	24	24	24	24	24	24	24	24	24

[a]Data extracted from Table 5, p. 81.
*Significantly different from control, $p<0.05$.
**Significantly different from control, $p<0.01$.

TABLE 16. F_1 Female Mean Body Weight (g) During Gestation and Lactation[a]

Group (Concentration - ppm)		Day *Post Coitum*					Day *Post Partum*				
		1	4	7	14	21	1	4	7	14	21
Group 1 (Control)	MEAN	291	312	326	361	455	335	348	353	368	364
	S.D.	33.1	31.1	31.6	32.5	42.8	35.3	33.3	32.2	34.5	29.2
	N	21	21	21	21	18	21	21	21	21	21
Group 2 (1000 ppm)	MEAN	296	312	325	363	454	337	342	348	368	353
	S.D.	24.8	27.6	29.4	33.8	44.6	34.0	30.6	31.9	31.5	32.1
	N	24	24	24	24	22	24	23	21	21	21
Group 3 (5000 ppm)	MEAN	294	309	323	361	465	342	346	352	366	358
	S.D.	28.5	26.5	29.2	31.7	39.9	29.0	35.5	35.7	32.7	28.7
	N	22	22	22	22	18	22	22	22	22	22
Group 4 (20,000 ppm)	MEAN	274	283**	293**	327**	422	303**	315**	324*	339*	335*
	S.D.	24.6	27.8	29.2	35.1	45.4	30.7	34.8	30.0	34.0	35.8
	N	21	21	21	21	20	21	21	21	21	21

[a]Data extracted from Tables 16 and 17, pp. 103 and 105, respectively.
*Significantly different from control, $p<0.05$.
**Significantly different from control, $p<0.01$.

TABLE 17. F_1 Male Mean Body Weight Gain (g)[a]

Group (Concentration - ppm)		Week of Measurement								
		19-20	19-21	19-22	19-23	19-24	19-25	19-26	19-27	19-28
Group 1 (Control)	MEAN	50.7	113.5	173.8	231.3	283.3	319.1	354.1	381.0	404.1
	S.D.	12.92	12.61	16.93	22.80	29.89	34.06	40.05	46.60	50.34
	N	24	24	24	24	24	24	24	24	24
Group 2 (1000 ppm)	MEAN	48.1	111.4	173.3	236.8	294.1	333.8	364.3	398.3	429.7
	S.D.	7.50	13.78	21.66	25.80	31.93	37.93	43.00	47.71	53.63
	N	24	24	24	24	24	24	24	24	24
Group 3 (5000 ppm)	MEAN	49.5	111.8	173.5	235.1	290.1	329.2	353.5	383.8	411.9
	S.D.	4.52	15.43	11.47	16.99	22.90	28.38	30.75	34.48	37.76
	N	24	24	24	24	24	24	24	24	24
Group 4 (20,000 ppm)	MEAN	45.6	100.2	154.9	217.4	268.1	304.7	332.8	355.9	373.6
	S.D.	5.38	9.58	17.44	27.46	22.01	22.92	29.96	34.71	40.72
	N	24	24	23	23	23	23	23	23	23

[a]Data extracted from Table 38, p. 165.

TABLE 18. F_1 Female Mean Body Weight Gain (g)[a]

Group (Concentration - ppm)		Week of Measurement								
		19-20	19-21	19-22	19-23	19-24	19-25	19-26	19-27	19-28
Group 1 (Control)	MEAN	39.6	79.0	106.3	131.5	151.4	171.1	183.2	192.1	204.0
	S.D.	5.35	9.3	12.64	15.05	18.12	23.26	22.45	22.03	23.71
	N	24	24	24	24	24	24	24	24	24
Group 2 (1000 ppm)	MEAN	36.3	74.8	102.0	125.8	147.9	168.4	179.6	192.1	205.1
	S.D.	4.88	7.24	10.96	13.78	16.06	21.06	22.97	23.84	24.79
	N	24	24	24	24	24	24	24	24	24
Group 3 (5000 ppm)	MEAN	45.3	77.7	105.9	132.1	155.0	177.4	186.1	197.7	210.0
	S.D.	13.39	7.51	10.75	15.88	20.81	25.77	18.94	19.85	22.24
	N	24	24	24	24	24	24	23	23	23
Group 4 (20,000 ppm)	MEAN	36.9	74.2	105.5	135.2	155.9	176.9	188.4	197.0	205.3
	S.D.	4.02	7.47	10.91	14.80	18.09	21.79	24.21	23.46	22.83
	N	24	24	24	24	24	24	24	24	24

[a]Data extracted from Table 39, p. 167.

TABLE 19. F_0 Male Mean Food Consumption (g/animal/day)[a]

Group (Concentration - ppm)		Week of Measurement													
		1	2	3	4	5	6	7	8	9	10	14	15	16	17
Group 1 (Control)	MEAN	26.4	25.7	29.6	29.3	29.5	26.8	28.5	29.0	29.1	28.3	29.2	29.7	28.4	29.8
	S.D.	0.9	3.9	1.0	0.7	0.8	2.9	1.7	1.1	0.5	2.6	1.3	1.3	1.6	1.3
	N	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Group 2 (1000 ppm)	MEAN	26.3	25.1	28.5	30.0	30.2	27.6	28.3	29.8	29.5	29.9	30.1	30.6	30.3	29.9
	S.D.	1.2	5.3	2.3	1.7	1.4	2.9	2.4	2.8	1.3	1.9	2.5	2.0	1.7	1.6
	N	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Group 3 (5000 ppm)	MEAN	27.0	26.0	29.2	29.3	29.4	28.2	28.2	27.9	28.3	28.6	28.7	29.3	29.4	28.3
	S.D.	0.8	3.6	1.5	1.0	0.9	1.3	0.9	1.5	1.1	1.4	0.9	1.2	1.4	1.5
	N	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Group 4 (20,000 ppm)	MEAN	27.3	23.4	28.9	29.8	29.2	28.9	28.1	28.3	28.0	29.0	30.4	29.3	29.3	29.5
	S.D.	0.6	4.6	2.2	4.4	1.5	0.4	1.6	0.4	1.2	1.0	5.3	1.4	1.2	1.2
	N	7	7	7	7	7	7	7	7	7	7	7	7	7	7

[a]Data extracted from Table 6, p. 82.

TABLE 20. F_0 Female Mean Food Consumption (g/animal/day) Before Pairing[a]

Group (Concentration - ppm)		Week of Measurement									
		1	2	3	4	5	6	7	8	9	10
Group 1 (Control)	MEAN	18.4	18.5	19.1	19.7	19.3	18.7	18.9	19.5	18.6	18.6
	S.D.	1.1	1.0	0.9	1.1	0.9	0.9	0.8	0.8	0.9	0.9
	N	7	7	7	7	7	7	7	7	7	7
Group 2 (1000 ppm)	MEAN	17.9	18.6	20.3	19.6	19.0	18.4	19.2	19.1	18.3	18.8
	S.D.	0.9	1.0	2.0	1.4	1.0	1.2	0.9	0.7	1.5	1.3
	N	7	7	7	7	7	7	7	7	7	7
Group 3 (5000 ppm)	MEAN	18.6	19.1	19.2	20.0	19.3	19.2	19.1	20.0	18.6	18.9
	S.D.	0.5	0.5	0.5	0.7	1.6	1.2	0.6	0.6	0.4	0.3
	N	7	7	7	7	7	7	7	7	7	7
Group 4 (20,000 ppm)	MEAN	19.2	18.8	19.8	19.7	20.8	19.3	19.9	19.8	18.6	19.0
	S.D.	0.8	1.5	1.1	0.6	1.2	1.3	1.2	1.2	1.0	1.1
	N	7	7	7	7	7	7	7	7	7	7

[a]Data extracted from Table 7, p. 84.

TABLE 21. F_0 Female Mean Food Consumption (g/animal/day) During Gestation and Lactation[a]

Group (Concentration - ppm)		Day *Post Coitum*			Day *Post Partum*		
		1-7	7-14	14-21	1-7	7-14	14-21
Group 1 (Control)	MEAN	25.0	25.9	26.1	39.3	52.4	67.6
	S.D.	1.8	3.0	4.5	7.3	13.1	6.4
	N	27	27	27	26	26	25
Group 2 (1000 ppm)	MEAN	24.3	26.2	25.9	38.9	56.9	67.4
	S.D.	3.2	3.2	4.4	6.0	10.5	7.8
	N	27	27	27	26	26	26
Group 3 (5000 ppm)	MEAN	24.5	26.6	25.0	37.8	55.6	68.2
	S.D.	2.8	2.3	3.6	6.4	11.9	5.1
	N	28	28	28	28	27	27
Group 4 (20,000 ppm)	MEAN	25.6	26.9	25.3	41.0	59.5	69.2
	S.D.	2.0	2.7	4.2	4.1	6.8	6.5
	N	27	27	27	27	27	27

[a]Data extracted from Table 18, p. 106.

TABLE 22. F_1 Male Mean Food Consumption (g/animal/day)[a]

Group (Concentration - ppm)		Week of Measurement												
		19	20	21	22	23	24	25	26	27	31	32	33	34
Group 1 (Control)	MEAN	15.5	20.3	28.9	28.7	29.9	29.5	30.4	30.4	29.8	28.1	29.5	27.7	29.9
	S.D.	1.4	1.5	5.9	1.6	1.6	1.2	1.5	1.6	1.4	6.4	3.3	2.0	1.5
	N	6	6	6	6	6	6	6	6	6	6	6	6	6
Group 2 (1000 ppm)	MEAN	15.1	20.5	26.8	29.5	31.4	30.8	29.3	33.5*	32.0	31.0	29.9	30.2	28.6
	S.D.	0.9	1.2	1.4	1.5	1.3	0.9	3.8	1.1	0.6	1.1	0.4	1.0	4.3
	N	6	6	6	6	6	6	6	6	6	6	6	6	6
Group 3 (5000 ppm)	MEAN	15.8	20.8	26.7	29.7	31.1	31.0	27.4	33.8	31.3	29.7	29.8	30.0	30.0
	S.D.	0.9	1.7	1.0	0.7	1.3	1.4	3.7	2.0	0.8	2.2	1.6	1.8	1.8
	N	6	6	6	6	6	6	6	6	6	6	6	6	6
Group 4 (20,000 ppm)	MEAN	14.4	18.5	24.0	26.5*	29.2	28.8	28.3	29.2	27.5	25.8	23.5***	24.2*	25.6*
	S.D.	1.2	1.1	1.9	1.8	2.0	2.3	4.5	3.3	2.2	1.3	2.1	2.6	1.8
	N	6	6	6	6	6	6	6	6	6	6	6	6	6

[a]Data extracted from Table 6, p. 83.

*Significantly different from control, $p<0.05$.

***Significantly different from control, $p<0.001$.

TABLE 23. F_1 Female Mean Food Consumption (g/animal/day) Before Pairing[a]

Group (Concentration - ppm)		Week of Measurement								
		19	20	21	22	23	24	25	26	27
Group 1 (Control)	MEAN	14.4	16.9	22.4	20.5	21.2	19.3	20.7	20.5	20.2
	S.D.	1.2	0.9	6.2	1.5	1.1	0.7	2.0	1.3	1.4
	N	6	6	6	6	6	6	6	6	6
Group 2 (1000 ppm)	MEAN	13.6	16.1	19.4	20.5	21.2	19.4	20.4	21.4	21.1
	S.D.	0.9	0.5	0.7	0.8	0.7	1.4	0.5	0.9	0.9
	N	6	6	6	6	6	6	6	6	6
Group 3 (5000 ppm)	MEAN	13.9	16.8	20.7	22.1	22.6	20.9	22.7	22.0	21.5
	S.D.	0.4	0.2	1.5	1.9	1.7	1.6	3.5	0.9	1.3
	N	6	6	6	6	6	6	6	6	6
Group 4 (20,000 ppm)	MEAN	13.5	16.0	22.0	24.0**	23.0*	20.5	21.3	20.3	18.6
	S.D.	1.0	1.1	2.4	1.3	1.2	0.7	1.2	1.0	1.3
	N	6	6	6	6	6	6	6	6	6

[a]Data extracted from Table 7, p. 85.

*Significantly different from control, $p<0.05$.

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

TABLE 24. F_1 Female Mean Food Consumption (g/animal/day) During Gestation and Lactation[a]

Group (Concentration - ppm)		Day *Post Coitum*			Day *Post Partum*		
		1-7	7-14	14-21	1-7	7-14	14-21
Group 1 (Control)	MEAN	27.5	27.5	28.9	40.4	61.9	69.7
	S.D.	3.6	3.2	4.5	6.2	6.7	10.2
	N	21	21	21	21	21	21
Group 2 (1000 ppm)	MEAN	27.6	27.3	29.1	38.3	61.3	75.2
	S.D.	3.1	3.7	5.3	9.4	10.5	6.0
	N	22	24	24	24	24	21
Group 3 (5000 ppm)	MEAN	26.8	27.4	29.1	40.4	60.3	73.6
	S.D.	2.3	2.8	2.9	5.6	6.3	4.7
	N	21	22	20	22	22	22
Group 4 (20,000 ppm)	MEAN	21.5***	22.9***	26.2	33.9*	58.6	67.9
	S.D.	4.9	4.2	4.6	7.0	6.5	8.8
	N	21	21	21	21	21	21

[a]Data extracted from Table 18; p. 107.
*Significantly different from control, $p<0.05$.
***Significantly different from control, $p<0.001$.

TABLE 25. F_0 Male and Female Mean Food Conversion Ratio Before Pairing[a]

Group (Concentration - ppm)	Week of Measurement									
	1	2	3	4	5	6	7	8	9	10
Males										
Group 1 (Control)	0.36	0.29	0.24	0.21	0.17	0.13	0.12	0.09	0.09	0.07
Group 2 (1000 ppm)	0.36	0.24	0.24	0.22	0.19	0.11	0.11	0.12	0.09	0.08
Group 3 (5000 ppm)	0.32	0.30	0.22	0.20	0.15	0.12	0.10	0.09	0.11	0.05
Group 4 (20,000 ppm)	0.33	0.24	0.23	0.23	0.16	0.15	0.09	0.11	0.07	0.08
Females										
Group 1 (Control)	0.21	0.17	0.14	0.12	0.09	0.06	0.06	0.07	0.05	0.02
Group 2 (1000 ppm)	0.22	0.18	0.13	0.12	0.08	0.09	0.07	0.06	0.04	0.03
Group 3 (5000 ppm)	0.22	0.16	0.13	0.11	0.08	0.07	0.07	0.06	0.06	0.03
Group 4 (20,000 ppm)	0.22	0.15	0.12	0.11	0.11	0.07	0.06	0.04	0.05	0.03

[a]Data extracted from Tables 8 and 9, pp. 86 and 88, respectively.

TABLE 26. F_1 Male and Female Mean Food Conversion Ratio Before Pairing[a]

Group (Concentration - ppm)	Week of Measurement								
	19	20	21	22	23	24	25	26	27
Males									
Group 1 (Control)	0.47	0.44	0.30	0.29	0.12	0.30	0.16	0.12	0.12
Group 2 (1000 ppm)	0.45	0.44	0.33	0.31	0.26	0.19	0.15	0.14	0.14
Group 3 (5000 ppm)	0.44	0.43	0.33	0.30	0.25	0.18	0.13	0.13	0.13
Group 4 (20,000 ppm)	0.46	0.42	0.32	0.34	0.24	0.18	0.14	0.11	0.09
Females									
Group 1 (Control)	0.39	0.34	0.17	0.17	0.13	0.15	0.08	0.06	0.08
Group 2 (1000 ppm)	0.39	0.34	0.20	0.17	0.15	0.15	0.08	0.09	0.09
Group 3 (5000 ppm)	0.46	0.28	0.19	0.17	0.15	0.16	0.05	0.07	0.09
Group 4 (20,000 ppm)	0.39	0.33	0.21	0.17	0.13	0.15	0.08	0.06	0.06

[a]Data extracted from Tables 8 and 9, pp. 87 and 89, respectively.

TABLE 27. F_0 Male and Female Mean Test Material Intake (mg/kg/day) Before Pairing[a]

Group (Concentration - ppm)	Week of Measurement										
	1	2	3	4	5	6	7	8	9	10	Mean
Males											
Group 2 (1000 ppm)	111.9	86.9	85.3	78.7	71.2	60.7	59.4	59.5	56.4	55.3	72.5
Group 3 (5000 ppm)	574.5	444.4	426.3	380.5	349.6	314.7	300.0	285.3	278.3	272.9	362.7
Group 4 (20,000 ppm)	2363.6	1653.7	1770.3	1593.6	1410.6	1296.0	1195.7	1156.3	1104.5	1110.0	1465.4
Females											
Group 2 (1000 ppm)	102.9	93.0	91.9	82.4	75.5	70.0	70.6	68.0	63.7	64.4	78.2
Group 3 (5000 ppm)	533.0	477.5	437.4	424.6	388.3	370.7	355.7	361.0	326.3	324.7	399.9
Group 4 (20,000 ppm)	2181.8	1870.6	1800.0	1669.5	1657.4	1464.9	1460.6	1414.3	1298.4	1301.4	1611.9

[a]Data extracted from Tables 10 and 11, pp. 90 and 92, respectively.

TABLE 28. F_1 Male and Female Mean Test Material Intake (mg/kg/day) Before Pairing[a]

Group (Concentration - ppm)	Week of Measurement									
	19	20	21	22	23	24	25	26	27	Mean
Males										
Group 2 (1000 ppm)	157.3	135.3	125.2	106.5	92.9	79.8	69.6	74.0	65.8	100.7
Group 3 (5000 ppm)	778.3	662.4	609.6	528.5	458.0	401.0	327.8	379.8	329.8	497.2
Group 4 (20,000 ppm)	3236.0	2652.3	2474.2	2099.0	1890.0	1634.0	1470.1	1422.7	1276.1	2017.1
Females										
Group 2 (1000 ppm)	150.3	125.8	120.9	110.2	101.4	84.2	82.8	82.8	77.9	104.0
Group 3 (5000 ppm)	743.3	634.0	635.0	581.6	526.8	440.9	435.6	415.2	390.5	533.7
Group 4 (20,000 ppm)	3272.7	2677.8	287.1	2601.6	2195.7	1778.7	1724.7	1579.8	1403.8	2232.4

[a]Data extracted from Tables 10 and 11, pp. 91 and 93, respectively.

TABLE 29. Selected F_0 Reproductive Observations[a]

		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Number of Males Paired	N	28	28	28	28
Number of Females Paired	N	28	28	28	28
Number of Females Mated	N	28	28	28	28
Number of Females Achieving Pregnancy	N	27	27[b]	28	27
Mating Index (%)		100	100	100	100
Pregnancy (%)		96.4	96.4	100	96.4
Females with liveborn offspring	N	26	26	28	27
Parturition Index (%)		96.3	96.3	100	100
Gestation Length (days)					
21.5	N	1	0	0	1
22	N	11	10	8	3
22.5	N	5	11	13	4
23	N	9	5	7	18
23.5	N	0	0	0	1
Liveborn					
Live Birth Index (%)		97.4	99.0	99.1	98.6
Viability Index 1 (%)		98.9	98.0	99.1	99.6
Viability Index 2 (%)		100	99.5	96.9	100
Viability Index 3 (%)		99.5	99.5	99.1	100
Viability Index 4 (%)		96.1	100	100	100
Viability Index 5 (%)		95.7	99.0	96.0	100

		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Litter Size					
Number born	MEAN	14.6	15.7	15.3	15.6
	S.D.	2.1	1.4	1.6	2.1
	N	26	26	28	27
Day 1	MEAN	14.2	15.5	15.2	15.3
	S.D.	2.0	1.5	1.7	2.1
	N	26	26	28	27
Day 4	MEAN	14.1	15.2	15.0	15.3
	S.D.	2.0	1.7	1.8	2.0
	N	26	26	28	27
Day 7	MEAN	8.0	8.0	7.8	8.0
	S.D.	0.0	0.2	1.3	0.0
	N	26	26	28	27
Day14	MEAN		7.9	8.0	8.0
	S.D.	8.0	0.3	0.2	0.0
	N	0.2	26	27	27
		26			
Day 21	MEAN	8.0	7.9	8.0	8.0
	S.D.	0.2	0.3	0.2	0.0
	N	25	26	27	27

		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Litter Weights (g)					
Day 1	MEAN	95.3	100.7	95.8	99.4
	S.D.	9.8	11.3	12.2	11.6
	N	26	26	28	27
Day 4	MEAN	131.1	137.6	133.8	143.9*
	S.D.	13.2	15.5	15.8	20.9
	N	26	26	28	27
Day 7	MEAN	126.1	122.0	115.9	122.0
	S.D.	14.7	11.3	23.7	12.4
	N	25	25	28	27
Day14	MEAN	248.6	262.1	246.8	251.6
	S.D.	51.5	28.3	39.5	25.9
	N	26	26	27	27
Day 21	MEAN	407.2	416.3	396.0	374.4*
	S.D.	63.9	47.6	45.7	33.7
	N	25	26	27	27

		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Individual Pup Weights (g)					
Day 1	MEAN	6.8	6.5	6.3**	6.5
	S.D.	0.8	0.5	0.5	0.5
	N	26	26	28	27
Day 4	MEAN	9.4	9.1	8.9	9.5
	S.D.	1.3	0.8	0.8	1.0
	N	26	26	28	27
Day 7	MEAN	15.8	15.3	14.7	15.3
	S.D.	1.8	1.4	1.9	1.6
	N	25	25	28	27
Day14	MEAN	31.3	33.1	31.0	31.5
	S.D.	6.2	3.4	4.8	3.2
	N	26	26	27	27
Day 21	MEAN	51.3	52.5	49.7	46.8*
	S.D.	7.4	5.6	5.7	4.2
	N	25	26	27	27

		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Sex Ratio					
Day 1 *Post Partum*					
Male	MEAN	7.2	7.8	7.2	8.0
	S.D.	2.2	2.0	1.6	2.2
	N	25	26	28	27
Female	MEAN	7.0	7.7	7.9	7.4
	S.D.	1.8	2.0	1.6	2.4
	N	25	26	28	27
% Male/litter	MEAN	50.3	50.5	47.5	52.1
	S.D.	12.8	12.4	9.0	14.1
	N	25	26	28	27
Day 21 *Post Partum*					
Male	MEAN	3.9	4.1	4.0	4.1
	S.D.	0.3	0.4	0.2	0.3
	N	25	26	27	27
Female	MEAN	4.0	3.8	4.0	3.9
	S.D.	0.3	0.5	0.0	0.3
	N	25	26	27	27
% Male/litter	MEAN	49.5	51.5	49.7	51.4
	S.D.	3.2	5.2	1.4	4.0
	N	25	26	27	27

[a]Data extracted from Tables 13, 15, 19, 20-22, and 25, pp. 96, 100, 108, 110, 112, 114, and 120, respectively.
[b]Includes one female that was killed due to suspected dystocia.
*Significantly different from control, $p<0.05$.

TABLE 30. Selected F_1 Reproductive Observations[a]

		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Number of Males Paired	N	24	24	23	22
Number of Females Paired	N	24	24	23	23
Number of Females Mated	N	24	24	22	23
Number of Females Achieving Pregnancy	N	22	24	22[b]	22
Mating Index (%)		100	100	95.7	100
Pregnancy (%)		91.7	100	100	95.7
Females with liveborn offspring	N	21	24	22	20
Parturition Index (%)		95.4	100	100	90.9
Gestation Length (days)	N				
22	N	10	14	15	8
22.5	N	5	3	7	4
23	N	6	7	0	8
23.5	N	0	0	0	0
Liveborn					
Live Birth Index (%)		97.5	94.9	98.5	96.4
Viability Index 1 (%)		96.1	91.2	98.8	95.9
Viability Index 2 (%)		98.8	92.8	100	100
Viability Index 3 (%)		96.9	100	100	100
Viability Index 4 (%)		100	99.4	99.4	100
Viability Index 5 (%)		95.8	92.3	99.4	100

		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Litter Size					
Total Implantation Count	MEAN	16.0	16.3	15.9	14.7
	S.D.	3.5	2.4	2.4	1.8
	N	22†	24	22	20‡
Number Born	MEAN	15.1	15.5	15.2	13.4*
	S.D.	1.7	2.4	2.6	1.5
	N	21	24	22	21
Day 1	MEAN	14.8	14.7	15.0	12.9*
	S.D.	2.1	3.1	2.5	1.4
	N	21	24	22	21
Day 4	MEAN	14.2	14.0	14.8	12.4
	S.D.	2.7	3.3	2.4	1.9
	N	21	23	22	21
Day 7	MEAN	7.8	8.0	8.0	8.0
	S.D.	0.7	0.0	0.0	0.0
	N	21	21	22	21
Day 14	MEAN	7.6	8.0	8.0	8.0
	S.D.	1.0	0.0	0.0	0.0
	N	21	21	22	21
Day 21	MEAN	7.6	8.0	8.0	8.0
	S.D.	1.0	0.2	0.2	0.0
	N	21	21	22	21

		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Litter Weights (g)					
Day 1	MEAN	96.4	96.3	95.6	83.7*
	S.D.	17.4	15.5	13.0	11.0
	N	21	21	22	21
Day 4	MEAN	129.3	135.1	137.9	117.0
	S.D.	30.8	18.8	18.3	22.3
	N	21	21	22	21
Day 7	MEAN	118.2	125.7	122.3	120.5
	S.D.	25.3	11.0	19.1	14.0
	N	21	21	22	21
Day 14	MEAN	258.2	278.2	264.7	253.4
	S.D.	46.0	18.6	28.0	20.7
	N	21	21	22	21
Day 21	MEAN	405.4	440.9	412.4	372.8
	S.D.	72.4	30.1	46.0	31.4
	N	21	21	22	21

		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Individual Pup Weights (g)					
Day 1	MEAN	6.5	6.5	6.5	6.5
	S.D.	0.8	0.7	0.8	0.6
	N	21	21	22	21
Day 4	MEAN	9.1	9.3	9.5	9.5
	S.D.	1.4	1.2	1.5	1.3
	N	21	21	22	21
Day 7	MEAN	15.0	15.7	15.3	15.2
	S.D.	2.6	1.4	2.4	1.8
	N	21	21	22	21
Day14	MEAN	33.9	34.8	33.1	31.9
	S.D.	3.2	2.3	3.5	2.7
	N	21	21	22	21
Day 21	MEAN	53.3	55.5	51.8	46.6***
	S.D.	5.2	3.7	5.3	3.9
	N	21	21	22	21

		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Sex Ratio					
Day 1 *Post Partum*					
Male	MEAN	7.8	6.4	7.8	6.0
	S.D.	2.2	2.4	2.1	1.9
	N	21	24	22	21
Female	MEAN	7.0	8.4	7.1	7.0
	S.D.	1.7	2.5	1.6	1.7
	N	21	24	22	21
% Male/litter	MEAN	52.5	43.0**	51.9	45.6
	S.D.	10.8	12.0	10.1	13.4
	N	21	24	22	21
Day 21 *Post Partum*					
Male	MEAN	4.0	3.9	4.0	3.8
	S.D.	0.5	0.3	0.4	0.7
	N	21	21	22	21
Female	MEAN	3.6	4.0	4.0	4.2
	S.D.	0.8	0.2	0.3	0.7
	N	21	21	22	21
% Male/litter	MEAN	52.7	49.1	49.7	47.6
	S.D.	8.2	3.1	4.1	9.4
	N	21	21	22	21

[a]Data extracted from Tables 13, 15, 19, 20-22, and 25, pp. 97, 101, 109, 111, 113, 115, and 121, respectively.

[b] One female mating not detected

† One female, with no live offspring, found to have 3 implantation sites

‡ Data not recorded in error for one female

*Significantly different from control, $p<0.05$.

***Significantly different from control, $p<0.001$.

TABLE 31. F_0 Male Mean Semen Concentration/Motility Analysis (Selected Findings)[a]

		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Lateral Amplitude (µm)	MEAN	24.7	24.2	23.3	21.6*
	S.D.	4.28	3.65	4.19	4.59
	N	27	28	26	27
Straightness (%)	MEAN	53.1	53.5	53.6	57.8*
	S.D.	3.05	2.86	2.61	7.97
	N	27	28	26	27

[a]Data extracted from Table 32, p. 137.
*Significantly different from control, $p<0.05$.

TABLE 32. F_1 Male Mean Semen Morphology Analysis (Selected Findings)[a]

		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Head Area (µm2)					
Normal	MEAN	7.7	8.0	8.3***	8.1*
	S.D.	0.44	0.44	0.43	0.40
	N	24	24	24	21
Abnormal	MEAN	0.2	0.3	0.0	0.0
	S.D.	1.14	1.27	0.00	0.00
	N	24	24	24	21

[a]Data extracted from Table 33, p. 140.
*Significantly different from control, $p<0.05$.
***Significantly different from control, $p<0.001$.

TABLE 33. Selected F_0 Male and Female Mean Absolute and Relative Organ Weight[a]

Group		F_0 Males				F_0 Females
		Absolute Organ Weight (g)			Relative Organ Weight (%)	Absolute Organ Weight (g)
		Thymus	Right Epididymis	Seminal Vesicles and Coagulating Gland	Spleen	Brain
Group 1 (Control)	MEAN S.D. N	0.393 0.1405 28	0.801 0.1175 28	2.881 0.4447 28	0.144 0.0147 28	1.941 0.0840 25
Group 2 (1000 ppm)	MEAN S.D. N	0.338 0.0804 28	0.717* 0.0841 28	2.627 0.5830 28	0.156 0.0250 28	1.926 0.1093 26
Group 3 (5000 ppm)	MEAN S.D. N	0.369 0.1054 28	0.755 0.0752 28	2.480* 0.4219 28	0.173** 0.0574 28	1.873* 0.0638 27
Group 4 (20,000 ppm)	MEAN S.D. N	0.313* 0.0947 28	0.736 0.0942 28	2.466** 0.3208 28	0.160** 0.0260 28	1.896 0.1013 27

[a]Data extracted from Tables 29 and 30, pp. 127-128 and 131-132, respectively.
*Significantly different from control, $p<0.05$.
**Significantly different from control, $p<0.01$.

TABLE 34. Selected F_1 Male and Female Mean Absolute Organ Weight (g)[a]

Group (Concentration - ppm)		F_1 Males							F_1 Females
		Adrenals	Kidneys	Thymus	Left Epididymis	Prostate	Seminal Vesicles and Coagulating Gland	Right Testis	Uterus
Group 1 (Control)	MEAN S.D. N	0.063 0.0124 24	3.895 0.4963 24	0.348 0.0825 24	0.693 0.0825 24	0.694 0.2025 24	2.725 0.3861 24	1.888 0.1421 24	0.523 0.1133 21
Group 2 (1000 ppm)	MEAN S.D. N	0.063 0.0087 24	3.986 0.6136 24	0.391 0.0985 24	0.729 0.0946 24	0.661 0.1683 24	2.717 0.4713 24	1.925 0.1303 24	0.535 0.1036 21
Group 3 (5000 ppm)	MEAN S.D. N	0.062 0.0133 24	3.784 0.4342 24	0.425* 0.0969 24	0.758* 0.0924 24	0.654 0.1528 24	2.632 0.2132 24	1.926 0.1602 24	0.502 0.1658 22
Group 4 (20,000 ppm)	MEAN S.D. N	0.054* 0.0101 21	3.277*** 0.2835 21	0.345 0.0798 21	0.678 0.1010 21	0.466*** 0.1215 21	2.368* 0.4263 21	1.747* 0.2709 21	0.377*** 0.0614 20

[a]Data extracted from Tables 29 and 30, pp. 129-130 and 133-134, respectively.
*Significantly different from control, $p<0.05$.
***Significantly different from control, $p<0.001$.

TABLE 35. Selected F_1 Male and Female Mean Relative Organ Weight (%)[a]

Group (Concentration - ppm)		F_1 Males							F_1 Females
		Brain	Kidneys	Thymus	Left Epididymis	Right Epididymis	Prostate	Left Testis	Uterus
Group 1 (Control)	MEAN	0.393	0.695	0.062	0.125	0.134	0.126	0.340	0.145
	S.D.	0.0431	0.0539	0.0146	0.0169	0.0178	0.0413	0.0393	0.0350
	N	24	24	24	24	24	24	24	21
Group 2 (1000 ppm)	MEAN	0.366*	0.659	0.065	0.122	0.133	0.110	0.319	0.153
	S.D.	0.0343	0.0725	0.0152	0.0232	0.0221	0.269	0.0599	0.0366
	N	24	24	24	24	24	24	24	21
Group 3 (5000 ppm)	MEAN	0.376	0.641**	0.071**	0.129	0.136	0.111	0.324	0.142
	S.D.	0.0385	0.0604	0.0107	0.0165	0.0154	0.0246	0.0308	0.0536
	N	24	24	24	24	24	24	24	22
Group 4 (20,000 ppm)	MEAN	0.431**	0.688	0.069	0.137*	0.159**	0.094**	0.367*	0.111***
	S.D.	0.0518	0.0790	0.0130	0.0177	0.0372	0.0215	0.0491	0.0219
	N	21	21	21	21	21	21	21	20

[a]Data extracted from Tables 29 and 30, pp. 129-130 and 133-134, respectively.
*Significantly different from control, $p<0.05$.
**Significantly different from control, $p<0.01$.
***Significantly different from control, $p<0.001$.

TABLE 36. F_0 Male and Female Summary of Selected Macroscopic *Post Mortem* Findings[a]

Observations	Number of Male Animals Affected				Number of Female Animals Affected			
	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Pancreas - dark/darkened/dark green color	0	0	24	27	0	0	17	24
Mesenteric Lymph Nodes - Dark	0	0	0	1	0	0	6	15
Thymus - darkened/brown/dark green					0	0	2	5

[a]Data extracted from Tables 27 and 28, pp. 123 and 125, respectively.

TABLE 37. F_1 Male and Female Summary of Selected Macroscopic *Post Mortem* Findings[a]

Observations	Number of Male Animals Affected				Number of Female Animals Affected			
	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Pancreas - dark/darkened/dark green color	0	0	20	22	0	0	21	24
Mesenteric Lymph Nodes - Dark	0	0	1	18	0	0	8	19
Thymus - darkened					0	0	0	2

[a]Data extracted from Tables 27 and 28, pp. 124 and 126, respectively.

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TABLE 38. F_0 Male and Female Summary of Selected Histopathological Findings[a]

Observations	Number of Male Animals Affected				Number of Female Animals Affected			
	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Lymph nodes mesenteric - Pigmented macrophages largely in sinuses								
Not examined	1	2	1	2	11	4	9	6
Absent	27	26	24	17	17	24	16	1
Minimal	0	0	3	9	0	0	3	2
Mild	0	0	0	0	0	0	0	19
Pancreas - Diffuse pigmented macrophages								
Not examined	0	0	0	0	9	3	8	4
Absent	28	28	15	0	19	25	1	1
Minimal	0	0	13	26	0	0	19	0
Mild	0	0	0	2	0	0	0	23

[a]Data extracted from Tables 35 and 36, pp. 143-147 and 152-157, respectively.

TABLE 39. F_1 Male and Female Summary of Selected Histopathological Findings[a]

Observations	Number of Male Animals Affected				Number of Female Animals Affected			
	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Pigmented macrophages largely in sinuses								
Not examined	0	0	0	2	1	0	2	0
Absent	24	24	23	7	22	23	12	1
Minimal	0	0	1	13	1	1	10	3
Mild	0	0	0	2	0	0	0	7
Moderate	0	0	0	1	0	0	0	13
Pancreas - Diffuse pigmented macrophages								
Not examined	0	0	0	2	1	0	0	0
Absent	24	23	2	2	23	24	1	0
Minimal	0	1	22	16	0	0	23	10
Mild	0	0	0	5	0	0	0	14

[a]Data extracted from Tables 35 and 36, pp. 148-151 and 158-162, respectively.

TABLE 40. Selected F_1 and F_2 Male and Female Pup Mean Organ Weight (g)[a]

Group (Concentration - ppm)		F_1 Male Pup	F_1 Female Pup	F_2 Male Pup	F_2 Female Pup
		Thymus	Thymus	Thymus	Thymus
Group 1 (Control)	MEAN S.D. N	0.221 0.0556 25	0.212 0.0509 25	0.209 0.0521 21	0.288 0.0655 21
Group 2 (1000 ppm)	MEAN S.D. N	0.212 0.0520 26	0.218 0.0523 26	0.299 0.0518 21	0.233 0.0742 21
Group 3 (5000 ppm)	MEAN S.D. N	0.172** 0.0394 27	0.190 0.0393 27	0.174 0.0530 22	0.185* 0.0481 22
Group 4 (20,000 ppm)	MEAN S.D. N	0.138*** 0.0304 27	0.144*** 0.0396 27	0.129*** 0.0446 21	0.144*** 0.0314 21

[a]Data extracted from Table 31, pp. 135-136.
*Significantly different from control, $p<0.05$.
**Significantly different from control, $p<0.01$.
***Significantly different from control, $p<0.001$.

APPENDIX A: DATA VALIDATION

Experimental Additive Number 9823-37:
Dietary Two Generation Reproduction Study in the Rat

I. ANIMALS FOLLOWED THROUGHOUT THE STUDY

Using the random number generator in Microsoft Excel 97, 20% of the 224 study animals in generation F_0 (Sprague-Dawley Crl:CD® IGS BR Strain male and female rats) and 20% of the 192 study animals in generation F_1 were selected for review. All individual animal data provided in the study report for the selected animals were reviewed, including all tables. The selected animals are listed in the table below.

F_0 Generation- Males

Group 1 Control Dose level: 0 ppm	Group 2 Dose Level: 1000 ppm	Group 3 Dose Level: 5000 ppm	Group 4 Dose Level: 20000 ppm
4	29	58	86
8	32	66	88
14	44	70	95
17	45	73	100
23	53	81	104
26	NA	83	111

F_0 Generation- Females

Group 1 Control Dose Level: 0 ppm	Group 2 Dose Level: 1000 ppm	Group 3 Dose Level: 5000 ppm	Group 4 Dose Level: 20000 ppm
114	143	169	200
120	147	173	207
123	150	180	213
127	154	185	218
135	162	192	222
138	168	195	NA

F_1 Generation- Males

Group 1 Control Dose Level: 0 ppm	Group 2 Dose Level: 1000 ppm	Group 3 Dose Level: 5000 ppm	Group 4 Dose Level: 20000 ppm
227	250	273	299
235	257	279	300
239	263	284	304
241	268	291	312
246	271	295	318

F_1 Generation- Females

Group 1 Control Dose Level: 0 ppm	Group 2 Dose Level: 1000 ppm	Group 3 Dose Level: 5000 ppm	Group 4 Dose Level: 20000 ppm
326	348	370	397
330	351	376	403
332	352	378	406
341	356	389	410
343	364	392	413

No problems or discrepancies were noted.

II. CRITICAL EFFECTS AND SPOT CHECKS

Incidence counts or means and standard deviation of the means were calculated as appropriate using the individual animal data provided in the study appendices. The results were compared to the corresponding tables in the study report. For each table reviewed, different data items were selected at random to provide "spot check" validations of the information presented in the tables.

Table 2: Group Summary of Clinical Observations- Males
Entire table

Table 5: Group Mean Bodyweights (g) Before Pairing- Females
F_0 Generation:
Group 1: Study Weeks 3, 5 and 11
Group 2: Study Weeks 3, 5 and 11

Group 3: Study Weeks 3, 5 and 11
Group 4: Study Weeks 3, 5 and 11

F_1 Generation:

Group 1: Study Weeks 19, 23 and 26
Group 2: Study Weeks 19, 23 and 26
Group 3: Study Weeks 19, 23 and 26
Group 4: Study Weeks 19, 23 and 26

Table 7: Group Mean Food Consumption (g/rat/day)- Females

F_0 Generation:

Group 1: Study Weeks 3 and 8
Group 2: Study Weeks 4 and 6
Group 3: Study Weeks 5 and 9
Group 4: Study Weeks 1 and 2

F_1 Generation:

Group 1: Study Weeks 20 and 24
Group 2: Study Weeks 19 and 21
Group 3: Study Weeks 22 and 27
Group 4: Study Weeks 23 and 25

Table 13: Group Summary of Mating Performance and Fertility

Entire table

Table 21: Group Mean Litter Weights (g)

F_0 - F_1 Generation:

Group 1: Day *post partum* 1 and 14
Group 2: Day *post partum* 7 and 14
Group 3: Day *post partum* 4 and 21
Group 4: Day *post partum* 4 and 7

F_1 - F_2 Generation:

Group 1: Day *post partum* 1 and 21
Group 2: Day *post partum* 4 and 14
Group 3: Day *post partum* 7 and 21
Group 4: Day *post partum* 1 and 7

Table 28: Group Summary of Macroscopic *Post mortem* Findings- Females

Entire table

Table 30: Group Mean Organ Weights (g)- Females

F_0 Generation:

Group 1:	Percentage of body weight: Adrenals, Pituitary Weight: Liver
Group 2:	Percentage of body weight: Liver, Thymus Weight: Kidneys
Group 3:	Percentage of body weight: Ovaries, Brain Weight: Spleen
Group 4:	Percentage of body weight: Uterus Weight: Adrenals, Kidneys

F_1 Generation:

Group 1:	Percentage of body weight: Brain Weight: Uterus
Group 2:	Percentage of body weight: Liver, Spleen
Group 3:	Percentage of body weight: Pituitary Weight: Kidneys
Group 4:	Percentage of body weight: Adrenals Weight: Thymus

Table 32: Group Mean Semen Analysis- Concentration/Motility

F_0 Generation:

- Group 1: Concentration (M/ml) and Lateral amplitude (µm)
- Group 2: Motility (%) and Progressive velocity (µm/s)
- Group 3: Track speed (µm/s) and Elongation (%)
- Group 4: Path velocity (µm/s) and Beat frequency (Hz)

F_1 Generation:

- Group 1: Progressive motility (%) and Straightness (%)
- Group 2: Path velocity (µm/s) and Linearity (%)
- Group 3: Lateral amplitude (µm) and Area (µm sq)
- Group 4: Motility (%) and Lateral amplitude (µm)

III. FINDINGS

No problems or discrepancies were noted.

Sara Eisenstat, B.A.

1/16/03
Date