

(072560)

(1-15-03)

DATA EVALUATION RECORD

Experimental Additive Number 9823-37

Study Type: Reproduction and Fertility Effects (Rat)

Prepared for

Antimicrobial Division  
Office of Pesticide Programs  
U.S. Environmental Protection Agency  
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Antimicrobials Division (7510C)

Date 3/13/07

**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 MRID 457694-02: Unpublished.**SPONSOR:** SafePharm Laboratories, Ltd.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 CrI:CD<sup>®</sup> IGS BR rats at dose levels of 0, 1000, 5000, or 20,000 ppm. Animals were exposed to the test article for 75 (F<sub>0</sub> animals) or 76 (F<sub>1</sub> 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<sub>1</sub> males and females), significantly decreased body weight during gestation and lactation (F<sub>1</sub> females), and significantly decreased mean food consumption (F<sub>1</sub> males and females). Additionally, 20,000-ppm F<sub>1</sub> 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<sub>0</sub> 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<sub>1</sub> dose group) and significant decrease in pup weight (F<sub>1</sub> and F<sub>2</sub> 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<sup>®</sup> IGS BR  
Source: Charles River (UK) Limited (Margate, Kent)  
Age on arrival: not provided  
Weight on arrival: not provided<sup>1</sup>  
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

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<sup>1</sup> Weight at start of treatment was 150-232 g (F<sub>0</sub> males) and 137-183 g (F<sub>0</sub> 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:<sup>2</sup>

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<sub>0</sub> 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<sub>0</sub> animals were designated F<sub>1</sub>, 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<sub>1</sub> pups were weaned on Day 21 *post partum* and treatment groups (totaling 24 animals/sex/group) were formed. The F<sub>1</sub> males and females were reared to maturity and mated to produce the F<sub>2</sub> generation.

TABLE 1. Animal Assignment

Test Group	Dose (ppm)	Number Assigned per Group			
		F <sub>0</sub> Males	F <sub>0</sub> Females	F <sub>1</sub> Males	F <sub>1</sub> 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

<sup>2</sup> 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 (Safeparm 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

<sup>a</sup>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<sup>a</sup>

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

<sup>a</sup>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  $\pm 16\%$  of the nominal target concentrations (range 84-110%). Although this range falls outside that which is normally accepted ( $\pm 10\%$ ), our reviewers do not believe this adversely affected the study results.

#### 5. Dosage Administration

All doses were administered through treated diets. F<sub>0</sub> 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<sub>1</sub> males and females were exposed to the test article for 76 days prior to mating. As with the F<sub>0</sub> 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<sub>0</sub> and F<sub>1</sub> generations as follows:

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

#### 6. Mating

F<sub>0</sub> and F<sub>1</sub> 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<sub>0</sub> and F<sub>1</sub> 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<sub>0</sub> and F<sub>1</sub> 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<sub>2</sub> followed by cervical dislocation. Animals were then 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<sub>1</sub> 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)*<sup>3</sup>
- *Pituitary gland*
- *Prostate*
- *Seminal vesicles (with coagulating gland)*
- *Significant lesions*
- **Spleen**
- **Testes (right testis)**
- **Thymus**
- *Uterus (with cervix and oviducts)*
- *Vagina*

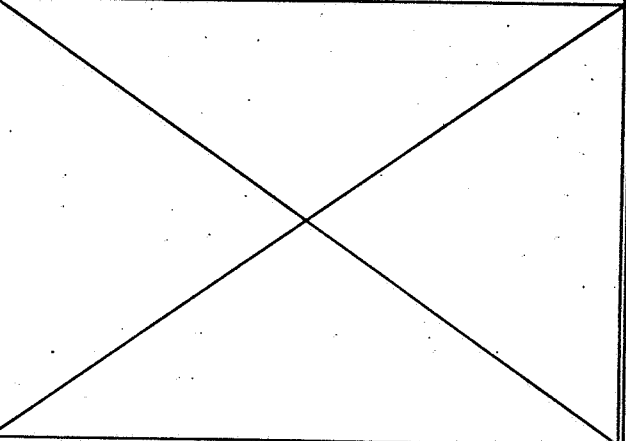
At the time of scheduled necropsy, F<sub>0</sub> and F<sub>1</sub> males were evaluated for sperm concentration, motility, and morphology. Descriptions of the sperm motility characteristics and morphology

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<sup>3</sup> The pancreas and mesenteric lymph nodes were not preserved for a small number of F<sub>0</sub> females from each dose group due to technical error. These females are identified in Appendix 31 of 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.	X

The number of oocytes also was evaluated by collecting the ovaries of 10 selected control and high-dose F<sub>1</sub> 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).<sup>4</sup>

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<sub>1</sub> pups selected to be F<sub>1</sub> 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*.

<sup>4</sup> 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.

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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<sub>1</sub> pups not selected to be F<sub>1</sub> mating adults and all F<sub>2</sub> pups alive at weaning were anesthetized with CO<sub>2</sub> 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 <sub>1</sub> pups	<ul style="list-style-type: none"> <li>Levene's test followed by one-way analysis of variance to establish homogeneity</li> <li>Dunnett's T3 Multiple Comparison Method for unequal variances</li> <li>Dunnett's Multiple Comparison Method for equal variances</li> </ul>

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Parameter	Statistical Method
Adult pre-coital intervals; female gestation lengths; pup reflexological responses; litter sex ratios; and adult organ weights relative to body weight	<ul style="list-style-type: none"> <li>• Kruskal-Wallis Nonparametric Rank Sum test on individual values</li> <li>• Mann-Whitney "U" test for pairwise comparison of control values vs. treated group values where significant differences were observed</li> </ul>
Pregnancy and parturition indices	<ul style="list-style-type: none"> <li>• Chi-squared analysis</li> </ul>
Histopathology findings	<ul style="list-style-type: none"> <li>• Histopathology computer program LABCAT version HP4.33</li> </ul>

## 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<sub>0</sub> 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<sub>0</sub> 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<sub>0</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>0</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>0</sub> animals, there were no significant changes in mean food consumption throughout the recorded periods for all treatment groups.

In 20,000-ppm F<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> females exhibited a significant increase in food consumption during study weeks 22 and 23 which was not considered biologically significant. High-dose F<sub>1</sub> 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<sub>1</sub> 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<sub>0</sub> and F<sub>1</sub> 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<sub>1</sub> animals had an overall higher test material intake than F<sub>0</sub> animals. This increase occurred because F<sub>1</sub> 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<sub>0</sub> and F<sub>1</sub> 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<sub>0</sub> mating pairs showed evidence of mating within the first four days of pairing. In F<sub>1</sub> 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<sub>0</sub> animals, and there were no significant differences between the number born when treatment groups were compared to the control group. In F<sub>1</sub> 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<sub>0</sub> or F<sub>1</sub> 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<sub>0</sub> 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<sub>1</sub> 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<sub>0</sub> 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<sub>0</sub> 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<sub>0</sub> males or females were toxicologically significant due to the lack of corresponding histopathological changes.

In F<sub>1</sub> 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<sub>1</sub> males exhibited a significant decrease in relative mean brain weight. In 20,000-ppm F<sub>1</sub> 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<sub>1</sub> 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<sub>0</sub> 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<sub>1</sub> 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<sub>0</sub> and F<sub>1</sub> animals surviving to terminal sacrifice exhibited a darkened or discolored pancreas. There also was an increased incidence of darkened mesenteric lymph nodes in F<sub>0</sub> females and F<sub>1</sub> males and females, with the F<sub>1</sub> 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<sub>1</sub> females, which may have been treatment-related according to the study author. Our reviewers note that 20,000-ppm F<sub>0</sub> 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<sub>0</sub> and F<sub>1</sub> 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<sub>0</sub> 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 findings 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<sub>0</sub> and F<sub>1</sub> 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<sub>1</sub> and F<sub>2</sub> offspring at any dose level. There were no significant differences observed in the sex ratio for F<sub>1</sub> offspring. In F<sub>2</sub> 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<sub>1</sub> or F<sub>2</sub> pups. Additionally, there were no treatment-related alterations in offspring reflexological responses for either F<sub>1</sub> or F<sub>2</sub> pups. At 20,000 ppm, there was a statistically-significant ( $p < 0.01$ ) increase in the proportion of F<sub>1</sub> pups successfully completing the surface righting reflex; however, the study author did not consider this treatment-related.<sup>5</sup>

2. Body Weights

Pup and litter weights are summarized in Tables 29-30 of this report. At 20,000 ppm, F<sub>1</sub> 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<sub>1</sub> 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*

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<sup>5</sup> Table 24, page 119, appears to be incorrectly labeled. The table title reads "Group Summary Offspring Reflexological Responses a) F<sub>0</sub>-F<sub>1</sub> Generation." Our reviewers believe that these data are actually for the F<sub>1</sub>-F<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> 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<sub>1</sub> male or female at any dose level.

4. Organ Weights

Organ weight data are summarized in Table 40 of this report. In F<sub>1</sub> and F<sub>2</sub> 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<sub>1</sub> and F<sub>2</sub> males and females. At 5000 ppm, a significant decrease in mean thymus weight was observed in F<sub>1</sub> males and F<sub>2</sub> 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<sub>1</sub> male 5000-ppm thymus weight is below the mean historical values provided (only when standard deviations were taken into account did F<sub>1</sub> 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<sub>0</sub> and F<sub>1</sub> animals. According to the authors, doses of 20,000 ppm caused significantly decreased body weights (F<sub>1</sub> males and females), significantly decreased body weight during gestation and lactation (F<sub>1</sub> females), and significantly decreased mean food consumption (F<sub>1</sub> males and females). Additionally, F<sub>1</sub> animals exhibited an overall higher test material intake than F<sub>0</sub> animals, which according to the study author, was the result of an earlier dosing initiation of F<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> adults.

In F<sub>0</sub> 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<sub>0</sub> females, a statistically-significant decrease in absolute mean brain weight at 5000 ppm was the only alteration in organ weight observed. F<sub>1</sub> 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<sub>0</sub> and F<sub>1</sub> males), decreased absolute and relative prostate weights (20,000-ppm F<sub>1</sub> 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<sub>0</sub> and F<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> mean litter weight and F<sub>1</sub> and F<sub>2</sub> 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<sub>1</sub> males and F<sub>2</sub> 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<sub>0</sub> and F<sub>1</sub> animals, including significantly decreased body weights during maturation (20,000-ppm F<sub>1</sub> males and females), significantly decreased body weight during gestation and lactation (20,000-ppm in F<sub>1</sub> females), and significantly decreased mean food consumption (20,000-ppm F<sub>1</sub> 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<sub>1</sub> 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<sub>0</sub> and F<sub>1</sub> males), decreased absolute and relative prostate weights (20,000-ppm F<sub>1</sub> 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<sub>0</sub> and F<sub>1</sub> 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<sub>0</sub> and F<sub>1</sub> females, as well as in 5000-ppm F<sub>0</sub> females. This differs slightly with the study author's assessment that 20,000-ppm F<sub>1</sub> 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<sub>0</sub> and F<sub>1</sub> 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<sub>1</sub> mean litter weight and F<sub>1</sub> and F<sub>2</sub> 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<sub>1</sub> males and F<sub>2</sub> females. Decreases at 5000-ppm did not fall outside of historical control data for F<sub>2</sub> females; however, the mean F<sub>1</sub> male 5000-ppm thymus weight is below the mean historical values provided (only when standard deviations were taken into account did F<sub>1</sub> 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<sub>0</sub> 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<sup>a</sup>

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

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

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

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

<sup>a</sup>Data extracted from Appendix 35, p. 743-746.

TABLE 9. F<sub>0</sub> Male Mean Body Weight (g)<sup>a</sup>

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		

<sup>a</sup>Data extracted from Table 4, p. 78.

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TABLE 10. F<sub>0</sub> Female Mean Body Weight (g) Before Pairing<sup>a</sup>

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	264	272	281	287	290
	S.D.	10.5	12.3	18.4	17.1	18.0	20.0	22.6	21.9	22.7	23.3
	N	28	28	28	28	28	28	28	28	28	28
Group 2 (1000 ppm)	MEAN	160	188	212	230	246	268	277	285	290	294
	S.D.	10.8	12.3	14.3	16.6	19.0	20.5	21.9	21.3	23.4	22.6
	N	28	28	28	28	28	28	28	28	28	28
Group 3 (5000 ppm)	MEAN	160	189	211	228	243	264	273	281	289	293
	S.D.	8.4	8.8	10.5	12.0	12.3	12.6	15.0	14.2	13.2	15.9
	N	28	28	28	28	28	28	28	28	28	28
Group 4 (20,000 ppm)	MEAN	161	191	211	229	243	268	277	283	290	294
	S.D.	9.1	11.5	13.6	14.4	16.3	18.4	19.0	17.9	18.0	18.5
	N	28	28	28	28	28	28	28	28	28	28

<sup>a</sup>Data extracted from Table 5, p. 80.

TABLE 11. F<sub>0</sub> Female Mean Body Weight (g) During Gestation and Lactation<sup>a</sup>

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	

<sup>a</sup>Data extracted from Tables 16 and 17, pp. 102 and 104, respectively

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TABLE 12. F<sub>0</sub> Male Mean Body Weight Gain (g)<sup>a</sup>

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

<sup>a</sup>Data extracted from Table 38, p. 164.

TABLE 13. F<sub>0</sub> Female Mean Body Weight Gain (g)<sup>a</sup>

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

<sup>a</sup>Data extracted from Table 39, p. 166.

TABLE 14. F<sub>1</sub> 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.

TABLE 15. F<sub>1</sub> Female Mean Body Weight (g) Before Pairing<sup>a</sup>

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

<sup>a</sup>Data extracted from Table 5, p. 81.

\*Significantly different from control, p<0.05.

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

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TABLE 16. F. Female Mean Body Weight (g) During Gestation and Lactation<sup>a</sup>

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

<sup>a</sup>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<sub>1</sub> Male Mean Body Weight Gain (g)<sup>a</sup>

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	113.5	173.8	231.3	283.3	319.1	354.1	381.0	404.1	
	S.D.	12.92	16.93	22.80	29.89	34.06	40.05	46.60	50.34	
	N	24	24	24	24	24	24	24	24	
Group 2 (1000 ppm)	MEAN	111.4	173.3	236.8	294.1	333.8	364.3	398.3	429.7	
	S.D.	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	
Group 3 (5000 ppm)	MEAN	111.8	173.5	235.1	290.1	329.2	353.5	383.8	411.9	
	S.D.	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	
Group 4 (20,000 ppm)	MEAN	100.2	154.9	217.4	268.1	304.7	332.8	355.9	373.6	
	S.D.	9.58	17.44	27.46	22.01	22.92	29.96	34.71	40.72	
	N	24	23	23	23	23	23	23	23	

<sup>a</sup>Data extracted from Table 38, p. 165.

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TABLE 18. F<sub>1</sub> Female Mean Body Weight Gain (g)<sup>a</sup>

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

<sup>a</sup>Data extracted from Table 39, p. 167.

TABLE 19. F<sub>0</sub> Male Mean Food Consumption (g/animal/day)<sup>a</sup>

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		

<sup>a</sup>Data extracted from Table 6, p. 82.

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TABLE 20. F<sub>0</sub> Female Mean Food Consumption (g/animal/day) Before Pairing<sup>a</sup>

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

<sup>a</sup>Data extracted from Table 7, p. 84.

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TABLE 21. F<sub>0</sub> Female Mean Food Consumption (g/animal/day) During Gestation and Lactation<sup>a</sup>

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	25.9	26.1	39.3	52.4	67.6
	S.D.	3.0	4.5	7.3	13.1	6.4
	N	27	27	26	26	25
Group 2 (1000 ppm)	MEAN	26.2	25.9	38.9	56.9	67.4
	S.D.	3.2	3.2	6.0	10.5	7.8
	N	27	27	26	26	26
Group 3 (5000 ppm)	MEAN	26.6	25.0	37.8	55.6	68.2
	S.D.	2.3	3.6	6.4	11.9	5.1
	N	28	28	28	27	27
Group 4 (20,000 ppm)	MEAN	26.9	25.3	41.0	59.5	69.2
	S.D.	2.7	4.2	4.1	6.8	6.5
	N	27	27	27	27	27

<sup>a</sup>Data extracted from Table 18, p. 106.

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TABLE 22. F<sub>1</sub> Male Mean Food Consumption (g/animal/day)<sup>a</sup>

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	1.6	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

<sup>a</sup>Data extracted from Table 6, p. 83.

\*Significantly different from control, p<0.05.

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

TABLE 23. F. Female Mean Food Consumption (g/animal/day) Before Pairing<sup>a</sup>

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

<sup>a</sup>Data extracted from Table 7, p. 85.

\*Significantly different from control, p<0.05.

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

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TABLE 24. F<sub>1</sub> Female Mean Food Consumption (g/animal/day) During Gestation and Lactation<sup>a</sup>

Group (Concentration - ppm)	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

<sup>a</sup>Data extracted from Table 18, p. 107.

\*Significantly different from control, p<0.05.

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

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TABLE 25. F<sub>0</sub> Male and Female Mean Food Conversion Ratio Before Pairing<sup>a</sup>

Group (Concentration - ppm)	Week of Measurement									
	1	2	3	4	5	6	7	8	9	10
<b>Males</b>										
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
<b>Females</b>										
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

<sup>a</sup>Data extracted from Tables 8 and 9, pp. 86 and 88, respectively.

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TABLE 26. F. Male and Female Mean Food Conversion Ratio Before Pairing<sup>a</sup>

Group (Concentration - ppm)	Week of Measurement									
	19	20	21	22	23	24	25	26	27	
<b>Males</b>										
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	
<b>Females</b>										
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	

<sup>a</sup>Data extracted from Tables 8 and 9, pp. 87 and 89, respectively.

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TABLE 27. F<sub>0</sub> Male and Female Mean Test Material Intake (mg/kg/day) Before Pairing<sup>a</sup>

Group (Concentration - ppm)	Week of Measurement										Mean
	1	2	3	4	5	6	7	8	9	10	
<b>Males</b>											
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
<b>Females</b>											
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

<sup>a</sup>Data extracted from Tables 10 and 11, pp. 90 and 92, respectively.

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TABLE 28. F<sub>1</sub> Male and Female Mean Test Material Intake (mg/kg/day) Before Pairing<sup>a</sup>

Group (Concentration - ppm)	Week of Measurement							Mean		
	19	20	21	22	23	24	25		26	27
<b>Males</b>										
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
<b>Females</b>										
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

<sup>a</sup>Data extracted from Tables 10 and 11, pp. 91 and 93, respectively.

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TABLE 29. Selected F<sub>0</sub> Reproductive Observations<sup>a</sup>

	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
N	28	28	28	28
Number of Males Paired	28	28	28	28
Number of Females Paired	28	28	28	28
Number of Females Mated	28	28	28	28
Number of Females Achieving Pregnancy	27	27 <sup>b</sup>	28	27
Mating Index (%)	100	100	100	100
Pregnancy (%)	96.4	96.4	100	96.4
Females with liveborn offspring	26	26	28	27
Parturition Index (%)	96.3	96.3	100	100
Gestation Length (days)				
21.5	1	0	0	1
22	11	10	8	3
22.5	5	11	13	4
23	9	5	7	18
23.5	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

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	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Litter Size	MEAN 14.6	15.7	15.3	15.6
Number born	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
Day 14	MEAN 8.0	7.9	8.0	8.0
	S.D. 0.2	0.3	0.2	0.0
	N 26	26	27	27
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

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	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	99.4
	S.D.	9.8	11.3	11.6
	N	26	26	27
Day 4	MEAN	131.1	137.6	143.9*
	S.D.	13.2	15.5	20.9
	N	26	26	27
Day 7	MEAN	126.1	122.0	122.0
	S.D.	14.7	11.3	12.4
	N	25	25	27
Day 14	MEAN	248.6	262.1	251.6
	S.D.	51.5	28.3	25.9
	N	26	26	27
Day 21	MEAN	407.2	416.3	374.4*
	S.D.	63.9	47.6	33.7
	N	25	26	27

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	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Individual Pup Weights (g)	MEAN	6.8	6.3**	6.5
	S.D.	0.8	0.5	0.5
	N	26	28	27
Day 4	MEAN	9.4	8.9	9.5
	S.D.	1.3	0.8	1.0
	N	26	28	27
Day 7	MEAN	15.8	14.7	15.3
	S.D.	1.8	1.4	1.6
	N	25	28	27
Day 14	MEAN	31.3	31.0	31.5
	S.D.	6.2	4.8	3.2
	N	26	27	27
Day 21	MEAN	51.3	49.7	46.8*
	S.D.	7.4	5.7	4.2
	N	25	27	27

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	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	7.2	8.0
	S.D.	2.0	1.6	2.2
	N	26	28	27
Female	MEAN	7.7	7.9	7.4
	S.D.	2.0	1.6	2.4
	N	26	28	27
% Male/litter	MEAN	50.5	47.5	52.1
	S.D.	12.4	9.0	14.1
	N	26	28	27
Day 21 Post Partum Male	MEAN	4.1	4.0	4.1
	S.D.	0.4	0.2	0.3
	N	26	27	27
Female	MEAN	3.8	4.0	3.9
	S.D.	0.5	0.0	0.3
	N	26	27	27
% Male/litter	MEAN	51.5	49.7	51.4
	S.D.	5.2	1.4	4.0
	N	26	27	27

<sup>a</sup>Data extracted from Tables 13, 15, 19, 20-22, and 25, pp. 96, 100, 108, 110, 112, 114, and 120, respectively.

<sup>b</sup>Includes one female that was killed due to suspected dystocia.

\*Significantly different from control, p<0.05.

TABLE 30. Selected F<sub>1</sub> Reproductive Observations<sup>a</sup>

	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
N	24	24	23	22
Number of Males Paired	24	24	23	22
Number of Females Paired	24	24	23	23
Number of Females Mated	24	24	22	23
Number of Females Achieving Pregnancy	22	24	22b	22
Mating Index (%)	100	100	95.7	100
Pregnancy (%)	91.7	100	100	95.7
Females with liveborn offspring	21	24	22	20
Parturition Index (%)	95.4	100	100	90.9
Gestation Length (days)				
22	10	14	15	8
22.5	5	3	7	4
23	6	7	0	8
23.5	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	16.0	16.3	15.9	14.7
Total Implantation Count	3.5	2.4	2.4	1.8
	22†	24	22	20†
Number Born	15.1	15.5	15.2	13.4*
	1.7	2.4	2.6	1.5
	21	24	22	21
Day 1	14.8	14.7	15.0	12.9*
	2.1	3.1	2.5	1.4
	21	24	22	21
Day 4	14.2	14.0	14.8	12.4
	2.7	3.3	2.4	1.9
	21	23	22	21
Day 7	7.8	8.0	8.0	8.0
	0.7	0.0	0.0	0.0
	21	21	22	21
Day 14	7.6	8.0	8.0	8.0
	1.0	0.0	0.0	0.0
	21	21	22	21
Day 21	7.6	8.0	8.0	8.0
	1.0	0.2	0.2	0.0
	21	21	22	21

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

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	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 S.D. 0.8 N 21	6.5 0.7 21	6.5 0.8 22	6.5 0.6 21
Day 4	MEAN 9.1 S.D. 1.4 N 21	9.3 1.2 21	9.5 1.5 22	9.5 1.3 21
Day 7	MEAN 15.0 S.D. 2.6 N 21	15.7 1.4 21	15.3 2.4 22	15.2 1.8 21
Day 14	MEAN 33.9 S.D. 3.2 N 21	34.8 2.3 21	33.1 3.5 22	31.9 2.7 21
Day 21	MEAN 53.3 S.D. 5.2 N 21	55.5 3.7 21	51.8 5.3 22	46.6*** 3.9 21

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	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 S.D. 2.2 N 21	6.4 2.4 24	7.8 2.1 22	6.0 1.9 21
Female	MEAN 7.0 S.D. 1.7 N 21	8.4 2.5 24	7.1 1.6 22	7.0 1.7 21
% Male/litter	MEAN 52.5 S.D. 10.8 N 21	43.0** 12.0 24	51.9 10.1 22	45.6 13.4 21
Day 21 Post Partum				
Male	MEAN 4.0 S.D. 0.5 N 21	3.9 0.3 21	4.0 0.4 22	3.8 0.7 21
Female	MEAN 3.6 S.D. 0.8 N 21	4.0 0.2 21	4.0 0.3 22	4.2 0.7 21
% Male/litter	MEAN 52.7 S.D. 8.2 N 21	49.1 3.1 21	49.7 4.1 22	47.6 9.4 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,  $p < 0.001$ .

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TABLE 31. F<sub>0</sub> Male Mean Semen Concentration/Motility Analysis (Selected Findings)<sup>a</sup>

		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

<sup>a</sup>Data extracted from Table 32, p. 137.

\*Significantly different from control, p<0.05.

TABLE 32. F<sub>1</sub> Male Mean Semen Morphology Analysis (Selected Findings)<sup>a</sup>

		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (5000 ppm)	Group 4 (20,000 ppm)
Head Area (µm <sup>2</sup> ) 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

<sup>a</sup>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<sub>0</sub> Male and Female Mean Absolute and Relative Organ Weights

Group	F <sub>0</sub> Males						F <sub>0</sub> 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	0.393	0.801	2.881	0.144	1.941	25	
	S.D.	0.1405	0.1175	0.4447	0.0147	0.0840		
	N	28	28	28	28	25		
Group 2 (1000 ppm)	MEAN	0.338	0.717*	2.627	0.156	1.926	26	
	S.D.	0.0804	0.0841	0.5830	0.0250	0.1093		
	N	28	28	28	28	26		
Group 3 (5000 ppm)	MEAN	0.369	0.755	2.480*	0.173**	1.873*	27	
	S.D.	0.1054	0.0752	0.4219	0.0574	0.0638		
	N	28	28	28	28	27		
Group 4 (20,000 ppm)	MEAN	0.313*	0.736	2.466**	0.160**	1.896	27	
	S.D.	0.0947	0.0942	0.3208	0.0260	0.1013		
	N	28	28	28	28	27		

<sup>a</sup>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<sub>1</sub> Male and Female Mean Absolute Organ Weight (g)<sup>a</sup>

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

<sup>a</sup>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.

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TABLE 35. Selected F<sub>1</sub> Male and Female Mean Relative Organ Weight (%)<sup>a</sup>

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

<sup>a</sup>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<sub>0</sub> Male and Female Summary of Selected Macroscopic Post Mortem Findings<sup>a</sup>

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

<sup>a</sup>Data extracted from Tables 27 and 28, pp. 123 and 125, respectively.

TABLE 37. F<sub>1</sub> Male and Female Summary of Selected Macroscopic Post Mortem Findings<sup>a</sup>

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

<sup>a</sup>Data extracted from Tables 27 and 28, pp. 124 and 126, respectively.

TABLE 38. F<sub>0</sub> Male and Female Summary of Selected Histopathological Findings<sup>a</sup>

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

<sup>a</sup>Data extracted from Tables 35 and 36, pp. 143-147 and 152-157, respectively.

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TABLE 39. F<sub>1</sub> Male and Female Summary of Selected Histopathological Findings<sup>a</sup>

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

<sup>a</sup>Data extracted from Tables 35 and 36, pp. 148-151 and 158-162, respectively.

TABLE 40. Selected F<sub>1</sub> and F<sub>2</sub> Male and Female Pup Mean Organ Weight (g)<sup>a</sup>

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

<sup>a</sup>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<sub>0</sub> (Sprague-Dawley CrI:CD<sup>®</sup> IGS BR Strain male and female rats) and 20% of the 192 study animals in generation F<sub>1</sub> 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<sub>0</sub> 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<sub>0</sub> 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<sub>1</sub> Generation- Males**

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

**F<sub>1</sub> Generation- Females**

<b>Group 1</b> <b>Control</b> <b>Dose Level: 0 ppm</b>	<b>Group 2</b> <b>Dose Level:</b> <b>1000 ppm</b>	<b>Group 3</b> <b>Dose Level:</b> <b>5000 ppm</b>	<b>Group 4</b> <b>Dose Level:</b> <b>20000 ppm</b>
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<sub>0</sub> 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<sub>1</sub> 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<sub>0</sub> 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<sub>1</sub> 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<sub>0</sub> - F<sub>1</sub> 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<sub>1</sub> - F<sub>2</sub> 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<sub>0</sub> 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<sub>1</sub> 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<sub>0</sub> Generation:

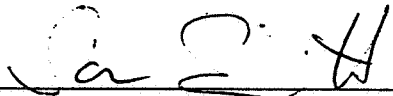
- Group 1: Concentration (M/ml) and Lateral amplitude ( $\mu\text{m}$ )
- Group 2: Motility (%) and Progressive velocity ( $\mu\text{m/s}$ )
- Group 3: Track speed ( $\mu\text{m/s}$ ) and Elongation (%)
- Group 4: Path velocity ( $\mu\text{m/s}$ ) and Beat frequency (Hz)

F<sub>1</sub> Generation:

- Group 1: Progressive motility (%) and Straightness (%)
- Group 2: Path velocity ( $\mu\text{m/s}$ ) and Linearity (%)
- Group 3: Lateral amplitude ( $\mu\text{m}$ ) and Area ( $\mu\text{m sq}$ )
- Group 4: Motility (%) and Lateral amplitude ( $\mu\text{m}$ )

**III. FINDINGS**

No problems or discrepancies were noted.

  
\_\_\_\_\_  
Sara Eisenstat, B.A.

1/16/03  
\_\_\_\_\_  
Date