



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

JUL - 8 2003

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: Toxicity Review on Silver Nitrate
ZEOMIC[®] Type AK Silver Zeolite A
EPA Reg. No.: 072674-E
DP Barcode: D287842
Case: 064467
PC Code: 072503

From: S. L. Malish, Ph.D., Toxicologist, *S. L. Malish 6/26/03*
Risk Assessment and Science Support Branch (RASSB), Antimicrobials Division
(AD)[7510C]

To: Marshall Swindell, PM 33
PM Team Reviewer, Tony Kish
Regulatory Management Branch
Antimicrobials Division [7510C]

Thru: Kay Montague, Acting Team Leader, *K. Montague 6/26/03*
Team One, RASSB/AD [7510C]

and

Norman Cook, Chief, RASSB/AD [7510C] *N. Cook 7/8/03*

Synonym: AgION[™] Silver Antimicrobial

FORMULATION:

<u>Active Ingredient:</u>	<u>% weight</u>
ZEOMIC Type AK Silver Zeolite A	5% a.i.

Laboratory: MPI Research, Mattawan, MI

Applicant: Sinanaen Co., Ltd., Tokyo, 105 Japan

Uses: This substance is a preservative and bacteriostatic agent for use in the manufacture of polymer, plastic and latex products for commercial and industrial use only.

ACTION REQUESTED:

Review A Dietary Two-Generation Reproduction and Fertility Study of Zeomic in Rats to support food use and drinking water use claims.

RECOMMENDATION:

The studies submitted, as noted in the Executive Summaries below is considered **Acceptable** by the reviewer and fulfill the guideline requirements for this type of study. A complete Data Evaluation Report (DER) is included.

EXECUTIVE SUMMARY: In a two-generation Reproduction and Fertility Effects study (MRID 458279-01), Zeomic Type AK Silver Zeolite A (5% a.i. silver) was administered via diet to male and female Sprague-Dawley CrI:CD® (SD) IGS BR rats at dose levels of 0, 1000, 6250, or 12,500 ppm (mean pre-mating phase of the P and F₁ generation ♂: 72, 472, 985 mg/kg/day, ♀: 87, 548, and 1109 mg/kg/day). Parental males and females were exposed to the test material for 70-75 days prior to mating. For both generations, treatment continued through the mating period until termination and included gestation and lactation periods for females.

Parental Effects: Effects on parental mortality were seen at the 6250 and 12,500 ppm dose levels. One P male and 8 F₁ animals (7 males and 1 female) died in the 6250 ppm group. In the 12,500 ppm group, 3 P males died and in the F₁ 28/30 males and 23/30 females died. Because of this mortality at the 12,500-ppm dose level, this group was terminated at completion of the F₁ pre-mating growth period; consequently, 6250 ppm became the high-dose level for F₁ animals.

Effects seen were significantly decreased body weights and body weight gains (6250- and 12,500-ppm P males; F₁ animals); significantly decreased body weights during gestation (6250- and 12,500-ppm P dams) and lactation (6250-ppm F₁ dams lactation), significantly decreased food consumption (6250- and 12,500-ppm P males; 12,500-ppm F₁ animals), and significantly decreased food consumption during lactation (12,500-ppm P dams).

Additional signs of toxicity included hematological changes (increased RBC and platelet counts and

lowered levels of hemoglobin, hematocrit and other blood parameters) in P animals (6250 and 12,500 ppm), increased cholesterol levels in P animals (6250 and 12,500 ppm), and decreased kidney weights (6250- and 12,500-ppm P animals; 1000- and 6250-ppm F₁ animals). Macroscopic and microscopic findings at 6250 ppm and 12,500 ppm were noted in the kidney

A NOAEL for is 1000 ppm (♂: 72, ♀: 87 mg/kg/day). The LOAEL is 6250 ppm (♂: 472, ♀: 548 mg/kg/day) based on decreases in body weight/body weight gain and food consumption, changes in hematology, clinical chemistry (cholesterol) and kidney histology.

A decrease in the live born index and an increase in the still born index was observed at 12,500 ppm in P and 6,250 ppm F₁ dams. Individual pup weights were decreased at 12,500 ppm on days 0 to 26. Pup weights were decreased at 6250 ppm on days 14 to 26.

Reproductive Effects: A NOAEL for reproductive toxicity is 1000 ppm (♂: 72, ♀: 87 mg/kg/day). The LOAEL of 6250 ppm (♂: 472, ♀: 548 mg/kg/day) is based on a decrease in the Live Born Index and an increase in the Stillborn Index in both the P and F₁ dams. Individual pup weights were decreased at 6250 ppm on days 14 to 26 and at 12,500 ppm on days 0 to 26.

Offspring Effects: Offspring effects occurred in the 6250 and 12,500-ppm pups, including decreased body weights during lactation, macroscopic alterations at weaning (small thymus, enlarged hearts, and pale kidneys, livers, and lungs), lower organ weight at weaning (brain, spleen, and thymus), and decreased pup survival during lactation (12,500-ppm F₁ litters). Significant dose related decreases in thymus weight (absolute and relative to body and brain weight) were observed at all dose levels in F₁ males pups.

The NOAEL for pup toxicity (both F₁ /F₂ generation) was considered to be 1000 ppm (♂: 72, ♀: 87 mg/kg/day) dose level. The LOAEL for pup toxicity was 6250 ppm (♂: ♂: 472, ♀: 548 mg/kg/day) based on decreases in thymus weight (absolute and relative to body and brain weight).

This reproductive toxicity study in the rat is classified as **Acceptable** and fulfills the guidelines of a Reproduction and Fertility Effects Study, OPPTS 870.3800.

Silver Zeolite

[§83-4] Reproduction and Fertility Effects/Rat

EPA Reviewer: Steven L. Malish, Ph.D., Toxicologist,
Team 1, RASSB/Antimicrobials Division (7510C)
Secondary Reviewer: Jonathan Chen, Ph.D., Toxicologist,
Team 3, RASSB/Antimicrobials Division (7510C)

S. L. Malish 6/18/03
Jonathan Chen 6/23/03

DATA EVALUATION RECORD

STUDY TYPE: Reproduction and Fertility Effects - Rat; OPPTS 870.3800, [§83-4]

DP BARCODE: D287842

SUBMISSION CODE: S627995

P.C. CODE: 072503 (Silver nitrate)

CASE: 064467

TEST MATERIAL (PURITY): Zeomic^R Type AK Silver Zeolite A (5% a.i.)

SYNONYMS: AgIONTM Silver Antimicrobial

CITATION: Schroeder, R.E. (2002). A Dietary Two-Generation Reproduction and Fertility Study of Zeomic in Rats. MPI Research (Mattawan, MI). Laboratory Study No. 892-002. December 17, 2002. MRID 458279-01. Unpublished.

SPONSOR: Sinanaen Co., Ltd.
4-22, Kaigan 1-Chome, Minato-Ku
Tokyo, 105 Japan

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Additional signs of toxicity included hematological changes (increased RBC and platelet counts and lowered levels of hemoglobin, hematocrit and other blood parameters) in P animals (6250 and 12,500 ppm), increased cholesterol levels in P animals (6250 and 12,500 ppm), and decreased kidney weights (6250- and 12,500-ppm P animals; 1000- and 6250-ppm F₁ animals). Macroscopic and microscopic findings at 6250 ppm and 12,500 ppm were noted in the kidney

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This reproductive toxicity study in the rat is classified as **Acceptable** and fulfills the guidelines of a Reproduction and Fertility Effects Study, OPPTS 870.3800.

COMPLIANCE: A signed and dated Compliance Statement is included in the study. The study was conducted according to U.S. EPA FIFRA Good Laboratory Practice Standards. A Statement of No Data Confidentiality Claims as well as a Flagging Statement. is also included

I. MATERIALS AND METHODS

A. MATERIALS

1. **Test Material:** Zeomic Type AJ Silver Zeolite A
Description: white powder
Supplier: AgION Technologies, LLC (Wakefield, MA)
Lot #: AK0038M

CAS #: not provided

Storage conditions: dry, at room temperature

Stability: at least 14 days in feed at room temperature.

2. Vehicle: administered as a dietary admixture

3. Test Animals: Rat

Strain: Sprague-Dawley CrI:CD® (SD) IGS BR

Source: Charles River Laboratories (Portage, MI)

Age on arrival: 4 weeks

Weight on arrival: 135-172 grams for males; 124-149 grams for females

Age at mating: not provided

Weight at mating: not provided

Housing: Individually housed, except during mating, in suspended, stainless steel cages except near parturition and during lactation. After gestation day (gd) 18 through lactation¹, females were individually housed in solid, plastic cages.

Acclimation period: ~ 14 days

Diet: Rodent Chow ® #5002 (supplied by PMI Nutrition International, Inc., St. Louis, MS) available *ad libitum* except during designated fasting periods.

Water: tap water available *ad libitum*.

Environmental conditions:

Temperature: 64-76° F

Humidity: 32-88%

Air changes: not provided

Photoperiod: 12 hours dark/12 hours light

B. PROCEDURES AND STUDY DESIGN

1. In Life Dates

Start: May 29, 2001; End: April 5, 2002

2. Animal Assignment

Healthy P males and females were randomized into 4 treatment groups (as shown in Table 1) through a standard (by weight) block randomization procedure.

Offspring from the P animals were designated F₁, and following weaning, treatment groups (totaling 30 animals/sex/group) were formed by selecting a minimum of 1 pup/sex/litter. When less than 30 litters were available per group, additional litters were randomly selected within the group to provide additional pups as needed.

¹ Twenty-six-day lactation period for P females; 21-day lactation period for F₁ females

*Verbal Communication from Amy Plato (regulatory Agent for Sinanaen Co., Ltd) to S. L. Malish, U.S. EPA on 4/22/2003.

TABLE 1. Animal Assignment

Test Group	Dose (ppm)	Number Assigned per Group			
		P Males	P Females	F ₁ Males	F ₁ Females
1	0 (control)	30	30	30	30
2	1000	30	30	30	30
3	6250	30	30	30	30
4	12,500	30	30	30*	30*

* Considerable mortality was observed at the 12,500-ppm dose level, causing the group to be terminated at completion of the pre-mating growth period; consequently, 6250 ppm became the high-dose level.

3. Dose Selection Rationale

The dose selection was determined by the Sponsor, or in consultation with the Sponsor. Selection was based on previous studies, and in particular, on a recent subchronic study in rats conducted at the testing laboratory (MPI Study No. 892-001). No details of this study were provided.

4. Test Diet Preparation and Analysis

Treated diets were prepared weekly, with each dose level prepared independently. For each dose level, the appropriate amount of test material was weighed, transferred into a mortar, and ground via a pestle. A small amount of Rodent Chow #5002 was added to the mortar, ground, and then transferred to a Hobart mixer where it was mixed for 5 minutes. The premix was then transferred to a blender and blended again after additional diet was added as needed to achieve the correct final dietary concentration. The formulated test diet was stored at room temperature.

The test material was largely comprised of silver and zinc; consequently, homogeneity and achieved concentrations were only assessed on these 2 compounds. To test for homogeneity, 9 samples (3 from the top, middle, and bottom) of low- and high-concentration test diets were collected prior to dosing initiation. The test diets were prepared by employing the same methods stated above and the samples were collected following mixing. For the concentration analysis, each formulation was sampled once per week during the first 4 weeks and then every 4 weeks until study completion. Samples were analyzed by KAR Laboratories, Inc. (Kalamazoo, MI). Stability of diets at similar concentrations were evaluated in a previous study (MPI Study No. 892-001) and were determined to be stable for at least 14 days at room temperature.

Results

Homogeneity Analysis: Homogeneity results are presented in Table 2 below.

Analytical data indicate that the test material was within $\pm 8\%$ of the mean nominal concentration (range 92-100%) for silver. Analytical data indicate that test material was within $\pm 15\%$ of the mean nominal concentration (range 85-91%) for zinc. Although this range falls outside that which is normally accepted ($\pm 10\%$), our reviewers do not believe this adversely affected the study results.

TABLE 2. Homogeneity Results^a

Compound	Dose Level (ppm)	Nominal Conc. (mg/kg)	Found Mean (mg/kg) \pm SD	Mean of Nominal Conc. (%)
Silver	1000	49	45.0 \pm 3.00	92
	12,500	613	613.0 \pm 36.10	100
Zinc	1000	130	110.0 \pm 7.09	85
	12,500	1625	1480 \pm 107	91

^aData extracted from MRID 458279-01, p. 30.
RSD: Relative standard deviation.

Concentration Analysis: Table 3 summarizes the concentration analysis results. The analytical data indicate that mean test material concentrations were within $\pm 9.3\%$ of the nominal target concentrations (range 90.7-91.5%) for silver. For zinc, the analytical data indicate that mean test material concentrations were within $\pm 3.5\%$ of the nominal target concentrations (range 96.5-102.1%).

TABLE 3. Analysis for Silver and Zinc Concentrations^a

Compound	Dose Level (ppm)	Nominal Conc. (mg/kg)	Mean of Nominal Conc.	
			mg/kg	% of nominal
Silver	0 (control)	0	0	NA
	1000	49	44.4	90.7
	6250	306	280.4	91.5
	12,500	613	552.1	90.2
Zinc	0 (control)	0	(63.5-81.3)	NA
	1000	130	132.7	102.1
	6250	813	821.9	101.1
	12,500	1625	1565.5	96.5

^aData extracted from MRID 458279-01, p. 31
() naturally occurring zinc.

5. Dosage Administration

All doses were administered through the treated diets. Parental males and females were exposed to the test material for 70-75 days prior to mating. Treatment continued through the mating period until termination and included gestation and lactation periods for females. Selected F₁ animals began dosing at weaning. F₁ and F₂ pups also were exposed to the control or test diets during lactation.

The mean doses in the pre-mating phase of the P and F₁ generations for males and females were used for calculation of the respective dose levels.

6. Mating

P and F₁ females were mated with males from the same group until evidence of mating was obtained (copulation plug in the vagina or presence of sperm in vaginal smear) or for a maximum of 14 days. Mating of siblings was avoided. A second litter was not required based on the results of the first mating; males were subsequently euthanized and necropsied.

7. Culling

On day 4 of lactation, P and F₁ litters were culled to 8 pups of equal sex distribution where possible.

C. OBSERVATIONS1. Parental Animals

Mortality, morbidity, injury, and availability of food and water were assessed twice daily. Detailed clinical examinations occurred weekly and included, but were not limited to, observations of the general condition, skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, as well as evaluation of respiratory and palpation or tissue masses. Towards the end of gestation, pregnant females were examined twice daily for signs of parturition. Duration of gestation and any difficulties with parturition were recorded. Day 0 of lactation was noted as the day that all pups were delivered. Dams also were observed twice daily for behavioral alterations in nesting and nursing. Body weights were recorded weekly before and during mating. After mating, males and unmated females were weighed weekly until termination; females that showed evidence of mating were weighed on gestation days (gd) 0, 7, 14, and 20. Body weights for females with litters were recorded on Days 0, 4, 7, 14 and 21 of lactation. P females with litters also were weighed on Day 26 of lactation, and terminal body weights were recorded for all parental generation animals. Individual food consumption was recorded one week pretest (data were not reported for P generation animals) and weekly thereafter except during mating. Food consumption for mated females was recorded on gd 0, 7, 14, and 20 and on Days 0, 4, 7, 14, and 21 of lactation.

The estrous stage of all parental females was determined by examining daily

vaginal lavage samples (three weeks prior to mating). Vaginal smears continued until there was positive evidence of mating. At necropsy, the stage of estrous cycle was determined for each female. Additionally, the number of uterine implantation sites were counted for females that cohabited with males.

Blood samples (approximately 3 mL) from 10 randomly-selected P generation animals/group were collected via the orbital sinus after CO₂/O₂ anesthesia during Study Week 2. Animals were fasted overnight, but had access to drinking water. The following parameters were evaluated: total and differential leukocyte counts; erythrocyte counts; hemoglobin; hematocrit; mean corpuscular hemoglobin, mean corpuscular volume, and mean corpuscular hemoglobin concentration; platelet count; prothrombin time; and activated partial thromboplastin time. The only clinical chemistry parameter measured was total cholesterol.

Complete necropsy examinations were performed on P and F₁ parental animals at the scheduled euthanasia (CO₂) and for those animals that died spontaneously or were euthanized *in extremis*. The organs and tissues listed below were preserved, removed, and placed in 10% neutral buffered formalin, except for the left testis and epididymis which were initially placed in Boulin's fixative prior to placement in 10% neutral buffered formalin. The right testis and epididymis were not fixed, but were store frozen for use in the sperm analysis. **Organs and tissues listed in bold below were weighed.** The epididymides, cauda portions, and right and left testis were weighed separately. Hematoxylin-eosin and periodic acid Schiff staining, as well as paraffin embedding, were used when processing the left testis.

• Adrenal (paired)	• Prostate
• Brain	• Seminal vesicle with coagulating gland (paired)
• Epididymides (paired organ; only the left side was microscopically examined)	• Spleen
• Gross Lesions	• Testis (paired)
• Kidneys (paired)	• Tissue masses
• Liver (3 sections collected; 2 examined)	• Uterus (both horns) with cervix and oviducts
• Ovary (paired)	• Vagina
• Pituitary	

Preserved tissues from 10 randomly-selected male and female control and high-dose animals from the P generation and 10 randomly-selected male and female control and 6250-ppm F₁ animals were subjected to histopathology examination. The kidneys of all parental animals were microscopically examined for treatment-related effects after abnormalities were observed during macroscopic examinations. Reproductive organs also were examined in animals suspected of low fertility (those who failed to mate, conceive, sire, or deliver, or had affected estrous cyclicity or sperm number, motility or morphology). Examination of the testes was given special attention, with the caput, corpus, and cauda of the epididymis being examined on a longitudinal section through the entire structure. In F₁ females, five ovarian sections were taken at least 100 µm apart from the inner third of each ovary, and the total number of primordial follicles (which may be combined with small growing follicles) was counted. All histopathology slides were examined by a veterinary pathologist, who used a four-step grading system of trace, mild, moderate, and severe to define gradable lesions for comparison between the treatment groups.

Daily sperm production (DSP) was generally determined using the procedure outlined by Blazak et al. (1993), in which the number of spermatids per testis is divided by 6.1 (the number of days spanned in homogenization-resistant form).² Evaluations were performed on high-dose (12,500 ppm for P males and 6250 ppm for F₁ males) and control animals. The right testis was decapsulated and homogenized, allowing the number of homogenization-resistant sperm heads to be evaluated using a hemacytometer. Sperm motility was evaluated by videotaping a section of the right vas deferens and utilizing the Hamilton-Thorne Computer Assisted Semen Analysis System. The percent motile and progressively motile sperm for all P males in the control and treated groups and F₁ males in the control, 1000-, and 6250-ppm dose groups was determined. The sperm count per gram of caudal epididymal tissue was measured by separating, weighing, and collecting a sperm sample for a manual concentration count from the right cauda epididymis. Epididymal sperm counts were measured for all P males in the control and treated groups and F₁ males in the control, 1000-, and 6250-ppm groups. Sperm morphology was evaluated for the same groups and was evaluated microscopically using the same sample from the motility assessment; at least 200 sperm/animal were evaluated.

2. Offspring

The following data were recorded as soon as possible for each litter:

- Litter size;
- Number of stillborn pups;

² Blazak WF, Treinen KA, Juniewicz PE. 1993. Application of testicular sperm head counts in the assessment of male reproductive toxicity. In Chapin RE, Heindel (eds.). *Methods in Toxicology, Volume 3, Part A, Male Reproductive Toxicology*. Academic Press, Inc.: San Diego.

- Number of live born pups;
- Gross abnormalities of pups;
- Pup body weight;
- Sex of all live pups.

Litters were observed twice daily for survival and behavioral alterations in nesting and nursing; the presence of dead pups was recorded. Dead pups recovered at birth or during lactation were necropsied if intact. Gross external examinations and individual weights were recorded on Days 0, 4, 7, 14, and 21 of lactation. F₁ pups also were individually weighed and examined for gross external abnormalities on Day 26 of lactation.

All F₁ pups selected to be F₁ mating adults also were monitored for sexual development. For females, sexual development was recorded as the day of vaginal opening. Examinations commenced on Day 28 of age and were performed daily until vaginal opening was achieved. For males, sexual development was recorded as the day of balanopreputial cleavage. Examinations commenced on Day 35 of age and were performed daily until balanopreputial separation occurred. The age and body weight of the males and females upon reaching these landmarks were recorded.

Complete necropsy examinations were performed on F₁ and F₂ pups culled on Day 4, F₁ pups not selected for mating, and all F₂ pups at weaning. Necropsy examinations also were performed on F₁ and F₂ pups that died or were euthanized *in extremis* during lactation or were littered from dams that died during lactation; the completeness of these examinations was not stated. Pups 14 days of age were euthanized via CO₂ inhalation, while pups 1 to 13 days of age were euthanized via intrathoracic injection of sodium pentobarbital. From one male and one female pup per litter (randomly selected), the brain, spleen, and thymus were weighed. Ten-percent neutral buffered formalin was used to save the thymus of selected F₂ pups, as well as any gross lesions from F₁ and F₂ pups. Any abnormalities characterized as developmental anomalies were microscopically examined, with an emphasis placed on reproductive organs during the necropsies.

Zinc, silver, and copper levels were determined for six F₂ pups/group (3/sex/group).

D. DATA ANALYSIS

The formula for various indexes were included in Appendix 2 of this report.

1. Statistical Analyses

Table 4 summarizes the parameters evaluated and the method used to determine their statistical significance.

TABLE 4. Statistical Analyses

Parameter	Statistical Method
<p>Parental In-life Data: Premating and postmating body weights and body weight change (week-to-week and over the premating period); premating and postmating food consumption; gestation body weights and body weight changes (between each weighing interval and over the entire gestation period); gestation food consumption; lactation body weights and body weight changes (between each weight interval and over the entire lactation period); lactation food consumption; estrous cyclicity data (mean cycle length, mean number of cycles/period)</p> <p>Fertility Indices: gestation length; copulatory interval (mean days to mating)</p> <p>Pathology: male organ weights; female organ weights; spermatogenesis concentration, homogenization (resistant sperm heads), DSP (daily sperm production), and DSP/gram tissue; ovarian primordial follicle count</p> <p>Uterine Exam: total implantations.</p> <p>Litter Data (F₁ and F₂): litter size; live pups; stillborn pups</p> <p>Developmental Indices (F₁): preputial separation (age and body weight at criteria); vaginal opening (age and body weight at criteria)</p> <p>Clinical Pathology: hematology (except leukocyte counts; clinical chemistry (total cholesterol)</p>	<p>Group Pairwise Comparisons: Levene's test was used to assess the homogeneity of group variances. Dunnett's test was used to compare each treatment group with the control if Levene's test was not significant ($p > 0.01$); Welch's t-test with a Bonferroni correction was used if Levene's test was significant ($p < 0.01$). Results of the pair-wise comparison were reported at the 0.05 and 0.01 significance levels, and all endpoints were analyzed using two-tailed tests unless indicated otherwise.</p>
<p>Fertility Indices: male and female mating, fertility, and fecundity indices; gestation index</p>	<p>Fisher's Exact Test: Treatment and control groups with binomial endpoints (except sex ratios) were compared using a Fisher's exact test with a Bonferroni correction. Results were reported at the 0.05 and 0.01 significance levels, and all endpoints were analyzed using two-tailed tests unless indicated otherwise.</p>
<p>Pathology: spermatogenesis % abnormal; % motility</p> <p>Litter Data (F₁ and F₂): live birth index; pup sex ratio (mean % male pups - Days 0, 4, prickle, 4 postcull, Day 21 and 26 [F₁ litters]); stillborn index; pup survival (Days 0-4 prickle, 4 postcull - day 21 [both F₁ and F₂], and Day 4-26 for the F₁)</p>	<p>Arcsin-Square-Root Transformation: Data comprised of percent values were transformed using the arcsin of the square root; group pairwise comparisons (as described above) were used to analyze the transformed percentage values.</p>
<p>Litter Data (F₁ and F₂): mean pup body weights.</p>	<p>Covariate Analysis: A test of assumptions was performed for each endpoint (listed to the left) and time period to determine whether litter size would be included as a covariate in the model. The model used tested the difference from the control by using Dunnett's test and each treatment group was compared to the control. Results were reported at the 0.05 and 0.01 significance levels, and all endpoints were analyzed using two-tailed tests unless indicated otherwise.</p>
<p>Clinical Pathology: total leukocyte counts; differential leukocyte counts</p>	<p>Log Transformation: A log transformation was performed on leukocyte counts (total and differential) because historically they are not normally distributed; group pairwise comparisons (as described above) were used to analyze the transformed data.</p>

3. Historical Control Data

Historical control data on prenatal and postnatal development are provided in original report, MRID 458279-01.

II. RESULTS

A. PARENTAL TOXICITY

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

1. Mortality and Clinical Observations

Mortality for the P generation is summarized below in Table 5. No mortality was observed in treated females; 1/30 control females died during week 11. In males, mortalities consisted of one 6250-ppm animal (died on Study Day 115) and three 12,500-ppm animals (died on Study Days 40, 113, and 148, respectively); these deaths were considered to be treatment-related. According to the study author, there were no treatment-related clinical observations.

TABLE 5. Summary of Mortality P Parental Generation *

Group (ppm)	Males ^a	Females ^a
1 (0)	0/30 (0%)	1/30 (3.3%)
2 (1000)	0/30 (0%)	0/30 (0%)
3 (6250)	1/30 (3.3%)	0/30 (0%)
4 (12,500)	3/30 (10%) ^b	0/30 (0%)

*Data extracted from MRID 458279-01, p. 32.

^aNumber of animals found dead or euthanized in extremis/total animals in the group.

^bExcludes one male that died following blood collection. Death of the animal was attributed to the blood collection procedure.

Mortality for the F₁ parental generation is summarized below in Table 6. No mortality occurred in the male and female control group, while one 1000-ppm male (male number 653) died on Study Day 11. Clinical and necropsy findings were inconclusive as to the reason of death. No 1000-ppm females died prior to study termination. At 6250 ppm, seven males and one female died, with mortality occurring between Weeks 4 through 10. These deaths were considered treatment-related; however, the cause of death reportedly was not apparent from clinical, macroscopic, or microscopic findings with the exception of one 6250-ppm male (male number 685) whose death may have been attributed to malocclusion and abrasion of the hard palate. At 12,500 ppm, weaned F₁ animals were approximately 50% the size of controls and failed to thrive postweaning. Deaths were first observed by Study Day 4, and by the end of the pre-mating period, 28/30 males and 23/30 females had died; all animals were terminated by the end of the pre-mating period (Study Day 78) due to the considerable mortality.

TABLE 6. Summary of Mortality F₁ Parental Generation^a

Group (ppm)	Males ^b	Females ^b
1 (0)	0/30 (0%)	0/30 (0%)
2 (1000)	1/30 (3.3%)	0/30 (0%)
3 (6250)	7/30 (23.3%)	1/30 (3.3%)
4 (12,500) ^c	28/30 (93.3%)	23/30 (76.7%)

^aData extracted from MRID 458279-01, p. 41.

^bNumber of animals found dead or euthanized in extremis/total animals in the group.

^cGroup terminated at completion of the pre-mating period prior to the start of pairing due to excessive mortality.

There were no remarkable clinical signs of toxicity observed at 1000 ppm in either F₁ parental males or females. At 6250 ppm, five males were observed with hunched posture. Two out of the five animals died, while the occurrence for the remaining three was transient and occurred between Study Weeks 10-18 and Weeks 15-18. At 12,500 ppm, the animals showed numerous clinical signs of toxicity that were attributed to failure to thrive. Males and females at this high dose exhibited an increased incidence of brown material around the nose, hunched posture, emaciation, sparse hair over the entire body, cold to touch, pale skin, and/or unkempt appearance while the male exhibited extended penises. Females at 12,500 ppm exhibited similar clinical symptoms as the males.

2. Body Weight

Male and female body weight and body weight change data are summarized in Tables 1- 8 of Appendix 1 of this report.

In 1000-ppm P males, there were no significant changes in body weight. Significant, treatment-related decreases were observed starting beginning Week 4 for 6250-ppm males [mean 7%] and Week 2 for 12,500-ppm males [mean 10%] which lasted throughout the study. Sporadic significant decreases in male body weight gain were observed for treatment groups in the pre-mating phase, 12% at 6250 ppm and 17% at 12,500 ppm. In the pairing and post-mating phases no consistent pattern was seen at the lower doses, however, the 12,500 ppm dose showed a weight gain decrease of 37% at 12-13 weeks of mating.

For females, body weight were comparable to controls at all dose levels up to the lactation periods, at which point decreases occasionally observed at dose levels of 6250 and 12,500 ppm. At 6250 ppm, significant body weight decreases were at lactation day 14 (7%); at 12,500 ppm significant decreases were seen at on gd 20

[6%] and lactation day 4, 7, 21 with a mean decrease of 9%. Body weight gain was generally comparable to controls, except during gd 14-20 [29%] and 0-20 [16%] at 12,500 ppm, and lactation days 7-14 at both 6250 ppm [>100%] and 12,500 ppm [98%].

In 1000-ppm F₁ males, there were no significant changes in body weight or in body weight gain. Significant, treatment-related decreases in body weight were observed beginning at Week 1 for 6250-ppm [≈11 to 25%] males and 12,500-ppm [≈55 to 60%] males and lasting until the animals were terminated.

At 12,500-ppm males, significant, treatment-related decreases [47%] in male body weight gain were observed from weeks 1 to 12. Decreases at 6250 ppm [6%] were considered to be of little toxicological importance.

For females, body weight and body weight gain were comparable to controls at 1000 ppm, except a decrease during lactation day 4 [7%]. Significant, treatment-related reductions in body weight were observed at 6250 ppm at Weeks 1 through 6 pre mating [9 - 19%] and lactation days 0, 4, 7, and 21 [mean 7%]. Body weight gain for 6250-ppm females, at times, was significantly higher than controls but was generally comparable to controls during the gestation and lactation periods.

During the pre mating period, week 1 to 12, females dosed with 12,500 ppm exhibited significantly decreased body weight [45%] and lower body weight gains [mean 40%].

3. Food Consumption

Male and female food consumption data are summarized in Tables 9-12 of Appendix 1 of this report.

For 1000-ppm P males, sporadic, significant decreases in food consumption occurred during the pre mating and post mating periods; however, these changes were not considered toxicologically meaningful. Significant, treatment-related decreases in food consumption were observed in 6250- and 12,500-ppm males during the pre mating and post mating periods [mean 7%] at 12,500 in the pre mating period (mean 22%) ppm and were consistent with decreases in body weights and body weight gains.

For P females, there were no alterations in food consumption observed at any dose level during the pre mating or gestation period. There also were no changes in food consumption at 1000 ppm during lactation. At 6250 ppm, sporadic alterations (a significant increase during lactation days 4-7 and a significant decrease during days 14-21) were considered unrelated to treatment. Decreases [mean 22%] in food consumption were observed during lactation days 0-4, 7-14, and 14-21 for 12,500-ppm females, suggested a treatment-related response.

There were no significant changes in food consumption for 1000-ppm F₁ males.

Decreases [mean 12%] in food consumption were observed throughout the study period for 6250-ppm males, with most differences reaching statistical significance. The toxicological significance of this finding is unclear since there were no consistent reductions in body weight gain during this period. At 12,500 ppm, significantly decreased [mean 53%] food consumption was observed in males, which was consistent with poor weight gain. In females, decreases in food consumption during the pre-mating, gestation, and lactation periods were observed at dose levels of 1000 and 6250 ppm; however, these sporadic changes were considered unrelated to treatment. Significant decreases [mean 37%] observed throughout the pre-mating period at 12,500 ppm were consistent with poor weight gain and were considered to be treatment-related.

4. Test Article Intake

The average test article intakes for P males during the pre-mating period were 73, 466, and 972 mg Zeomic/kg body weight/day based on food consumption and nominal concentrations of 1000, 6250, and 12,500 ppm, respectively. The average test article intakes for P females were 86, 513, and 1056 mg Zeomic/kg body weight/day based on food consumption and nominal concentrations of 1000, 6250, and 12,500 ppm, respectively.

For F₁ males, the average test article intakes during the pre-mating period were 71, 477, and 996 mg Zeomic/kg body weight/day based on food consumption and nominal concentrations of 1000, 6250, and 12,500 ppm, respectively. The average test article intakes for F₁ females were 87, 582, and 1161 mg Zeomic/kg body weight/day based on food consumption and nominal concentrations of 1000, 6250, and 12,500 ppm, respectively.

The mean doses in the pre-mating phase of the P + F₁ generations, respectively, for males and females were used for calculation of the dose levels.

5. Estrous Cycling Evaluation

There were no treatment-related effects on estrous cycling (mean estrous cycle length and mean number of estrous cycles) for P and F₁ females at any evaluated dose level. Estrous cyclicity was not evaluated for 12,500-ppm F₁ females due to the excessive mortality and the small number of females surviving for evaluation.

6. Mating, Fertility, and Reproduction

Data on mating, fertility, and reproduction are summarized in Tables 13 (Parental) and Table 14 (F₁) of Appendix 1 of this report.

There were no treatment-related effects observed in the parturition endpoints measured for P animals treated with 1000- and 6250-ppm test material, except for a significantly increased mean gestation length observed in 6250-ppm dams (22.3 days vs. 21.9 days for controls). The magnitude of change, although statistically significant, was not sufficient enough to be considered a toxicologically meaningful effect. High-dose animals also exhibited statistically-significant

increases in gestation length (22.3 days vs. 21.9 days for controls). As with the mid-dose dams the magnitude of change was not sufficient to be considered toxicologically significant. Treatment-related, significant alterations in high-dose dams included decreases in the live birth index, number of pups born at Day 0, mean live born/litter, and mean litter size on Days 4 (pre and postculling), 7, 14, 21, and 26. A significant increase in the stillborn index also was observed. All females in the control and treated groups retained litters to weaning, except for six 12,500-ppm dams who experienced complete pup mortality in their litters.

For F₁ animals, there were no treatment-related effects observed in the mating, fertility, and reproduction endpoints measured for 1000-ppm dams. A slight, insignificant decrease in the number of live pups and total pups at birth in this dose group was noted; however, due to the lack of statistical significance and absence of similar results in the 6250-ppm dose group, this decline was considered spurious and not related to treatment. Additionally at 1000 ppm, there was a significant decrease in the number of live pups/litter observed on lactation days 7, 14, and 21. Because litter size at 6250 ppm was comparable to controls, this decrease was considered by the study author not to be toxicologically meaningful or related to treatment. At the 6250-ppm dose, a significant decrease in the live birth index and a significant increase in the stillborn index was observed. Additionally, the mean number of dams with stillborn pups (mean = 10) was higher than that of controls (mean = 3). These effects were considered treatment-related. All dams in the control and 6250-ppm treatment group weaned litters. Two females (out of a total of 18) in the 1000-ppm dose group failed to wean litters and all pups died prior to Day 4 of lactation. The study author considered this occurrence to be incidental in nature because similar responses were not observed in the 6250-ppm dose group. There were no statistical differences in the mean number of uterine implantation scars in either the P or F₁ treated dams when compared to controls.

7. Sperm Analysis

There were no treatment-related effects on any sperm parameters at necropsy for P males, including sperm motility and caudal epididymal concentration, homo-genation-resistant sperm heads, calculated daily sperm production, spermatogenic efficiency, and percent normal sperm (at 12,500 ppm). For F₁ males, sperm endpoints in treatment groups were comparable to controls except for significant increases in the percent abnormal sperm at 1000 ppm and percent motility and percent progressive motility at 6250 ppm. These changes were considered incidental and not treatment-related due to the lack of a dose-response.

8. Primordial Follicle Count

There were no treatment-related effects on primordial follicle counts in F₁ parental animals treated with 1000 or 6250 ppm. Counts were lower at 1000 ppm, but in the absence of a dose-response relationship, were considered this to be unrelated to treatment.

9. Clinical Pathology

Hematology and clinical chemistry data are summarized in Tables 15-16 of Appendix 1 of this report.

a. Hematology

Significant decreases in hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) values and significant increases in erythrocytes and platelet counts were observed in high-dose males. MCV and MCH values also were significantly decreased in 6250-ppm males.

High-dose females experienced identical hematology alterations except that hematocrit decreases did not reach statistical significance and eosinophil values were significantly increased. Significant decreases in MCV, MCH, and MCHC and significant increases in erythrocyte values were observed in mid-dose females. These hematological alterations were believed to be treatment related.

b. Clinical Chemistry

Cholesterol values were significantly increased in mid- and high-dose animals; these increases also were believed to be treatment-related.

10. Organ Weight

Organ weight data are summarized in Tables 17-21 of Appendix 1 of this report.

There were no significant organ weight alterations observed in 1000-ppm P males. Mid-dose males exhibited significant decreases in terminal body weight, absolute brain weight, kidney weight (absolute and relative to body and brain weight), and absolute pituitary weight, as well as significantly increased spleen weight (absolute and relative to body weight). In 12,500-ppm males, significant decreases in terminal body weight, brain weight (relative to body weight), and kidney weight (absolute and relative to brain weight) were observed. Significant increases included left and right epididymis weight relative to body weight, left and right testis weight relative to body weight, and absolute spleen weight.

In P females, there were no significant changes in organ weight at 1000 ppm, and only sporadic alterations were observed at 6250 and 12,500 ppm (significantly decreased kidney/brain weight at 12,500 ppm; significantly decreased absolute pituitary weight and relative pituitary/brain weight at 6250 ppm). These alterations were considered incidental and not related to treatment. Treatment-related changes in kidney weight may have been associated with the higher incidence of renal chronic inflammatory processes and hydronephrosis noted in these groups.

In F₁ animals, treatment-related organ weight alterations were observed in both sexes at 1000 and 6250 ppm; there was no statistical analysis performed on 12,500-ppm animals. Significant decreases in 1000-ppm males were observed in the following: kidney weight (absolute and relative to body and brain weight) and pituitary weight (relative to body and brain weight). In 6250-ppm F₁ males, significant decreases were observed in the following: terminal body weight; absolute brain weight; adrenal weight (absolute and relative to brain weight); left epididymis weight (absolute and relative to brain weight); absolute right epididymis weight; kidney weight (absolute and relative to body and brain weight); absolute liver weight; relative pituitary weight to body weight; prostate weight (absolute and relative to brain weight); absolute seminal vesicle weight; absolute left testis weight; and right testis weight (absolute and relative to brain weight). Also at 6250 ppm, a significant increase in relative spleen to body weight was observed. Females treated with 1000 ppm exhibited significant decreases in kidney weight (absolute and relative body and brain weight), liver weight (absolute and relative to brain and body weight), and absolute spleen weight. In 6250-ppm females, decreases were observed in absolute brain weight, kidney weight (absolute and relative to brain and body weight), absolute liver weight, and absolute uterus, oviducts, and cervix weight. Consequently, the study author concluded that treatment-related changes in kidney weight (in both males and females) may have been associated with the higher incidence of renal chronic inflammatory processes and hydronephrosis noted in these groups. Sporadic alterations observed in liver weights were not considered treatment-related due to the lack of a dose-response.

11. Gross Pathology

Discoloration of several organs was observed at all dose levels; however, mild discoloration exhibited in low-dose animals was not believed to be treatment-related. Treatment-related, mild to severe discoloration (green to tan/brown) of several organs was exhibited by both sexes of P animals at doses of 6250 and 12,500 ppm. Organs noted by the study author included: pancreas, thymus, mandibular salivary glands and lymph nodes, Harderian glands, exorbital lacrimal glands, glandular stomach, duodenum, urinary bladder, prostate gland, and clitoral glands.

Also noted was an increased frequency in irregular renal cortical surfaces, with 1/30, 6250-ppm males, 8/30, 12,500-ppm males, and 2/30, 12,500-ppm females exhibiting granularity. This change may correspond to chronic interstitial nephritis and/or infarction noted in the Histopathology Section of this report. High-dose males also exhibited an increased incidence of pelvic dilation and urinary tract lesions (which may be the consequence of lower urinary tract obstruction). Females also exhibited pelvic dilation, this effect only occurred in the low and mid dose groups and, therefore, a treatment response relationship could not be established.

F₁ animals exhibited similar gross pathology alterations as the P animals.

Animals treated with 1000 ppm exhibited mild to moderate discoloration in the thymus (2 males and 5 females) and pancreas (17 females). At 6250 ppm, treatment-related mild to moderate discoloration (green to tan/brown) of the following organs was observed in both sexes: pancreas, thymus, glandular stomach, duodenum, jejunum, mandibular salivary gland, Harderian gland, exorbital lacrimal glands (females only), pineal gland (males only), and urinary bladder.

As with P animals, treatment-related alterations also were observed in the urinary tract of animals dosed with 6250 ppm and included an increased incidence of renal cortical surface irregularity (mild to moderate), calculi (mild), and pelvic dilation (mild to moderate). Mild calculus formation also was observed in the urinary bladder in two 6250-ppm males; the study author noted that urinary calculi were not observed in P animals. Additionally, mild to moderate decreases in thymus size were observed in one 1000-ppm male and in two 6250-ppm males. This low incidence of thymus atrophy could have been the result of a physiologic involution of the thymus or spontaneous changes; therefore, changes in thymus size could not be definitively attributed to the test material.

F₁ animals fed diets of 12,500 ppm were examined for macroscopic lesions. Lesions noted at this concentration level were generally similar to other treated groups. One exception noted was the increased incidence of penile distension/extension and red discoloration. These changes may have been associated with other alterations in the urinary tract (urolithiasis and chronic inflammation). Additional noted macroscopic lesions at 12,500-ppm included: green to brown discoloration of the pancreas, duodenum and prostate gland; renal calculi, cortical surface irregularity, and pelvic dilation; decreased thymic size; and cardiac and splenic enlargement.

12. Histopathology

Histopathology findings are summarized in Tables 22-25 of Appendix 1 of this report.

The most significant treatment-related alterations occurred in the kidneys of mid- and high-dose males and females and included: chronic interstitial nephritis, hydronephrosis, and pelvic urothelial hyperplasia. According to the study author, these increases in incidence and severity were, in part, due to the presence of calculi and associated traumatic injury to adjacent tissues.

Additionally, treatment-related pigmentation, occurring predominately in P high-dose males and females, was observed within the interstitium of the pancreas, thymus, mandibular salivary glands, Harderian glands and prostate gland, the lamina propria of the glandular stomach and duodenum, renal glomerular and tubular basement membranes, and the submucosa of the renal pelvis and urinary bladder. Higher incidence rates were observed in the pancreas and kidneys for males and females combined and in the Harderian glands, thymus, and urinary

bladder for females only. Because there were no corresponding inflammatory or degenerative responses, pigmentation was not considered a toxic effect.

Histological alterations observed in F₁ animals were similar to those seen in P animals. The most significant treatment-related alterations occurred in the kidneys. Increased incidences and severity of chronic interstitial nephritis, hydronephrosis, infarction, and pelvic urothelial hyperplasia were observed in both sexes at 6250 ppm. These findings were most likely attributable to the presence of calculi and associated tissue trauma. Additionally, calculi were observed in the urinary bladder of one 6250-ppm male.

Other treatment-related histological changes, such as brown to black pigmentation, were observed in both 1000- and 6250-ppm animals. At 1000-ppm, pigment deposition was observed in the kidneys and thymus (both males and females), as well as the pancreas (females only). At 6250 ppm, pigment deposition was noted in the interstitium of the pancreas, thymus, mandibular salivary glands, exorbital lacrimal glands, Harderian glands, and pineal gland, the lamina propria of the glandular stomach, duodenum and jejunum, the submucosa of the renal pelvis and urinary bladder, renal tubular and glomerular basement membranes, and medullary sinuses of the mandibular lymph nodes. Due to the lack of inflammation, pigment deposition was not considered a toxic effect.

F₁ animals dosed with 12,500 ppm that died during the study or were euthanized at study termination also were evaluated. Treatment-related alterations were noted as thymic atrophy, increased splenic extramedullary hematopoiesis, and penile congestion and inflammation. Increased splenic extramedullary hematopoiesis was associated with splenomegaly, which was observed during the gross pathology examination. Penile congestion and inflammation were suggested to be sequelae of urolithiasis. Additional treatment-related microscopic lesions included trace to mild pigment deposition in the thymus, pancreas, kidneys, glandular stomach, duodenum, and colon. Other alterations were not considered treatment-related.

B. OFFSPRING TOXICITY

1. Mortality, Viability, and Clinical Observations

Data on offspring mortality and viability are summarized in Tables 13-14 of the Appendix of this report.

There were no significant effects on the pup survival indices for 1000- or 6250-ppm F₁ offspring. Also low- and mid-dose pups showed no statistical differences in sex ratios and exhibited no clinical signs of toxicity related to treatment. At 12,500 ppm, there were significant decreases observed in the pup survival index at Days 0-4 preculling and sex ratio for pups on Day 4 (preculling). High-dose pups also exhibited an increased incidence of paleness at weaning on Day 26. High-dose animals also exhibited an increase in blue skin discoloration at the

cervical region and difficulty breathing.

There were no significant effects on the pup survival indices or sex ratios for 1000- or 6250-ppm F₂ pups. Also, there were no clinical signs of toxicity related to treatment observed at either dose level.

2. Body Weights

Pup weights are summarized in Tables 13-14 of the Appendix 1 of this report.

Pup body weights were assessed by sex and for both sexes combined. At 1000 ppm, F₁ pup weights were generally comparable to the controls. At the 6250-ppm dose, pup weights were generally comparable to controls, up to Day 7, where an insignificant decrease in body weight was observed. Decreased body weight values reached statistical-significance on Day 14 for both males and females and remained significantly lower than controls throughout the weaning period (lactation day 26). High-dose pups exhibited significantly decreased body weights at birth and throughout lactation. Changes observed at the 6250 and 12,500 dose levels are considered treatment-related.

In the F₂ generation, body weights were comparable to the controls for all low-dose pups throughout lactation. For pups dosed at 6250 ppm, significant decreases were observed in pup weight at birth and throughout most of lactation (Days 4 [preculling and postculling], 7, 14, and 21). These effects observed in the 6250-ppm group are considered treatment-related.

3. Sexual Maturation

Sexual maturation data for the F₁ generation are summarized in Table 26 of the Appendix of this report.

Treatment-related significant delays in vaginal opening and preputial separation occurred in 6250- and 12,500-ppm animals. Body weights at vaginal opening for females at all dose levels were comparable to the control (data not provided in table); body weights at preputial separation in 6250- and 12,500-ppm males were significantly decreased. Sexual maturation data for both males and females were comparable to the controls at 1000 ppm.

4. Organ Weights

Organ weight data are summarized in Tables 27-30 of the Appendix of this report.

In F₁ offspring, treatment-related effects were observed in body weight and organ weights for both sexes. Decreased body weight was observed in all groups, reaching statistical significance at 6250 and 12,500 ppm. Significant decreases in thymus weight (absolute and relative to body and brain weight) were observed at all dose levels in males and at the mid- and high-dose levels for females; 1000-ppm females also exhibited decreased relative thymus weights. According to the study author, decreases in thymus weight were considered treatment-related at

6250 and 12,500 ppm. A significant decrease in thymus weight (relative to body weight) was observed in male F₂ pups at both 1000 and 6250 ppm and in females at 6250 ppm; an insignificant decrease also was observed in 1000-ppm F₂ females. Significant decreases in absolute spleen and brain weights at 6250 and 12,500

ppm also were noted and were stated to be associated with lower mean body weight of these animals compared to the controls.

In F₂ offspring, treatment-related effects were observed in body weight and organ weights for both sexes. Significant decreases in terminal body weights were observed at 6250 ppm for both sexes. Significant, treatment-related decreases in thymus weight (absolute and relative to body and brain weight) were observed in both sexes at 6250 ppm. The only significant decrease in organ weights at 1000 ppm occurred in F₂ males, who exhibited a decrease in mean thymus weight relative to body weight. At 1000 ppm, F₂ generation thymus weight (absolute and relative to brain and body weight) for both sexes was decreased, (not significant) showing a possible dose-related trend. Significant decreases in absolute spleen and brain weights in 6250-ppm males and absolute brain weights in 6250-ppm females also were noted and appeared associated with lower mean body weight of these animals compared to the controls.

5. Gross Pathology

Gross pathology alterations (mild decrease in testicular and epididymal size) were observed in a 1000-ppm F₁ male pup; however, these changes were not considered treatment-related. Treatment-related macroscopic alterations were noted in 6250- and 12,500-ppm F₁ pups (both sexes) that were weaned at Day 26. These changes included mild to moderate decreased thymic size (4/32 12,500-ppm pups), mild cardiac enlargement (9/53 6250-ppm pups and 12/32 12,500-ppm pups), mild to moderate renal pallor (4/53 6250-ppm pups and 14/32 12,500-ppm pups), mild renal pelvic dilation (1/32 12,500-ppm pups, male only), and mild to moderate hepatic pallor (10/53 6250-ppm pups and 16/32 12,500-ppm pups). Other alterations were noted to be common in pups of this age and were not considered treatment-related.

Treatment-related macroscopic alterations were only noted in 6250-ppm F₂ pups (both sexes) that were weaned at Day 21. These changes included mild to moderate decreased thymic size (16/171 pups), mild cardiac enlargement (43/171 pups), mild renal pallor (18/171), mild hepatic pallor (22/171 pups), and mild pulmonary pallor (9/171 pups). Our reviewers also note an increase in mild enlargement of the spleen (7/171 pups), as well as 1 female pup exhibiting moderate hepatic pallor. These effects appear to be treatment-related.

According to the study authors, a slight increase was observed in the incidence and severity of renal pelvic dilation: 9/58 [15.5%] in the 1000-ppm male pups; 7/81 [8.6%] in the 6250-ppm male pups and 6/92 [6.5%] in the control; 1/49

[2.0%] in the 1000-ppm female pups; and 2/90 [2.2%] in the 6250-ppm female pups compared to 0 in the control. Lack of a dose response indicates that these effects were not related to compound administration.

6. Determination of Zinc, Silver, and Copper Levels in F₂ Day 4 Culled Pups

Mean zinc, silver, and copper levels are presented in Tables 31-32 of the Appendix this report.

Zinc and silver levels were higher in treated F₂ pups than in controls, while copper levels were lower. One exception was noted, in which the zinc levels of the 1000-ppm F₂ female pups were slightly lower than controls.

III. DISCUSSION

A. Parental Toxicity

Effects on parental mortality were seen at the 6250 and 12,500 ppm dose levels. One P male and 8 F₁ animals (seven males and 1 female) died in the 6250 ppm group. In the 12,500 ppm group, 3 P males died and in the F₁, 28/30 males and 23/30 females died. Because of this mortality at the 12,500-ppm dose level, this group was terminated at completion of the F₁ pre-mating growth period; consequently, 6250 ppm became the high-dose level for F₁ animals.

Effects seen were significantly decreased body weights and body weight gains (6250- and 12,500-ppm P males; F₁ animals); significantly decreased body weights during gestation (6250- and 12,500-ppm P dams) and lactation (6250-ppm F₁ dams lactation), significantly decreased food consumption (6250- and 12,500-ppm P males; 12,500-ppm F₁ animals), and significantly decreased food consumption during lactation (12,500-ppm P dams).

Additional signs of toxicity including hematological changes (increased RBC and platelet counts and lowered levels of derived values for hemoglobin, hematocrit, and other blood parameters) in P animals (12,500 ppm), increased cholesterol levels in P animals (6250 and 12,500 ppm), and decreased kidney weights (6250- and 12,500-ppm P animals; 1000- and 6250-ppm F₁ animals) were observed. A decrease in the live born index and an increase in the stillborn index was observed at 12,500 ppm in P dams, as well as at 6250 ppm in F₁ dams. Dams treated with 12,500 ppm also exhibited decreases in litter size.

Treatment-related macroscopic changes in both generations, including mild to severe green to tan/brown discoloration of multiple organs predominately glandular tissues (pancreas, thymus, mandibular salivary glands and lymph nodes, Harderian glands, exorbital lacrimal glands, glandular stomach, duodenum, urinary bladder, prostate gland and clitoral glands) in 6250- and 12,500-ppm animals. These macroscopic findings corresponded to pigment deposition, which

was not considered a toxic effect due to the lack of a inflammatory response.

More significant macroscopic findings at the 6250- and 12,500-ppm dose levels involved the kidneys and included mild calculi, mild to moderate pelvic dilation, and increased incidence of mild to moderate cortical surface irregularities, which corresponded to the histological alteration of chronic interstitial nephritis and/or infarction. F₁ males treated with 12,500 ppm of test material also exhibited an increased incidence of penile distention/extension and discoloration. These changes possibly could be correlated with urolithiasis and chronic inflammation.

A treatment-related decrease in kidney weight (absolute and relative to body and brain weights) was observed in 1000-ppm F₁ animals. These decreases were not considered biologically significant because there were no corresponding macroscopic or microscopic kidney alterations at this dose. Macroscopic and microscopic lesions in the kidney were seen at 6250 and 12,500 ppm and suggested that decreased kidney weight in the low dose animals may be a preliminary sign of kidney toxicity.

2. Offspring Toxicity

The offspring of animals exposed to 6250 and 12,500 ppm Zeomic exhibited toxicological effects. At these doses, pups exhibited lower body weights during lactation, macroscopic alterations at weaning (small thymus, enlarged hearts, and pale kidneys, livers, and lungs), lower organ weight at weaning (brain, spleen, and thymus), and decreased pup survival during lactation (12,500-ppm F₁ litters). Significant decreases in thymus weight (absolute and relative to body and brain weight) were observed at all dose levels in F₁ males. Only a significant difference occurred in the relative thymus weight of F₂ males which was not considered to be of any toxicological significance.

APPENDIX 1

TABLE 1. P Male Mean Body Weight (g)^a

Week of Measurement		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Premating					
1	MEAN S.D. N	171.9 10.93 30	170.8 11.84 30	170.1 11.35 30	170.5 10.68 30
3	MEAN S.D. N	281.1 18.19 30	277.6 15.84 30	271.0 16.67 30	266.7** 17.47 30
5	MEAN S.D. N	368.8 25.94 30	356.7 22.19 30	349.6** 20.23 30	340.4** 21.69 30
7	MEAN S.D. N	423.5 29.7 30	411.5 28.77 30	396.4** 24.12 30	380.9** 30.10 29
8	MEAN S.D. N	445.8 31.98 30	433.5 32.59 30	415.6** 24.29 30	399.9** 30.50 29
9	MEAN S.D. N	464.3 34.79 30	448.4 35.29 30	431.0** 26.97 30	415.9** 30.96 29
11	MEAN S.D. N	501.5 37.57 30	481.6 39.45 30	461.4** 27.81 30	444.2** 33.28 29
Pairing					
12	MEAN S.D. N	502.9 36.65 30	487.8 41.02 30	467.4** 28.74 30	451.4** 34.40 29
13	MEAN S.D. N	522.2 37.62 30	501.6 40.19 30	483.1** 28.65 30	463.6** 36.90 29
Postmating					
14	MEAN S.D. N	526.5 39.61 30	506.9 42.31 30	490.2** 29.23 30	470.4** 35.63 29
16	MEAN S.D. N	549.5 43.26 30	524.7 46.68 30	509.7** 32.42 30	488.2** 38.38 29
17	MEAN S.D. N	555.7 44.33 30	536.8 47.03 30	517.2** 34.83 30	498.2** 36.85 28
18	MEAN S.D. N	557.5 44.69 30	545.9 50.62 30	524.3** 33.40 29	501.7** 39.20 28
20	MEAN S.D. N	569.3 47.63 30	556.7 51.75 30	532.5** 33.28 29	511.9** 38.66 28
21	MEAN S.D. N	574.4 45.05 30	560.9 52.22 30	535.7** 38.67 29	515.1** 39.54 27
22	MEAN S.D. N	580.8 46.52 30	568.5 52.98 30	544.6** 33.78 29	520.2** 42.20 26

^aData extracted from Table 5, p. 70.

*Significantly different from control, p<0.05

**Significantly different from control, p<0.01.

TABLE 2. P Female Mean Body Weight (g)^a

Week of Measurement		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Premating					
1	MEAN S.D. N	145.2 5.90 30	145.4 7.37 30	145.8 7.29 30	147.6 7.68 30
3	MEAN S.D. N	188.2 18.47 30	190.5 13.10 30	191.2 12.60 30	190.1 12.29 30
4	MEAN S.D. N	208.5 12.57 30	208.9 15.35 30	209.7 14.34 30	207.2 13.32 30
7	MEAN S.D. N	238.3 19.21 30	240.9 19.51 30	248.0 19.03 30	241.0 17.94 30
10	MEAN S.D. N	260.6 19.96 29	258.8 21.23 30	264.3 23.76 30	257.1 20.81 30
Gestation					
0	MEAN S.D. N	269.3 20.92 28	266.3 22.01 25	272.7 24.00 26	265.7 20.26 25
20	MEAN S.D. N	392.6 27.72 28	388.4 27.14 25	388.6 28.05 26	369.0** 18.13 25
Lactation					
0	MEAN S.D. N	305.6 22.07 28	300.1 28.51 26	299.7 23.63 28	293.8 19.06 28
4	MEAN S.D. N	305.7 21.82 28	296.4 21.93 26	298.1 21.99 28	283.7** 21.62 22
7	MEAN S.D. N	306.3 24.06 28	302.7 21.64 26	307.6 21.71 28	287.8* 19.49 22
14	MEAN S.D. N	324.9 25.26 28	323.7 21.57 26	303.1** 30.74 28	288.2** 17.32 22
21	MEAN S.D. N	328.8 17.64 28	322.0 17.30 26	316.0 29.81 28	299.7** 20.34 21
26	MEAN S.D. N	307.6 20.59 28	301.4 21.52 26	311.5 19.23 28	302.7 22.51 21

^aData extracted from Tables 6-8, pp. 71, 72, and 73, respectively.

*Significantly different from control, p<0.05.

**Significantly different from control, p<0.01.

TABLE 3. P Male Mean Body Weight Change (g)^a

Week of Measurement		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Premating					
1-2	MEAN S.D. N	62.3 6.09 30	61.3 4.11 30	57.1** 5.27 30	54.7** 6.20 30
2-3	MEAN S.D. N	46.9 6.91 30	45.5 6.59 30	43.7 6.56 30	41.5** 7.22 30
4-5	MEAN S.D. N	41.2 7.22 30	33.3** 7.83 30	36.4 8.49 30	31.7** 7.91 30
8-9	MEAN S.D. N	18.5 4.54 30	14.9* 5.36 30	15.4 6.21 30	16.0 5.77 29
9-10	MEAN S.D. N	13.9 6.22 30	13.9 6.03 30	11.8 11.72 30	7.8 13.96 29
10-11	MEAN S.D. N	23.3 6.95 30	19.2 6.62 30	18.6 11.19 30	20.6 6.76 29
1-11	MEAN S.D. N	329.7 32.43 30	310.8* 36.57 30	291.3** 23.23 30	274.3* 28.20 29
Pairing					
11-12	MEAN S.D. N	1.3 8.94 30	6.2 7.61 30	5.9 12.01 30	7.2* 6.67 29
12-13	MEAN S.D. N	19.3 7.84 30	13.7* 7.42 30	15.7 5.88 30	12.2** 11.56 29
Postmating					
13-14	MEAN S.D. N	4.3 7.94 30	5.4 6.38 30	7.2 5.45 30	6.8 11.26 29
14-15	MEAN S.D. N	7.1 7.34 30	7.1 4.77 30	6.6 5.20 30	6.8 6.08 29
15-16	MEAN S.D. N	15.9 6.19 30	10.7** 7.92 30	12.8 5.45 30	11.1* 5.99 29
16-17	MEAN S.D. N	6.2 19.62 30	12.1 5.76 30	7.5 6.75 30	9.1 7.05 28
17-18	MEAN S.D. N	1.7 15.33 30	9.0* 6.26 30	5.0 5.38 29	3.5 7.50 28
21-22	MEAN S.D. N	6.4 8.57 30	7.6 6.72 30	8.9 10.52 29	6.1 8.18 26

^aData extracted from Table 9, p. 74.

*Significantly different from control, p<0.05

**Significantly different from control, p<0.01.

TABLE 4. P Female Mean Body Weight Change (g)^a

Week of Measurement		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Premating					
1-2	MEAN S.D. N	29.1 4.74 30	27.7 6.69 30	27.7 4.84 30	25.5 7.04 30
3-4	MEAN S.D. N	20.3 10.08 30	18.4 5.62 30	18.4 4.96 30	17.1 5.07 30
4-5	MEAN S.D. N	15.8 7.04 30	16.7 6.01 30	19.4* 5.4230	16.6 4.21 30
7-8	MEAN S.D. N	10.0 9.95 30	7.7 4.24 30	6.3 4.50 30	6.6 4.74 30
10-11	MEAN S.D. N	9.4 7.21 29	10.8 4.82 30	12.3 6.52 30	10.7 6.94 30
1-11	MEAN S.D. N	125.0 19.99 29	124.2 18.87 30	130.8 22.80 30	120.1 18.53 30
Gestation					
0-7	MEAN S.D. N	32.0 10.65 28	29.1 13.72 25	33.6 7.92 26	31.8 5.68 25
7-14	MEAN S.D. N	31.2 6.45 28	30.6 8.09 25	28.6 7.63 26	28.9 5.55 25
14-20	MEAN S.D. N	60.1 16.07 28	62.5 10.66 25	53.7 16.06 26	42.5** 11.26 25
0-20	MEAN S.D. N	123.3 19.49 28	122.2 14.72 25	115.9 18.97 26	103.3** 13.39 25
Lactation					
0-4	MEAN S.D. N	0.1 17.82 28	-3.7 15.78 26	-1.5 17.19 28	-9.7 11.99 22
4-7	MEAN S.D. N	0.6 22.78 28	6.3 20.19 26	9.5 15.90 28	4.1 20.52 22
7-14	MEAN S.D. N	18.6 19.97 28	21.0 21.50 26	-4.5** 22.21 28	0.4** 19.39 22
14-21	MEAN S.D. N	3.9 17.28 28	-1.7 20.05 26	13.0 19.61 28	12.4 17.50 21
21-26	MEAN S.D. N	-21.2 14.02 28	-20.5 16.6 26	-4.5 22.25 28	3.0** 10.97 21
0-26	MEAN S.D. N	2 18.13 28	1.3 18.94 26	11.8 17.76 28	10.1 20.61 21

^aData extracted from Tables 10-12 pp. 75, 76, and 77, respectively.

*Significantly different from control, p<0.05.

**Significantly different from control, p<0.01.

TABLE 5. F₁ Male Mean Body Weight (g)^a

Week of Measurement		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Premating					
1	MEAN S.D. N	218.6 21.95 30	216.0 24.02 30	163.2** 22.57 30	98.0** 18.34 27
3	MEAN S.D. N	326.1 29.5 30	323.9 33.92 29	263.1** 27.34 30	130.1** 25.03 24
5	MEAN S.D. N	394.4 37.71 30	392.9 39.55 29	330.4** 30.60 28	161.2** 29.27 13
7	MEAN S.D. N	439.1 32.70 30	439.8 44.17 29	378.3** 39.46 27	181.9** 39.98 8
8	MEAN S.D. N	462.8 35.37 30	461.8 48.74 29	397.1** 51.08 27	198.7** 32.84 6
9	MEAN S.D. N	483.9 39.35 30	481.4 49.83 29	423.7** 40.80 26	214.8** 49.06 4
10	MEAN S.D. N	495.6 38.84 30	492.6 52.53 29	431.4** 46.47 26	219.0** 77.16 3
11	MEAN S.D. N	513.5 42.13 30	511.5 53.71 29	444.8** 45.16 26	222.3** 66.53
Pairing					
13	MEAN S.D. N	527.1 47.24 30	524.6 55.24 29	450.9** 47.24 26	NA
14	MEAN S.D. N	535.8 44.95 30	532.2 56.64 29	461.6** 51.73 26	NA
Postmating					
15	MEAN S.D. N	540.3 47.32 30	536.4 57.31 29	469.2** 54.41 26	NA
17	MEAN S.D. N	560.0 51.30 30	558.9 63.82 29	488.5** 58.63 25	NA
19	MEAN S.D. N	583.5 54.29 30	579.9 68.16 29	511.0** 50.0 24	NA
21	MEAN S.D. N	588.6 55.63 30	592.9 70.55 29	520.8** 52.44 23	NA
22	MEAN S.D. N	597.4 57.71 30	597.9 69.52 29	527.9** 53.58 23	NA
23	MEAN S.D. N	604.8 57.03 30	599.9 67.80 29	534.3** 56.36 23	NA

^aData extracted from Table 44, p. 154.

NA - Not available, animals were sacrificed at completion of the pre-mating growth period.

*Significantly different from control, p<0.05.

**Significantly different from control, p<0.01.

TABLE 6. F, Female Mean Body Weight (g)^a

Week of Measurement		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Premating					
1	MEAN S.D. N	167.4 12.40 30	161.9 17.03 30	135.6** 18.65 30	91.5** 15.14 29
3	MEAN S.D. N	217.4 16.00 30	209.4 21.86 30	186.1** 21.23 30	116.9** 21.12 25
5	MEAN S.D. N	249.0 18.48 30	241.3 23.81 30	227.2** 22.32 29	137.4** 29.50 18
6	MEAN S.D. N	265.7 21.04 30	256.3 25.67 30	242.8** 23.17 29	150.5** 27.98 14
7	MEAN S.D. N	269.0 26.69 30	260.8 23.76 30	253.6 23.85 29	158.6** 29.33 11
9	MEAN S.D. N	289.7 23.23 30	278.3 29.24 30	275.0 28.00 29	149.7** 42.36 10
11	MEAN S.D. N	294.2 22.53 30	284.9 29.89 30	286.9 29.98 29	166.0** 38.63 7
Gestation					
0	MEAN S.D. N	292.2 20.15 22	280.7 32.07 16	277.3 27.77 19	NA
7	MEAN S.D. N	323.6 22.14 22	309.4 32.74 16	310.8 31.84 19	NA
14	MEAN S.D. N	351.4 21.40 22	334.8 35.06 16	337.2 33.28 19	NA
20	MEAN S.D. N	413.7 26.30 22	391.0 37.00 16	390.1 37.40 19	NA
Lactation					
0	MEAN S.D. N	322.4 27.10 25	315.2 39.22 18	301.2* 31.66 23	NA
4	MEAN S.D. N	340.0 27.34 25	317.4** 30.60 17	307.3** 27.50 23	NA
7	MEAN S.D. N	333.0 29.58 25	322.2 28.72 16	311.4* 28.43 23	NA
14	MEAN S.D. N	326.6 33.36 25	326.4 33.32 16	307.2 27.96 23	NA
21	MEAN S.D. N	342.8 17.99 25	328.4 21.94 16	325.6* 21.68 23	NA

^aData extracted from Tables 45-47, pp 155, 156, and 157, respectively.

NA - Not available, animals were sacrificed at completion of the pre-mating growth period.

*Significantly different from control, p<0.05.

**Significantly different from control, p<0.01.

TABLE 7. F, Male Mean Body Weight Change (g)^a

Week of Measurement		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Premating					
1-2	MEAN S.D. N	60.2 8.17 30	61.8 5.70 30	53.0** 7.71 30	15.9** 11.15 26
3-4	MEAN S.D. N	39.4 7.38 30	39.0 8.83 29	37.0 9.48 29	6.8** 20.17 19
4-5	MEAN S.D. N	28.8 5.67 30	30.0 9.52 29	30.6 7.32 28	12.2** 15.46 13
5-6	MEAN S.D. N	29.6 8.29 30	29.6 6.95 29	31.0 9.05 27	6.7** 16.59 10
6-7	MEAN S.D. N	15.1 8.94 30	17.3 11.29 29	16.3 9.41 27	-6.1 26.25 8
7-8	MEAN S.D. N	23.7 10.00 30	22.0 9.41 29	18.8 17.46 27	3.5** 12.34 6
8-9	MEAN S.D. N	21.2 6.47 30	19.7 6.10 29	19.4 10.04 26	2.3 23.68 4
10-11	MEAN S.D. N	17.9 7.59 30	18.9 8.25 29	13.4 7.97 26	3.3* 11.68 3
1-12	MEAN S.D. N	303.0 37.63 30	304.7 35.70 29	285.5 46.27 26	160.5 14.85
Pairing					
12-13	MEAN S.D. N	5.7 9.42 30	4.1 6.94 29	1.2 19.46 26	NA
13-14	MEAN S.D. N	8.7 13.50 30	7.6 7.34 29	10.7 18.85 26	NA
Postmating					
14-15	MEAN S.D. N	4.5 11.44 30	4.2 9.12 29	7.6 8.43 26	NA
15-16	MEAN S.D. N	5.6 8.86 30	5.6 10.49 29	5.3 7.37 26	NA
17-18	MEAN S.D. N	15.7 8.01 30	15.0 6.18 29	13.8 8.68 25	NA
19-20	MEAN S.D. N	2.0 9.43 30	5.2 9.29 29	4.7 8.12 23	NA
21-22	MEAN S.D. N	8.8 8.08 30	5.0 13.12 29	7.1 8.26 23	NA

^aData extracted from Table 48, p. 158.

NA - Not available, animals were sacrificed at completion of the premating growth period.

*Significantly different from control, p<0.05.

**Significantly different from control, p<0.01.

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TABLE 8. F, Female Mean Body Weight Change (g)^a

Week of Measurement		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Premating					
1-2	MEAN S.D. N	27.1 7.66 30	23.1 13.20 30	26.9 5.00 30	12.3** 10.71 27
3-4	MEAN S.D. N	17.9 4.34 30	18.3 4.77 30	23.3** 5.25 29	5.7** 13.17 22
5-6	MEAN S.D. N	16.7 5.13 30	14.9 4.86 30	15.6 4.75 29	4.6** 11.75 14
7-8	MEAN S.D. N	8.5 13.47 30	9.2 8.75 30	13.1 6.35 29	-5.4** 13.63 10
9-10	MEAN S.D. N	1.2 6.28 30	2.6 7.40 30	6.9** 6.05 29	-2.3 11.78 8
1-12	MEAN S.D. N	128.6 18.8 30	125.7 19.83 30	155.0 23.48 29	76.7 35.99
Gestation					
0-7	MEAN S.D. N	31.5 5.84 22	28.8 8.08 16	33.5 8.36 19	NA
7-14	MEAN S.D. N	27.8 6.00 22	25.3 6.35 16	26.4 7.78 19	NA
14-20	MEAN S.D. N	62.3 13.50 22	56.3 20.81 16	52.9 11.98 19	NA
0-20	MEAN S.D. N	121.5 13.90 22	110.3 22.88 16	112.7 16.88 19	NA
Lactation					
0-4	MEAN S.D. N	17.5 16.24 25	7.6 15.16 17	6.1* 13.38 23	NA
4-7	MEAN S.D. N	-6.9 13.05 25	2.6* 6.15 16	4.1** 10.74 23	NA
7-14	MEAN S.D. N	-6.4 23.23 25	4.2 20.27 16	-4.3 33.47 23	NA
14-21	MEAN S.D. N	16.2 27.52 25	2.1 22.78 16	18.4 26.62 23	NA
0-21	MEAN S.D. N	20.4 20.22 25	15.8 19.01 16	24.3 31.65 23	NA

^aData extracted from Tables 49-51 pp. 159, 160, and 161, respectively.

NA - Not available; animals were sacrificed at completion of the premating growth period.

*Significantly different from control, p<0.05

**Significantly different from control, p<0.01.

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TABLE 9. P Male Mean Food Consumption (g/animal/day)^a

Week of Measurement		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Premating					
1-2	MEAN S.D. N	24.5 1.88 30	24.2 1.45 30	24.0 1.55 30	25.2 1.80 30
3-4	MEAN S.D. N	26.9 2.00 30	26.0 2.29 30	25.9 1.94 30	26.6 4.71 30
5-6	MEAN S.D. N	28.8 2.23 30	27.2* 2.68 30	26.5** 2.33 29	27.6 2.58 30
7-8	MEAN S.D. N	29.1 2.40 30	27.9 2.48 30	27.3* 1.96 30	27.5* 2.92 29
9-10	MEAN S.D. N	28.4 2.43 30	26.4** 2.31 30	26.5** 1.92 30	26.1** 2.74 29
10-11	MEAN S.D. N	29.5 2.38 30	28.0 2.21 30	27.2** 2.10 30	27.1** 2.59 29
Postmating					
13-14	MEAN S.D. N	27.1 2.55 30	26.1 2.31 30	26.7 2.24 30	26.7 2.38 29
15-16	MEAN S.D. N	28.4 2.79 30	26.0 4.48 30	26.7 2.49 30	28.3 6.79 29
17-18	MEAN S.D. N	26.9 4.11 30	27.9 2.75 30	27.4 2.35 29	27.9 2.58 28
19-20	MEAN S.D. N	27.0 3.71 29	25.3 2.39 30	25.1* 1.71 28	26.1 2.43 28
20-21	MEAN S.D. N	25.9 3.12 30	24.1* 2.13 30	24.1* 2.29 29	24.7 1.90 27
21-22	MEAN S.D. N	28.4 3.05 30	27.3 2.56 30	26.9 2.37 29	27.4 1.93 26

^aData extracted from Table 13, p. 78.

*Significantly different from control, p<0.05.

**Significantly different from control, p<0.01.

TABLE 10. P Female Mean Food Consumption (g/animal/day)^a

Week of Measurement		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Premating					
1-2	MEAN S.D. N	18.7 2.06 30	17.8 1.47 30	17.7 1.70 30	18.3 1.96 30
3-4	MEAN S.D. N	19.1 1.60 30	19.4 2.10 30	18.8 2.06 30	18.8 1.26 30
6-7	MEAN S.D. N	19.7 4.09 29	20.2 3.28 30	19.5 1.99 30	19.1 1.77 30
8-9	MEAN S.D. N	19.1 2.18 30	19.7 5.12 30	19.3 2.24 30	19.9 3.67 30
10-11	MEAN S.D. N	19.5 1.83 29	19.8 2.70 30	19.5 3.06 30	19.6 3.41 30
Gestation					
0-7	MEAN S.D. N	23.9 2.87 28	22.2 3.99 25	24.1 2.79 26	23.7 2.70 25
7-14	MEAN S.D. N	25.1 2.40 28	24.6 1.86 25	25.1 2.61 26	25.2 2.68 25
14-20	MEAN S.D. N	23.7 2.72 28	23.4 1.84 25	22.7 2.04 26	22.9 2.38 25
Lactation					
0-4	MEAN S.D. N	27.7 4.92 28	27.4 6.38 26	29.7 6.92 28	20.2** 5.51 22
4-7	MEAN S.D. N	36.3 6.36 28	37.5 7.76 26	41.8* 9.90 28	32.1 9.69 22
7-14	MEAN S.D. N	44.7 12.23 28	38.8 19.67 26	42.5 11.23 26	35.4** 7.37 21
14-21	MEAN S.D. N	67.3 4.83 28	69.8 3.51 26	60.2** 7.66 28	49.1** 12.95 21

^aData extracted from Tables 14-16 pp. 79, 80, and 81, respectively.

*Significantly different from control, p<0.05.

**Significantly different from control, p<0.01.

TABLE 11. F₁ Male Mean Food Consumption (g/animal/day)^a

Week of Measurement		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Premating					
1-2	MEAN S.D. N	27.7 2.19 30	27.5 2.28 30	23.7** 2.47 30	12.2** 3.20 29
3-4	MEAN S.D. N	30.7 2.54 30	29.3 2.73 29	27.2** 2.73 29	13.1** 3.59 19
5-6	MEAN S.D. N	30.3 2.04 27	29.9 3.31 28	28.2* 2.96 27	15.0** 3.84 10
7-8	MEAN S.D. N	30.8 2.75 30	30.1 3.85 29	27.0** 4.90 27	15.1** 3.67 6
8-9	MEAN S.D. N	30.3 2.25 30	28.8 3.31 29	26.9** 3.29 25	13.6* 6.84 4
9-10	MEAN S.D. N	30.2 3.31 30	29.2 2.87 29	26.0** 4.72 26	15.6** 7.77 3
11-12	MEAN S.D. N	32.1 4.70 30	29.8 3.30 29	25.4* 5.56 26	NA
Postmating					
14-15	MEAN S.D. N	31.0 2.16 28	29.0 2.25 20	27.4** 4.78 19	NA
15-16	MEAN S.D. N	31.2 3.98 30	30.4 3.85 29	28.0** 3.28 26	NA
16-17	MEAN S.D. N	30.0 6.20 30	30.0 3.33 29	29.3 3.53 25	NA
17-18	MEAN S.D. N	30.8 2.93 30	29.8 3.36 29	28.5* 2.71 25	NA
18-19	MEAN S.D. N	30.8 2.26 30	29.9 2.94 29	30.3 11.24 25	NA
19-20	MEAN S.D. N	30.9 4.50 30	30.7 6.86 29	26.6** 2.39 23	NA
20-21	MEAN S.D. N	30.3 2.01 30	29.7 2.65 29	27.5** 2.34 23	NA
21-22	MEAN S.D. N	31.6 2.77 30	29.3** 3.42 29	27.7** 2.44 23	NA
22-23	MEAN S.D. N	31.0 2.32 30	28.3* 5.27 29	27.4** 2.39 23	NA

^aData extracted from Table 52, p. 162.

NA - Not available; animals were sacrificed at completion of the premating growth period.

*Significantly different from control, p<0.05.

**Significantly different from control, p<0.01.

TABLE 12. F, Female Mean Food Consumption (g/animal/day)^a

Week of Measurement		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Premating					
1-2	MEAN S.D. N	21.2 2.53 29	20.2 2.03 30	19.9 1.67 30	12.6** 2.24 28
3-4	MEAN S.D. N	22.7 2.12 30	23.1 4.75 30	23.4 3.24 29	13.3** 3.87 22
5-6	MEAN S.D. N	24.5 4.50 30	22.4 2.63 30	23.8 3.06 29	14.2** 4.30 14
7-8	MEAN S.D. N	23.7 4.56 30	22.5 3.79 30	23.1 2.19 29	12.8** 4.56 10
9-10	MEAN S.D. N	22.2 2.28 29	20.4* 2.45 30	21.1 1.92 29	14.1* 5.92 8
10-11	MEAN S.D. N	20.6 3.44 29	18.9 2.56 30	19.9 2.52 29	12.1** 3.58 7
11-12	MEAN S.D. N	23.0 4.10 30	20.1** 2.59 30	20.6* 2.24 29	12.4** 2.35 7
Gestation					
0-7	MEAN S.D. N	27.4 3.33 22	25.0* 2.56 16	25.5* 3.16 19	NA
7-14	MEAN S.D. N	27.9 3.42 22	26.5 2.63 16	26.8 3.21 19	NA
14-20	MEAN S.D. N	26.5 1.92 17	25.8 3.05 11	24.8 2.71 18	NA
Lactation					
0-4	MEAN S.D. N	33.1 9.19 25	30.3 7.77 17	27.9 6.47 23	NA
4-7	MEAN S.D. N	41.5 5.70 25	42.5 6.83 16	41.5 6.29 23	NA
7-14	MEAN S.D. N	48.0 11.94 25	48.6 11.62 16	47.5 7.30 23	NA
14-21	MEAN S.D. N	74.4 11.30 25	64.9* 12.16 16	65.8* 7.52 23	NA

^aData extracted from Tables 53-55, pp. 163, 164, and 165, respectively.

NA - Not available, animals were sacrificed at completion of the premating growth period

*Significantly different from control, p<0.05

**Significantly different from control, p<0.01.

TABLE 13. Selected P Reproductive Observations^a

	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Number of Females Paired	29	30	30	30
Number of Females Mated	29	28	29	30
Number of Females Achieving Pregnancy	28	26	28	28
Female Mating Index	100.0	93.3	96.7	100.0
Female Fertility Index	96.6	86.7	93.3	93.3
Female Fecundity Index	96.6	92.9	96.6	93.3
Number of Males Paired	29	30	30	29
Number of Males Mated	29	28	29	29
Number of Males Impregnating a Female	26	26	28	27
Male Mating Index	100.0	93.3	96.7	100.0
Male Fertility Index	96.6	86.7	93.3	93.1
Male Fecundity Index	96.6	92.9	96.6	93.1
Females with Confirmed Mating Day	29	27	27	27
Copulatory Interval (days)	MEAN 2.8 S.D. 1.10 N 29	2.3 1.10 27	3.0 2.17 27	2.6 1.42 27
Gestation Length (days)	MEAN 21.9 S.D. 0.50 N 28	22.3 0.44 25	22.3** 0.63 26	22.3* 0.46 25
Gestation Index	MEAN 100.0 N 28	100.0 26	100 28	96.4 28

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	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Females Delivering Litters ¹	N	26	28	28

¹ Not statistically analyzed.

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	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Females with Stillborn Pups ¹				
N	2	3	5	13
%	7.1	11.5	17.9	46.4
Females with all Stillborn ¹				
N	0	0	0	0
%	0.0	0.0	0.0	0.0
Number of Pups at Day 0				
MEAN	14.2	13.2	13.1	12.1*
S.D.	2.31	2.17	3.56	3.15
N	28	26	28	28
Liveborn/Litter				
MEAN	14.1	12.8	12.8	10.3**
S.D.	2.37	2.38	3.51	4.13
N	28	26	28	28
Live Birth Index				
Mean %/Litter	98.2	97.6	97.4	85.5**
S.D.	3.13	7.03	7.42	23.02
N	28	26	28	28
Stillborn Index				
Mean %/Litter	0.8	2.0	2.6	12.2**
S.D.	3.13	6.41	7.42	18.87
N	28	26	28	28
Total Implantation Scars/Litter				
MEAN	14.9	14.3	14.2	13.6
S.D.	2.38	1.76	3.68	3.33
N	28	26	28	28

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	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Number Live Pups/Litter Day 4 (Precullling)	MEAN S.D. N 13.9 2.27 28	12.7 2.41 26	12.1 3.76 28	7.6** 4.46 22
Day 4 (Postcullling)	MEAN S.D. N 7.9 0.57 28	8.0 0.20 26	7.7 1.09 28	5.9** 2.49 22
Day 7	MEAN S.D. N 7.9 0.57 28	8.0 0.28 26	7.6 1.10 28	5.8** 2.50 22
Day 14	MEAN S.D. N 7.9 0.57 28	8.0 0.28 26	7.6 1.10 28	5.7** 2.45 22
Day 21	MEAN S.D. N 7.9 0.57 28	8.0 0.28 26	7.5 1.14 28	5.7** 2.33 21
Day 26	MEAN S.D. N 7.9 0.57 28	8.0 0.45 26	7.4 1.20 28	5.6** 2.33 21
Pup Survival Indices Days 0-4 Precullling	MEAN S.D. N 98.9 2.47 28	98.8 3.04 26	96.0 15.10 28	53.1** 38.12 27
Day 4 Postcullling-Day 21	MEAN S.D. N 100.0 0.00 28	99.5 2.45 26	98.2 5.60 28	90.3 22.15 22
Day 4 Postcullling-Day 26	MEAN S.D. N 100.0 0.00 28	99.0 4.90 26	96.9 8.07 28	89.7 22.71 22
Sex Ratio Pups Day 0	MEAN S.D. N 52.1 13.01 28	51.8 15.98 26	45.3 12.73 28	46.4 12.89 27
Pups Day 4 (Precullling)	MEAN S.D. N 52.4 13.17 28	51.4 16.24 26	47.2 16.70 28	38.5** 22.86 22

	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Pups Day 4 (Postculling)	MEAN S.D. N 49.6 3.89 28	51.7 9.91 26	49.1 15.32 28	40.0 22.54 22
Pups Day 21	MEAN S.D. N 49.6 3.89 28	52.0 9.96 26	48.5 15.40 28	39.0 23.52 21
Pups Day 26	MEAN S.D. N 49.6 3.89 28	51.7 9.91 26	48.8 15.96 28	39.5 23.85 21

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	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Individual Pup Weights (g) Day 0 - Males	MEAN S.D. N 6.54 (6.66) 0.584 28	6.71 (6.74) 0.628 26	6.55 (6.52) 0.839 28	5.62 (5.49)◆ 0.574 27
Day 0 - Females	MEAN S.D. N 6.11 (6.11) 0.491 28	6.35 (6.35) 0.556 26	6.18 (6.18) 0.810 28	5.19 (5.19)★ 0.509 27
Day 0 - Males + Females	MEAN S.D. N 6.34 (6.34) 0.539 28	6.53 (6.53) 0.573 26	6.35 (6.35) 0.810 28	5.40 (5.40)★ 0.504 27
Day 4 Preculling - Males	MEAN S.D. N 9.83 (10.11) 1.219 28	10.21 (10.29) 1.324 26	9.99 (9.90) 2.006 28	8.07 (7.65)◆ 1.431 18
Day 4 Preculling - Females	MEAN S.D. N 9.28 (9.28) 1.246 28	9.68 (9.68) 1.142 26	9.56 (9.56) 1.838 27	7.51 (7.51)★ 1.414 21
Day 4 Preculling - Males + Females	MEAN S.D. N 9.58 (9.58) 1.217 28	9.94 (9.94) 1.190 26	9.71 (9.71) 1.927 28	7.73 (7.73)★ 1.395 21
Day 4 Postculling - Males	MEAN S.D. N 9.85 (9.85) 1.283 28	10.18 (10.18) 1.346 26	9.95 (9.95) 2.014 28	8.09 (8.09)★ 1.427 18
Day 4 Postculling - Females	MEAN S.D. N 9.33 (9.31) 1.243 28	9.63 (9.62) 1.141 26	9.51 (9.49) 1.921 27	7.55 (7.61)◆ 1.449 21
Day 4 Postculling - Males + Females	MEAN S.D. N 9.59 (9.59) 1.232 28	9.90 (9.90) 1.191 26	9.67 (9.67) 1.948 28	7.77 (7.77)★ 1.413 21
Day 7 - Males	MEAN S.D. N 15.39 (15.42) 2.159 28	15.30 (15.38) 2.034 26	15.03 (15.00) 2.448 28	11.88 (11.77)◆ 2.249 18
Day 7 - Females	MEAN S.D. N 14.58 (14.54) 2.013 28	14.52 (14.52) 1.877 26	14.30 (14.23) 2.365 27	11.29 (11.43)◆ 2.269 21

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	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Day 7 - Males + Females	MEAN S.D. N 14.98 (14.98) 2.011 28	14.92 (14.92) 1.874 26	14.56 (14.56) 2.459 28	11.50 (11.50)♦ 2.243 21
Day 14 - Males	MEAN S.D. N 28.83 (28.91) 4.483 28	29.21 (29.43) 4.845 26	24.97 (24.91)♦ 4.635 28	21.13 (20.80)♦ 3.782 18
Day 14 - Females	MEAN S.D. N 27.56 (27.56) 4.314 28	27.58 (27.58) 5.110 26	24.08 (24.08)▼ 4.753 27	20.42 (20.42)♦ 3.819 21
Day 14 - Males + Females	MEAN S.D. N 28.18 (28.26) 4.240 28	28.41 (28.51) 4.879 26	24.43 (24.46)▼ 4.606 28	20.779 (20.53)♦ 3.728 21
Day 21 - Males	MEAN S.D. N 48.43 (48.67) 6.643 28	48.01 (48.57) 5.687 26	36.62 (36.39)♦ 7.335 27	30.54 (29.68)♦ 4.863 17
Day 21 - Females	MEAN S.D. N 46.28 (46.28) 5.770 28	45.17 (45.17) 5.670 26	34.90 (34.90)♦ 7.343 27	29.86 (29.86)♦ 5.456 20
Day 21 - Males + Females	MEAN S.D. N 47.34 (47.72) 5.906 28	46.59 (47.03) 5.499 26	35.71 (35.80)♦ 6.953 28	30.31 (29.08)♦ 4.868 20
Day 26 - Males	MEAN S.D. N 74.72 (74.97) 8.581 28	72.39 (72.96) 7.623 26	52.89 (52.62)♦ 11.560 28	37.87 (37.02)♦ 7.751 17
Day 26 - Females	MEAN S.D. N 69.45 (69.38) 6.868 28	66.78 (66.77) 7.302 26	49.45 (49.36)♦ 11.355 27	37.41 (37.65)♦ 8.385 20
Day 26 - Males + Females	MEAN S.D. N 72.06 (72.30) 7.385 28	69.61 (69.87) 6.872 26	50.94 (50.96)♦ 10.755 28	37.88 (37.17)♦ 7.512 20

^aData extracted from Tables 32, 34, and 36, pp. 119-120, 122-126, 129-132.

() - Least square mean
 * - Significantly different from control, p<0.05.
 ** - Significantly different from control, p<0.01.
 ♦ - Significantly different from control, p<0.01. Covariate analysis
 ▼ - Significantly different from control, p<0.05. Group pairwise
 ♠ - Significantly different from control, p<0.01. Group pairwise

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TABLE 14. Selected F₁ Reproductive Observations^a

	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)
Number of Females Paired	30	30	29
Number of Females Mated	27	25	27
Number of Females Achieving Pregnancy	25	19	23
Female Mating Index	90.0	83.3	93.1
Female Fertility Index	83.3	63.3	79.3
Female Fecundity Index	92.6	76.0	85.2
Number of Males Paired	30	29	26
Number of Males Mated	27	24	25
Number of Males Impregnating a Female	25	18	22
Male Mating Index	90.0	82.8	96.2
Male Fertility Index	83.3	62.1	84.6
Male Fecundity Index	92.6	75.0	88.0
Females with Confirmed Mating Day	24	22	23
Copulatory Interval (days)	MEAN 3.3 S.D. 2.31 N 24	3.1 2.51 22	3.3 1.96 23
Gestation Length (days)	MEAN 22.2 S.D. 0.50 N 22	22.4 0.63 16	22.3 0.48 19
Gestation Index	MEAN %/Litter 100.0 N 25	94.7 18	100.0 23

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	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)
Females Delivering Litters ²	N 25 100.0 %	18 94.7 %	23 100.0 %
Females with Stillborn Pups ²	N 3 12.0 %	3 15.8 %	10 43.5 %
Females with all Stillborn ²	N 0 0.0 %	0 0.0 %	0 0.0 %
Number of Pups at Day 0	MEAN 13.1 S.D. 2.76 N 25	11.3 4.38 18	13.0 3.11 23
Liveborn/Litter	MEAN 12.9 S.D. 2.68 N 25	10.9 4.39 18	12.2 3.30 23
Live Birth Index	Mean %/Litter 98.3 S.D. 3.60 N 25	96.0 6.98 18	93.1* 8.17 23
Stillborn Index	Mean %/Litter 1.1 S.D. 3.12 N 25	2.6 6.13 18	5.4* 7.28 23
Total Implantation Scars/Litter	MEAN 13.9 S.D. 2.92 N 25	12.5 4.22 18	14.4 2.92 23

² Not statistically analyzed.

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Zeomic

Reproduction and Fertility Effects

	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)
Number Live Pups/Liter Day 4 (Precullling)	MEAN S.D. N 12.2 2.78 25	10.3 4.51 16	11.2 2.91 23
Day 4 (Postcullling)	MEAN S.D. N 7.8 0.62 25	7.0* 1.71 16	7.8 0.65 23
Day 7	MEAN S.D. N 7.8 0.65 25	6.8* 1.80 16	7.7 0.78 23
Day 14	MEAN S.D. N 7.8 0.65 25	6.7** 1.82 16	7.6 0.95 23
Day 21	MEAN S.D. N 7.8 0.65 25	6.7** 1.82 16	7.5 0.95 23
Pup Survival Indices Days 0-4 Precullling	MEAN S.D. N 95.0 9.56 25	83.4 33.34 18	93.2 11.41 23
Day 4 Postcullling-Day 21	MEAN S.D. N 99.5 2.50 25	95.6 10.51 16	95.7 9.69 23
Sex Ratio Pups Day 0	MEAN S.D. N 50.2 14.42 25	53.3 18.19 18	48.7 18.74 23
Pups Day 4 (Precullling)	MEAN S.D. N 49.7 15.02 25	54.9 17.36 16	48.2 19.99 23
Pups Day 4 (Postcullling)	MEAN S.D. N 48.1 9.68 25	54.8 12.86 16	46.1 13.97 23
Pups Day 21	MEAN S.D. N 48.4 9.84 25	54.0 13.28 16	46.9 14.91 23

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Zeomic

Reproduction and Fertility Effects

	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)
Individual Pup Weights (g) Day 0 - Males	MEAN S.D. N 6.71 (6.75) 0.427 25	6.82 (6.80) 0.899 18	6.31 (6.29)▲ 0.712 23
Day 0 - Females	MEAN S.D. N 6.26 (6.29) 0.518 25	6.33 (6.27) 0.951 18	5.95 (5.97) 0.775 23
Day 0 - Males + Females	MEAN S.D. N 6.49 (6.58) 0.435 25	6.59 (6.45) 0.903 18	6.14 (6.15)▲ 0.725 23
Day 4 Precouling - Males	MEAN S.D. N 10.35 (10.35) 0.902 25	10.25 (10.25) 1.856 16	9.21 (9.21)▼ 1.697 23
Day 4 Precouling - Females	MEAN S.D. N 9.81 (9.85) 1.128 25	9.59 (9.50) 1.823 16	8.62 (8.63)▲ 1.905 23
Day 4 Precouling - Males + Females	MEAN S.D. N 10.13 (10.13) 0.932 25	9.93 (9.93) 1.788 16	8.96 (8.96)▼ 1.830 23
Day 4 Postcouling - Males	MEAN S.D. N 10.34 (10.34) 0.884 25	10.27 (10.27) 1.784 16	9.16 (9.16)▼ 1.634 23
Day 4 Postcouling - Females	MEAN S.D. N 9.86 (9.86) 1.118 25	9.65 (9.65) 1.807 16	8.63 (8.63)▼ 1.948 23
Day 4 Postcouling - Males + Females	MEAN S.D. N 10.12 (10.12) 0.922 25	9.99 (9.99) 1.752 16	8.91 (8.91)▼ 1.795 23
Day 7 - Males	MEAN S.D. N 16.60 (16.60) 1.696 25	16.32 (16.32) 3.164 16	14.23 (14.23)★ 2.742 NA
Day 7 - Females	MEAN S.D. N 15.87† 1.548 25	15.54† 3.150 16	13.31† 3.303 23

	Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)
Day 7 - Males + Females	MEAN S.D. N 16.29† 1.634 25	15.96† 3.072 16	13.83† 3.002 23
Day 14 - Males	MEAN S.D. N 31.27 (21.27) 4.071 25	32.68 (32.68) 4.540 16	25.98 (25.98)◆ 5.319 23
Day 14 - Females	MEAN S.D. N 30.17 (30.20) 3.342 25	31.71 (31.63) 4.365 16	24.52 (24.54)◆ 5.412 23
Day 14 - Males + Females	MEAN S.D. N 30.83 (31.04) 3.275 25	32.18 (31.75) 4.307 16	25.35 (25.42)◆ 4.947 23
Day 21 - Males	MEAN S.D. N 50.33 (50.31) 4.617 25	52.38 (52.37) 5.988 16	40.40 (40.53)◆ 5.527 23
Day 21 - Females	MEAN S.D. N 48.29 (48.29) 4.439 25	49.68 (49.69) 5.289 16	38.31 (38.31)◆ 7.824 23
Day 21 - Males + Females	MEAN S.D. N 49.41 (49.65) 4.039 25	51.07 (50.63) 5.352 16	39.58 (39.63)◆ 6.724 23

† Data extracted from Tables 67, 70, and 72, pp. 214-215, 218-221, 223-225.

0 - Least square mean
NA - Not Available
* Significantly different from control, p<0.05
** Significantly different from control, p<0.01
*** Significantly different from control, p<0.005; Covariate analysis
▲ Significantly different from control, p<0.05; Covariate analysis
◆ Significantly different from control, p<0.01; Covariate analysis
▼ Significantly different from control, p<0.05; Group pairwise
❖ Significantly different from control, p<0.01; Group pairwise; † Welch's test performed.

TABLE 15. Selected P Male Mean Hematology and Clinical Chemistry Values (Study Week 20)^a

Endpoint		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Hematology Endpoints					
Erythrocytes (M/mm ³)	MEAN	9.002	8.972	9.433	10.196**
	S.D.	0.4599	0.4388	0.3340	0.4463
	N	10	10	10	10
Hemoglobin (g/dL)	MEAN	16.06	16.05	15.83	13.55**
	S.D.	0.638	0.711	0.646	0.968
	N	10	10	10	10
Hematocrit (%)	MEAN	50.48	49.72	49.88	45.96**
	S.D.	1.551	1.662	1.480	2.550
	N	10	10	10	10
MCV (fL)	MEAN	56.12	55.47	52.92**	45.13**
	S.D.	1.886	1.864	1.792	2.959
	N	10	10	10	10
MCH (pg)	MEAN	17.84	17.90	16.78*	13.31**
	S.D.	0.615	0.400	0.898	1.029
	N	10	10	10	10
MCHC (mg/dL)	MEAN	31.81	32.28	31.74	29.49**
	S.D.	0.599	0.561	0.942	0.642
	N	10	10	10	10
Platelets (K/mm ³)	MEAN	1030.9	1162.9	1022.8	1468.4**
	S.D.	224.69	160.81	237.72	348.03
	N	10	10	10	10
Clinical Chemistry Endpoint					
Cholesterol (mg/dL)	MEAN	65.2	81.2	97.3*	99.3**
	S.D.	13.23	17.79	24.00	35.02
	N	10	10	10	10

^aData extracted from Tables 21 and 23, pp. 86-88 and 92, respectively.

*Significantly different from control, p<0.05.

**Significantly different from control, p<0.01.

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TABLE 16. Selected P Female Mean Hematology and Clinical Chemistry Values (Study Week 20)^a

Endpoint		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Hematology Endpoints					
Erythrocytes (M/mm ³)	MEAN	8.317	8.401	9.241*	9.593**
	S.D.	0.5015	0.6539	0.9936	0.5894
	N	10	10	10	10
Hemoglobin (g/dL)	MEAN	16.02	16.06	15.55	14.16**
	S.D.	1.074	0.771	1.030	1.873
	N	10	10	10	10
MCV (fL)	MEAN	59.32	59.10	53.84**	48.25**
	S.D.	1.921	2.542	4.057	4.522
	N	10	10	10	10
MCH (pg)	MEAN	19.26	19.17	16.95**	14.76**
	S.D.	0.753	1.053	1.604	1.736
	N	10	10	10	10
MCHC (mg/dL)	MEAN	32.46	32.41	31.46*	30.50**
	S.D.	0.636	0.818	0.734	0.826
	N	10	10	10	10
Platelets (K/mm ³)	MEAN	1025.9	1091.1	1161.0	1487*
	S.D.	146.83	166.83	323.63	582.85
	N	10	10	10	10
Eosinophils (X10.e3/ μ l)	MEAN	0.095	0.089	0.069	0.213*
	S.D.	0.0360	0.0273	0.0285	0.1581
	N	10	10	10	10
Clinical Chemistry Endpoint					
Cholesterol (mg/dL)	MEAN	75.7	71.6	114.7**	115.2**
	S.D.	16.00	17.08	14.07	25.49
	N	10	10	10	10

^aData extracted from Tables 22 and 24, pp. 89-91 and 93, respectively.

*Significantly different from control, p<0.05.

**Significantly different from control, p<0.01.

TABLE 17. Selected P Male Mean Absolute Organ Weight (g)^a

		Body Weight	Brain	Kidney	Pituitary	Spleen
Group 1 (Control)	MEAN	574	2.04	4.34	13	0.81
	S.D.	46.6	0.102	0.433	2.0	0.115
	N	30	29	30	30	30
Group 2 (1000 ppm)	MEAN	563	2.05	4.12	12	0.85
	S.D.	52.9	0.110	0.466	1.7	0.146
	N	30	30	30	30	30
Group 3 (6250 ppm)	MEAN	536**	1.97*	3.78**	11**	0.92*
	S.D.	30.1	0.067	0.253	1.5	0.378
	N	29	29	28	29	29
Group 4 (12,500 ppm)	MEAN	513**	2.00	3.75**	12	0.87*
	S.D.	40.4	0.130	0.354	1.9	0.160
	N	26	26	26	29	26

^aData extracted from Table 27, pp. 103-106.

*Significantly different from control, p<0.05.

**Significantly different from control, p<0.01.

TABLE 18. Selected P Male Mean Relative Organ Weight^a

Group (Concentration - ppm)		Relative to Body Weight							Relative to Brain Weight
		Brain (%)	Left Epididymis (% X 10)	Right Epididymis (% X 10)	Kidney (% X 10)	Spleen (% X 10)	Left Testis (% X 10)	Right Testis (% X 10)	Kidney (% X 10 ²)
Group 1 (Control)	MEAN	0.358	1.23	1.27	7.59	1.42	3.12	3.16	2.12
	S.D.	0.0334	0.092	0.096	0.769	0.203	0.303	0.290	0.211
	N	29	30	30	30	30	30	30	29
Group 2 (1000 ppm)	MEAN	0.367	1.28	1.30	7.34	1.51	3.22	3.22	2.01
	S.D.	0.0332	0.145	0.146	0.586	0.243	0.343	0.387	0.204
	N	30	30	30	30	30	30	30	30
Group 3 (6250 ppm)	MEAN	0.368	1.29	1.31	7.06**	1.72*	3.22	3.27	1.92**
	S.D.	0.0214	0.178	0.142	0.469	0.688	0.354	0.361	0.135
	N	29	29	29	28	29	29	29	28
Group 4 (12,500 ppm)	MEAN	0.391**	1.36**	1.38**	7.33	1.68	3.49**	3.47**	1.88**
	S.D.	0.0275	0.085	0.097	0.647	0.267	0.335	0.368	0.193
	N	26	26	26	26	26	26	26	26

^aData extracted from Table 27, pp. 103-106.

*Significantly different from control, p<0.05.

**Significantly different from control, p<0.01.

TABLE 19. Selected F, Male Mean Absolute Organ Weight (g)^a

Group (Concentration - ppm)		Absolute Organ Weight (g)										
		Body	Brain	Adrenal	Left Epididymis	Right Epididymis	Kidney	Liver	Prostate	Seminal Vesicle	Left Testis	Right Testis
Group 1 (Control)	MEAN	603	2.14	60	0.74	0.74	4.72	22.43	0.70	2.71	1.92	1.91
	S.D.	57.0	0.131	12.0	0.061	0.051	0.525	2.884	0.166	0.325	0.215	0.140
	N	30	30	30	30	30	30	30	30	30	30	30
Group 2 (1000 ppm)	MEAN	602	2.09	55	0.71	0.72	4.29**	22.36	0.68	2.58	1.89	1.88
	S.D.	70.6	0.105	10.4	0.087	0.080	0.477	4.041	0.155	0.386	0.184	0.197
	N	29	29	28	29	29	29	28	29	29	29	29
Group 3 (6250 ppm)	MEAN	537**	1.99**	49**	0.64**	0.66**	3.81**	19.95*	0.56**	2.48*	1.69**	1.68**
	S.D.	56.9	0.108	10.8	0.057	0.071	0.408	3.034	0.120	0.330	0.166	0.147
	N	23	23	23	23	23	23	23	23	23	23	23

^aData extracted from Table 62, 184-191.
 *Significantly different from control, p<0.05.
 **Significantly different from control, p<0.01.

TABLE 20. Selected F, Male Mean Relative Organ Weight^a

Group (Concentration - ppm)		Relative to Body Weight			Relative to Brain Weight					
		Kidney (% X 10)	Pituitary (% X 10 ⁻²)	Spleen (% X 10)	Adrenal (%)	Left Epididymis (% X 10 ⁻²)	Kidney (% X 10 ⁻²)	Pituitary (% X 10)	Prostate (% X 10 ⁻¹)	Right Testis (% X 10 ⁻²)
Group 1 (Control)	MEAN	7.84	2.49	1.41	2.81	0.35	2.21	6.97	3.28	0.90
	S.D.	0.686	0.349	0.187	0.536	0.031	0.230	0.995	0.733	0.076
	N	30	29	30	30	30	30	29	30	30
Group 2 (1000 ppm)	MEAN	7.16**	2.26*	1.40	2.61	0.34	2.05*	6.50*	3.25	0.90
	S.D.	0.585	0.311	0.187	0.457	0.040	0.190	0.896	0.725	0.088
	N	29	29	28	28	29	29	29	29	29
Group 3 (6250 ppm)	MEAN	7.13**	2.46**	1.57*	2.47*	0.32*	1.92**	6.59	2.84*	0.84*
	S.D.	0.618	0.362	0.294	0.464	0.027	0.215	0.977	0.572	0.076
	N	23	22	23	23	23	23	22	23	23

^aData extracted from Table 62, 184-191.
 *Significantly different from control, p<0.05.
 **Significantly different from control, p<0.01.

TABLE 21. Selected F, Female Mean Absolute and Relative Organ Weight^a

Group (Concentration - ppm)		Absolute Organ Weight (g)					Relative to Body Weight		Relative to Brain Weight	
		Brain	Kidney	Liver	Spleen	Uterus/Oviducts/Cervix	Kidney (% X 10)	Liver (%)	Kidney (% X 10 ⁻²)	Liver (% X 10 ⁻²)
Group 1 (Control)	MEAN	1.86	2.81	14.86	0.59	0.679	8.27	4.36	1.52	8.01
	S.D.	0.144	0.296	1.926	0.098	0.2032	0.590	0.314	0.170	1.000
	N	30	30	30	30	30	30	30	30	30
Group 2 (1000 ppm)	MEAN	1.84	2.57**	13.51**	0.54*	0.646	7.80*	4.09*	1.40**	7.36*
	S.D.	0.118	0.256	1.924	0.072	0.2241	0.751	0.403	0.129	1.047
	N	30	30	30	30	30	30	30	30	30
Group 3 (6250 ppm)	MEAN	0.176**	2.49**	13.73*	0.59	0.543*	7.60**	4.20	1.42*	7.83
	S.D.	0.142	0.297	1.521	0.077	0.1397	0.677	0.374	0.160	0.779
	N	29	29	29	29	29	29	29	29	29

^aData extracted from Table 63, 192-197.
 *Significantly different from control, p<0.05.
 **Significantly different from control, p<0.01.

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TABLE 22. Selected P Male Microscopic Findings^a

Observation	Group 1 (Control)		Group 2 (1000 ppm)		Group 3 (6250 ppm)		Group 4 (12,500 ppm)	
	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Kidney - Number of Animals Examined	0	30	0	30	1	29	4	26
Chronic interstitial nephritis	0	16	0	13	0	16	2	21
— trace	0	15	0	13	0	11	1	7
— mild	0	1	0	0	0	5	1	13
— moderate	0	0	0	0	0	0	0	1
Calculus/calculi, trace	0	0	0	0	0	2	0	7
Hydronephrosis	0	3	0	2	0	7	0	8
— trace	0	1	0	1	0	4	0	2
— mild	0	1	0	1	0	3	0	6
— severe	0	1	0	0	0	0	0	0
Urothelial papillary hyperplasia	0	0	0	0	0	4	0	4
— trace	0	0	0	0	0	4	0	2
— mild	0	0	0	0	0	0	0	2

^aData extracted from Table 29, pp. 110-113.

DOS: died on study

SAC: terminal sacrifice

TABLE 23. Selected P Female Microscopic Findings^a

Observation	Group 1 (Control)		Group 2 (1000 ppm)		Group 3 (6250 ppm)		Group 4 (12,500 ppm)	
	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Kidney - Number of Animals Examined	1	29	0	30	0	30	0	30
Chronic interstitial nephritis	0	9	0	9	0	9	0	14
— trace	0	9	0	9	0	9	0	12
— mild	0	0	0	0	0	0	0	2
Calculus/calculi	0	0	0	0	0	2	0	5
— trace	0	0	0	0	0	2	0	4
— mild	0	0	0	0	0	0	0	1
Hydronephrosis	0	0	0	1	0	2	0	2
— trace	0	0	0	0	0	0	0	2
— mild	0	0	0	1	0	1	0	0
— moderate	0	0	0	0	0	1	0	0
Urothelial papillary hyperplasia	0	0	0	0	0	0	0	4
— trace	0	0	0	0	0	0	0	2
— mild	0	0	0	0	0	0	0	2

^aData extracted from Table 30, pp. 114-117.

DOS: died on study

SAC: terminal sacrifice

TABLE 24. Selected F₁ Male Microscopic Findings^a

Observation	Group 1 (Control)		Group 2 (1000 ppm)		Group 3 (6250 ppm)		Group 4 (12,500 ppm)	
	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Kidney - Number of Animals	0	30	0	29	2	23	4	2
Chronic interstitial nephritis	0	16	0	16	1	19	1	2
— trace	0	15	0	15	1	10	1	1
— mild	0	1	0	1	0	9	0	1
Calculus/calculi	0	0	0	0	1	14	5	1
— trace	0	0	0	0	1	13	3	1
— mild	0	0	0	0	0	1	2	0
Hydronephrosis	0	0	0	3	2	10	4	2
— trace	0	0	0	3	1	1	2	2
— mild	0	0	0	0	1	9	2	0
Urothelial papillary hyperplasia, trace	0	0	0	0	0	2	---	---

^aData extracted from Table 64, pp. 198-206.
 DOS: died on study; SAC: terminal sacrifice

TABLE 25. Selected F₁ Female Microscopic Findings^a

Observation	Group 1 (Control)		Group 2 (1000 ppm)		Group 3 (6250 ppm)		Group 4 (12,500 ppm)	
	DOS	SAC	DOS	SAC	DOS	SAC	DOS	SAC
Kidney - Number of Animals	0	30	0	30	0	29	0	5
Chronic interstitial nephritis	0	6	0	10	0	16	0	5
— trace	0	6	0	10	0	11	0	2
— mild	0	0	0	0	0	5	0	3
Calculus/calculi	0	0	0	0	0	7	0	1
— trace	0	0	0	0	0	4	0	1
— mild	0	0	0	0	0	1	0	0
Hydronephrosis	0	0	0	1	0	4	0	1
— trace	0	0	0	0	0	3	0	2
— mild	0	0	0	1	0	1	0	0
Healed infarct, mild	0	0	0	0	0	3	—	---
Urothelial papillary hyperplasia	0	0	0	0	0	3	—	---
— trace	0	0	0	0	0	2	—	---
— mild	0	0	0	0	0	1	—	---

^aData extracted from Table 65, pp. 207-212.

DOS: died on study

SAC: terminal sacrifice

TABLE 26. Selected F₁ Sexual Maturation Values^a

Endpoint		Group 1 (Control)	Group 2 (1000 ppm)	Group 3 (6250 ppm)	Group 4 (12,500 ppm)
Vaginal Opening (Days)	MEAN	35.1	35.6	39.8**	59.9**
	S.D.	2.25	2.16	3.59	10.82
	No. of pups passing	30	29	30	22
Preputial Separation (Days)	MEAN	44.5	44.2	47.4**	56.7**
	S.D.	3.71	1.81	3.01	6.44
	No. of pups passing	30	30	30	23
Body Weight on Day Passed Preputial Separation (g), Male	MEAN	209.1	203.2	183.0**	130.3**
	S.D.	19.09	19.93	22.65	18.49
	No. of pups	29	30	30	23

^aData extracted from Table 39, p. 146

**Significantly different from control, p<0.01

TABLE 27. F₁ Male Pup Mean Absolute and Relative Organ Weight^a

Group (Concentration - ppm)		Absolute Organ Weight (g)				Relative to Body Weight			Relative to Brain Weight	
		Body	Brain	Spleen	Thymus	Brain (%)	Spleen (% X 10)	Thymus (% X 10)	Spleen (% X 10 ³)	Thymus (% X 10 ⁴)
Group 1 (Control)	MEAN	72	1.47	0.35	0.31	2.054	4.82	4.25	2.36	2.08
	S.D.	8.8	0.096	0.051	0.055	0.1994	0.757	0.587	0.345	0.311
	N	28	28	28	28	28	28	28	28	28
Group 2 (1000 ppm)	MEAN	70	1.46	0.34	0.27*	2.106	4.91	3.84*	2.36	1.85*
	S.D.	10.0	0.091	0.076	0.058	0.2480	0.958	0.586	0.504	0.363
	N	26	26	26	26	26	26	26	26	26
Group 3 (6250 ppm)	MEAN	51**	1.35**	0.32	0.13**	2.699**	6.35**	2.59**	2.37	0.98**
	S.D.	9.6	0.109	0.076	0.039	0.3040	1.442	0.477	0.547	0.247
	N	27	27	27	27	27	27	27	27	27
Group 4 (12,500 ppm)	MEAN	38**	1.20**	0.24**	0.08**	3.329**	6.03	2.02**	1.92*	0.65**
	S.D.	11.2	0.177	0.105	0.039	0.7637	1.756	0.677	0.715	0.266
	N	14	14	14	14	14	14	14	14	14

^aData extracted from Table 38, p. 144.
 *Significantly different from control, p<0.05.
 **Significantly different from control, p<0.01.

TABLE 28. Selected F₁ Female Pup Mean Absolute and Relative Organ Weight^a

Group (Concentration - ppm)		Absolute Organ Weight (g)				Relative to Body Weight			Relative to Brain Weight
		Body	Brain	Spleen	Thymus	Brain (%)	Spleen (% X 10)	Thymus (% X 10)	Thymus (% X 10 ⁴)
Group 1 (Control)	MEAN	67	1.44	0.31	0.31	2.174	4.74	4.56	2.12
	S.D.	8.5	0.103	0.035	0.060	0.1897	0.644	0.547	0.331
	N	28	28	28	28	28	28	28	28
Group 2 (1000 ppm)	MEAN	66	1.42	0.31	0.27	2.165	4.73	4.13*	1.93
	S.D.	7.8	0.086	0.046	0.054	0.2048	0.675	0.651	0.363
	N	25	25	25	25	25	25	25	25
Group 3 (6250 ppm)	MEAN	49**	1.29**	0.30	0.14**	2.769**	6.44**	2.77**	1.05**
	S.D.	12.1	0.125	0.065	0.050	0.4775	1.455	0.522	0.351
	N	26	26	26	26	26	26	26	26
Group 4 (12,500 ppm)	MEAN	36**	1.18**	0.23*	0.09**	3.426**	6.20**	2.44**	0.76**
	S.D.	10.5	0.153	0.103	0.041	0.8385	1.749	0.830	0.290
	N	18	18	18	18	18	18	18	18

^aData extracted from Table 38, p. 145.
 *Significantly different from control, p<0.05; **Significantly different from control, p<0.01.

TABLE 29. Selected F₂ Male Pup Mean Absolute and Relative Organ Weight^a

Group (Concentration - ppm)		Absolute Organ Weight (g)				Relative to Body Weight		Relative to Brain Weight
		Body	Brain	Spleen	Thymus	Brain (%)	Thymus (% X 10)	Thymus (% X 10 ⁴)
Group 1 (Control)	MEAN	50	1.43	0.22	0.22	2.850	4.41	1.56
	S.D.	4.5	0.085	0.042	0.039	0.2318	0.602	0.257
	N	24	24	24	24	24	24	24
Group 2 (1000 ppm)	MEAN	52	1.41	0.23	0.20	2.761	3.93*	1.45
	S.D.	6.5	0.088	0.044	0.047	0.3472	0.706	0.334
	N	16	16	16	16	16	16	16
Group 3 (6250 ppm)	MEAN	38**	1.29**	0.18*	0.11**	3.439**	2.77**	0.83**
	S.D.	5.9	0.113	0.049	0.029	0.4655	0.496	0.213
	N	23	23	23	23	23	23	23

^aData extracted from Table 74, p. 236.
 *Significantly different from control, p<0.05.
 **Significantly different from control, p<0.01.

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TABLE 30. Selected F₂ Female Pup Mean Absolute and Relative Organ Weight^a

Group (Concentration - ppm)		Absolute Organ Weight (g)			Relative to Body Weight		Relative to Brain Weight
		Body	Brain	Thymus	Brain (%)	Thymus (% X 10)	Thymus (% X 10 ³)
Group 1 (Control)	MEAN	48	1.37	0.24	2.869	5.01	1.75
	S.D.	4.7	0.090	0.042	0.2897	0.979	0.296
	N	25	25	25	25	25	25
Group 2 (1000 ppm)	MEAN	50	1.38	0.22	2.842	4.51	1.62
	S.D.	5.9	0.089	0.058	0.3930	0.922	0.457
	N	15	16	16	15	15	16
Group 3 (6250 ppm)	MEAN	37**	1.27**	0.11**	3.576**	2.91**	0.87**
	S.D.	9.3	0.140	0.053	0.7816	0.766	0.354
	N	23	23	23	23	23	23

^aData extracted from Table 74, p. 237.

*Significantly different from control, p<0.05.

**Significantly different from control, p<0.01.

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TABLE 31. Mean Levels of Zinc, Copper, and Silver in Males (mg/kg body weight)^a

Group (ppm)	Zinc	Copper	Silver
Group 1 (Control)	7.407	2.153	NA
Group 2 (1000 ppm)	8.747	1.923	1.05 ^c
Group 1 (6250 ppm)	8.273	1.96 ^b	1.28

^aData extracted from section 5.10.8, pp. 51-52.

^bRepresents value for one animal; two values were <1.5.

^cRepresents value for two animals; one value was <1.

NA - Not available; could not be calculated because all values were <1.

TABLE 32. Mean Levels of Zinc, Copper, and Silver in Females (mg/kg body weight)^a

Group (ppm)	Zinc	Copper	Silver
Group 1 (Control)	7.977	2.463	NA
Group 2 (1000 ppm)	6.853	1.68	1.06 ^c
Group 1 (6250 ppm)	9.953	1.69 ^b	2.02 ^d

^aData extracted from section 5.10.8, pp. 51-52.

^bRepresents value for two animals; one value was <1.5.

^cRepresents value for one animal; two values were <1.

^dRepresents value for two animals; one value was <1.

NA - Not available; could not be calculated because all values were <1.

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APPENDIX 2

INDICES MEASURED

Fecundity index or pregnancy index in males was calculated as: [number of males impregnating a female/number of males with evidence of mating] X 100.

Fecundity index or pregnancy index in females was calculated as: [number of pregnant females/number of females with evidence of mating] X 100.

Fertility index in males was calculated as: [number of males impregnating a female/number of males paired] X 100.

Fertility index in females was calculated as: [number of pregnant females/number of females paired] X100.

Gestation index was calculated as: [number of females delivering at least 1 live pup/number of pregnant females] X 100.

Lactation index on Day 21 was calculated as: [number of pups surviving 21 days (weaning)/number of live pups at 4 days (postculling)] X100.

Live birth index was calculated as: [number of live pups at birth/number of pups born] X 100.

Mating index for males was calculated as: [number of males with evidence of mating/number of males paired] X 100.

Mating index for females was calculated as: [number of females with evidence of mating/number of females paired] X 100.

Stillborn index was calculated as: [number of stillborn pups/number of pups born] X 100.

Viability index at Day 4 was calculated as: [number of pups surviving 4 days (preculling)/number live pups at birth] X 100.