Report Title: Segment I Study of Fertility in Rats

Test Type: Reproduction Toxicity

Conducting Laboratory and Location: International Research and Development Corporation, Mattawan, MI

Test Substance(s): G0539.03 – Octopirox in PEG/methylcellulose/water vehicle

Species: Rat

# of Animals: 35 males and 35 females per group

Test Conditions: Rats were dosed via gavage with 1, 10, 100, and 250 mg/kg/day OP. 35 males and 35 females per group. Males were dosed 64 days prior to mating through sacrifice. Females were dose 14 days prior to mating through 3 wks after parturition.

Results:
NOEL for general toxicity: 10 mg/kg/day
NOEL for neonatal growth: 100 mg/kg/day
NOEL for reproductive parameters: 250 mg/kg/day

Study #: IRDC-191-1395
Report Date: 05/08/89
QA Statement and GLP compliance: Yes

Accession #: 35225

BIOLOGICAL SAFETY TEST SUMMARY REVIEW

Test Substance: Octopirox®

Test Substance Identification Number: 60539.03

Contract Laboratory: IR&DC — Report #: 191-1395

Type of Study: Segment I Study of Fertility in Rats — DRD #: BY0764

Toxicologist: G. S. Aligood — Division: BYC

Date Report Written: 5-8-89 — Date Rec'd by Operations Section: 5-19-89

[ ] This report was not selected for review by the Operations Section.

Operations Section Monitor: _____ Date: _____

This report has been reviewed and found in agreement with the Protocol and to comply with all applicable Federal Regulations:

Operations Section Monitor: G. A. Nixon — Date: 5/31/89

This report has been reviewed for specific scientific content:

HSD Scientific Reviewer: G. R. Johnson — Date: 6/6/89

This report has been reviewed or scientific quality and is summarized, with comments (if any), as follows: Where applicable, the retention limits for specimens to be returned to the P&G Archive are given.

A Segment I Fertility/Reproduction Study was conducted in Charles River rats dosed via gavage with 0, 10, 100, and 250 mg/kg/day octopirox (35 males & 35 females per group). Males were dosed 64 days prior to mating thru sacrifice. Females were dosed 14 days prior to mating thru 3 weeks after parturition (10 females/group were sacrificed at day 13 of gestation).
The no observable effect levels were: 10 mg/kg/day for general toxicity (effects were reduced body weight & food consumption in mid-dose males); 100 mg/kg/day for neonatal growth (effects were reduced body weight, food consumption, and water in males, reduced mean weight in offspring growth, & several hematological parameters at high dose); 250 mg/kg/day with respect to reproductive parameters.

Retention Limits (month & year)	
Slides:	indefinitely
Blocks:	6/99
Wet Tissues:	6/94
Teratology:	6/94

Divisional Toxicologist: G. S. Aligood — Date: 6/8/89

CIRCULATE BACK TO THE HSD SCIENTIFIC REVIEWER; THEN TO HSD LIAISON

This report is approved for entry into the Safety Data System and microfilming.

HSD Scientific Reviewer: G. R. Johnson — Date: 6/12/89

Corporate HSD Liaison: G. R. Johnson — Date: 6/12/89

Return to Marilyn Brown, Room 2N211, MVL

Entered into Safety Data System by M. Brown — Date: 6-14-89

Microfilming Completed by _____ Date: _____

Pass

International Research
and Development Corporation
MATTAWAN, MICHIGAN, U.S.A. 49071 TELEPHONE (616) 668-3336

SPONSOR: The Procter and Gamble Company

TEST ARTICLE: G0539.03

DRD NO.: BY0764

SUBJECT: Segment 1 Study of Fertility in Rats

DATE OF STUDY COMPLETION: May 8, 1989

Volume 1 of 2

191-1395

RECEIVED BY
MAY 17 1989
OPERATIONS SECTION

"credence through research"

TABLE OF CONTENTS

		Page
I.	Quality Assurance Statement	1
II.	Synopsis	2
III.	Introduction	4
	A. Objective	4
	B. Test Article Identification	4
	C. Vehicle Control Identification	5
IV.	Methods and Procedures	6
	A. Experimental Design	6
	1. Animal Receipt and Maintenance	6
	2. Rationale for Selection of Species and Strain	7
	3. Organization of Test Groups	7
	B. Test Article Administration	8
	C. Test Article Analyses	10
	D. F_0 Parental Observations	10
	1. Survival, Appearance and Behavior	10
	2. Body Weights	10
	3. Food Consumption	11
	4. Estrous Cycle Determinations	11
	E. Mating Procedure	12
	F. Gestation Day 13 Uterine Examination	12
	G. F_0 Parturition and Litter Observations	13
	H. Disposition of Animals	14
	1. F_0 Males	14
	2. F_0 Females	14
	3. F_1 Pups	14
	I. Hematology and Biochemistry	14
	J. Anatomic Pathology	16
	1. Macroscopic	16
	2. Organ Weights	17

TABLE OF CONTENTS
(Continued)

		Page
	K. Data Retention	17
	L. Statistical Analysis	18
V.	Results	19
	A. General Observations	19
	1. Survival, Appearance and Behavior	19
	2. Body Weights	20
	3. Food Consumption	21
	4. Estrous Cycle Observations	21
	5. Gestation Day 13 Uterine Examination Observations	21
	B. Reproduction and Litter Parameters	22
	1. Reproductive Parameters	22
	2. Offspring Viability	22
	3. Offspring Growth	22
	4. Offspring Assessment	22
	C. Uterine Observations on Lactation Day 21	23
	D. Hematological and Biochemical Parameters	24
	1. Hematology	24
	2. Biochemistry	24
	E. Anatomic Pathology	25
	1. Macroscopic	25
	2. Organ Weights	25
VI.	Signatures	26
VII.	Discussion and Conclusion	27
VIII.	References	28

TABLE NO.

1-2.	Summary of Antemortem Observations	30-31
3-4.	Summary of Body Weight Values	32-37
5.	Summary of Maternal Body Weights and Body Weight Changes During Gestation and Lactation - F_0 Dams	38
6-7.	Summary of Food Consumption Values	39-40

TABLE OF CONTENTS
(Continued)

		Page
8.	Summary of Maternal Food Consumption Values - F_0 Dams	41
9.	Summary of Estrous Cycle Abnormalities	42
10.	Summary of Maternal and Embryonic Observations at 13-Day Uterine Examination - F_0 Dams	43
11.	Summary of Reproductive Parameters - F_0 Parents	44
12.	Summary of Offspring Viability - F_1 Offspring	45
13.	Summary of Offspring Growth Data - F_1 Offspring	46
14.	Summary of Uterine Observations on Lactation Day 21 - F_0 Dams	47
15-17.	Summary of Hematological Values	48- 56
18.	Summary of Biochemical Values	57- 60
19.	Incidence of Macroscopic Observations	61- 64
20.	Summary of Organ Weight Values	65- 67
APPENDIX A		
	Quality Assurance Inspections	68- 69
APPENDIX B		
	Individual Experimental Data	70-155
APPENDIX C		
	Individual Hematological Values	156-237
APPENDIX D		
	Individual Biochemical Values	238-246
APPENDIX E		
	Individual Organ Weight Values	247-258
APPENDIX F		
	Individual Animal Data Record: Pathology	259-316
APPENDIX G		
	Historical Control Data	317-327
APPENDIX H		
	Protocol and Protocol Addenda	328-356

I. QUALITY ASSURANCE STATEMENT

Study Title: Segment I Study of Fertility in Rats
Test Article: G0539.03

The conduct of this study has been subjected to periodic inspections. The dates of inspection and the dates that findings were reported to management and the Study Director are listed in Appendix A.

This report has been reviewed by the International Research and Development Corporation Quality Assurance Department in accordance with the United States Food and Drug Administration Good Laboratory Practice Regulations of June 20, 1979 and as modified by the final rule effective October 5, 1987.

Approved By: Margery J. Wirth, B.S. 5/8/89
Director of Quality Assurance Date

191-1395

II. SYNOPSIS

Charles River CDB5® CD® rats, randomly assigned to one control and three treatment groups of 70 animals (35 male and 35 female) each, were used to determine the effect of G0539.03 on reproductive performance, fertility, parturition, and neonatal viability.

The test article was administered orally by gavage to three groups of male rats beginning 64 days prior to mating and continuing until sacrifice, and to three groups of female rats beginning 14 days prior to mating and continuing until sacrifice. Animals in the treated groups received the test material as a single daily dose at dosage levels of 10, 100 and 250 mg/kg/day, at a volume of 2.5 ml/kg. The control group received the vehicle only, a combination of 1.0% methylcellulose (4000 cps) and polyethylene glycol 400, on a comparable regimen.

Ten randomly selected mated females underwent a uterine examination on gestation day 13; the remaining females were allowed to deliver. Blood samples were collected from all parental animals during acclimation and prior to sacrifice for hematological and biochemical (gestation day 13 females) characterization. The parental animals were necropsied and tissues were saved for possible histopathological examination.

Effects induced by the test article were seen at the mid- and high-dose levels. Approximately 11% of the high-dose males had rales; reduced body weight and food consumption were noted among the mid- and high-dose males. Several hematological parameters were adversely affected at the high-dose level. Offspring growth was inhibited for the high-dose group as evidenced by significantly reduced mean weight values throughout lactation.

The remaining parameters assessed, including mating behavior and reproductive performance, were not affected by treatment at any dosage level tested.

In summation, the no observable effect level of G0539.03 with respect to general toxicity was considered to be 10 mg/kg/day. Neonatal growth was not affected at 100 mg/kg/day or less, and the no observable effect level with respect to reproductive parameters was 250 mg/kg/day.

III. INTRODUCTION

A. OBJECTIVE

The objective of this study was to determine the effect of the test article on fertility, parturition, neonatal viability, and reproductive performance in rats. This study utilized treatment of both sexes with the test material.

B. TEST ARTICLE IDENTIFICATION

The test article was received from The Procter and Gamble Company, Cincinnati, Ohio on February 26 and July 5, 1988 as indicated below:

IRDC No.	Label	Description
9542B	TEST SUBST. (TSIN) G0539.03 DIV. REQUEST DOC. (DRD) BY0764 DATE REC'D. (OPER SECTION) 2/24/88 TYPE OF TEST Segment I Fertility Study in rats GROSS WT. (INC. LID, CONT., LABEL) 1397.56 *TARE WT. 147.56g NET WT. 1250.0g STORAGE CONDITIONS ambient EXPIRATION DATE 2/89 HAZARD non-hazardous D.O.T. HAZARD non-hazardous RETURN TO DIVISIONAL TOXICOLOGIST WHEN TEST IS COMPLETED *CONTAINER, LID, LABEL CAUTION: THE TOXICITY OF THIS MATERIAL HAS NOT BEEN COMPLETELY EVALUATED	white powder (1 container)

IRDC No.	Label	Description
9542C	TEST SUBST. (TSIN) G0539.03 DIV. REQUEST DOC. (DRD) BY0764 DATE REC'D. (OPER SECTION) TYPE OF TEST Segment I Fertility GROSS WT. (INC. LID, CONT, LABEL) 655.07 *TARE WT. 343.2 NET WT. 301.5 STORAGE CONDITIONS room temperature EXPIRATION DATE 2/89 HAZARD none D.O.T. HAZARD non-hazardous RETURN TO DIVISIONAL TOXICOLOGIST WHEN TEST IS COMPLETED *CONTAINER, LID, LABEL CAUTION: THE TOXICITY OF THIS MATERIAL HAS NOT BEEN COMPLETELY EVALUATED	white powder (1 container)

C. VEHICLE CONTROL IDENTIFICATION

The vehicle control article used throughout the study was a combination of 1.0% methylcellulose (4000cps) and polyethylene glycol 400. Specific receipt, label and descriptive information is available upon Sponsor request.

IV. METHODS AND PROCEDURES

This study was conducted in accordance with the protocol as approved by the Sponsor and in compliance with the Standard Operating Procedures of International Research and Development Corporation (IRDC). Procedures pertinent to this study are described herein.

A. EXPERIMENTAL DESIGN

1. Animal Receipt and Maintenance

One hundred seventy untreated, sexually mature, 70-day old, virgin female and 177, 34-day old male Charles River COBS® CD® rats were received from Charles River Laboratories, Inc., Portage, Michigan. The males were received on March 31, 1988 and the females were received on May 11, 1988. Upon receipt, the animals were assigned temporary animal numbers and housed individually in suspended wire-mesh cages. During the 11- and 20-day acclimation periods (males and females, respectively), the animals were carefully observed for changes in appearance and behavior. Six days after receipt of the males, and five days after receipt of the females, blood samples were collected into tubes containing EDTA anticoagulant according to SOP (Standard Operating Procedures). Hemoglobin, hematocrit, white blood cell count, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count and differential white blood cell were determined. From acquisition until sacrifice, each animal was provided with basal laboratory diet of Certified Rodent Chow® #5002 and tap water available *ad libitum*.

The basal laboratory diet was analyzed by the manufacturer for the presence of pesticides, heavy metals and aflatoxins; each diet-lot used was recorded. The drinking water at IRDC is analyzed quarterly for the presence of pesticides, heavy metals and coliforms. The results of these analyses are stored in the IRDC Archives in Mattawan, Michigan and are available upon request. The

Study Director was not aware of any potential contaminants of either diet or drinking water which might have interfered with the results of this study.

Throughout the study, all animals were housed in an environmentally controlled room. Temperature ranged between 69°F and 76°F, with a mean temperature ± standard deviation of 72 ± 1.5°F; humidity ranged between 42% and 62% with a mean humidity ± standard deviation of 50 ± 5.7%. Fluorescent lighting provided illumination 12 hours per day. Each parental rat was identified by cage, group and individually by a Monel® metal ear tag bearing its animal number. The individual animal number plus the IRDC study number provided a unique identification number for each animal.

The study initiated with Study Director approval of the protocol on March 9, 1988. At treatment initiation the male rats were 45 days old and weighed between 189 and 240 grams; the females were 90 days old and weighed between 226 and 293 grams. Treatment of the F_0 males began on April 11, 1988 and the last F_1 pup was sacrificed on August 21, 1988.

2. Rationale for Selection of Species and Strain

The Charles River CORS® CD® rat is an acceptable model for reproduction studies. This laboratory has historical control data on fertility, reproductive performance, and neonatal survival indices and growth rates of this strain from this source.

3. Organization of Test Groups

Prior to randomization, all animals were weighed and subjected to a detailed physical examination.

The animals were randomly assigned to one control and three treatment groups by the following method: animal numbers and their corresponding body weights were entered onto magnetic tape which was used as the data source for the randomization procedure. The

mean body weight and standard deviation were calculated by sex and a computer-generated edit developed a listing of male and female animals whose body weights were within ± 2.0 and ± 1.5 standard deviations of their respective means. From the qualifying animals, the randomization procedure selected and assigned the required number of animals. Bartlett's test for homogeneity of variances was performed on these groups; the groups were determined to be homogeneous.

B. TEST ARTICLE ADMINISTRATION

Although the anticipated major route of exposure by humans is dermal, the selected route of administration was oral as this would maximize systemic exposure. The dose levels were selected based on a pilot study conducted by IRDC (191-1394).

The vehicle control article was prepared as follows: The required amounts of PEG 400 (polyethylene glycol) and 1.0% methylcellulose (4000 cps) in deionized distilled water were weighed into a beaker and mixed using a magnetic stir bar and stir plate. The resulting suspension was sonicated for approximately 90 seconds. Suspension pH was adjusted to 7.0 using 1M citric acid or 1N NaOH as necessary. The suspension was dispensed into amber containers, capped and stored under refrigeration prior to use.

Test material administered to animals in the treated groups was prepared as follows: The required amount of G0539.03 was weighed and dissolved in a beaker with an appropriate amount of PEG 400 using a stir bar and stir plate. The PEG 400 was warmed to approximately 37°C to facilitate dissolution of the test article. The required amount of 1.0% methylcellulose was weighed into a separate beaker, then added slowly to the PEG/test article suspension. This suspension was stirred using a magnetic stir bar and stir plate, then sonicated for approximately 90 seconds. The pH of the suspension was adjusted to 7.0 using 1M citric acid or 1N NaOH as needed.

The prepared test material was dispensed into amber capped containers and stored under refrigeration until ready for use.

Test material suspensions were prepared fresh weekly at concentrations to permit the administration of dosage levels of 10, 100 and 250 mg/kg/day at a dose volume of 2.5 ml/kg. Test material prepared on July 25, 1988 was utilized for eight days of dosing. Administration of the test material to the males began 64 days prior to mating and continued until sacrifice. Administration to the females began 14 days prior to mating and continued until sacrifice on gestation day 13 or lactation day 21. Females which did not deliver were dosed through gestation day 24. The F_1 offspring, although potentially exposed to the test article in utero and during lactation through nursing, were untreated. The control group received the vehicle only on a comparable regimen. Dosing suspensions were warmed to room temperature and sonicated prior to dispensation for dosing. Dosing began approximately 6.5 to 10 hours after initiation of the illuminated phase of the photoperiod. Individual dosage volumes were based on the most recently recorded individual body weights. Vehicle and test material administration was accomplished by intragastric intubation using 16 gauge, 7.6 cm long straight stainless steel intubation needles and 1 or 3 cc plastic disposable syringes. A dosing error on July 29, 1988 resulted in several control females receiving test material for the low-dose group. These animals and the lactation days they were misdosed are as follows: 50215 (day 16); 50218, 50228, 50216 and 50237 (day 18); 50207, 50206, 50219, 50214 and 50239 (day 19); 50236, 50220 and 50221 (day 20). This error did not appear to adversely affect any of these animals and was not considered a consequence to the outcome of the study.

191-1395

C. TEST ARTICLE ANALYSES

Homogeneity evaluations, concentration and/or stability analyses were conducted by the Sponsor. Approximately 20 ml samples from the top, middle and bottom of the mixtures were collected and sent under ambient conditions to the Sponsor. A test article sample was returned to the Sponsor at the end of the study. Samples of dosing suspensions from study weeks 1, 6 and 12 were sent to the Sponsor for analysis. A sample of the vehicle was sent to the Sponsor per request on July 7, 1988.

D. F_0 PARENTAL OBSERVATIONS

1. Survival, Appearance and Behavior

Throughout the study, male and female rats were observed twice daily, seven days a week, for mortality and overt changes in appearance and behavior. The animals were examined in detail on a daily basis beginning with treatment. Any clinical findings observed were recorded. Animals found dead or sacrificed in extremis were subjected to a routine necropsy procedure and the appropriate tissues were saved.

2. Body Weights

Individual male body weights were recorded every three days for the first three weeks of treatment, then weekly until sacrifice. Individual female body weights were recorded weekly until evidence of copulation was observed or until sacrifice. Those dams selected for gestation day 13 uterine examination were weighed on gestation days 0, 7 and 13. The remaining dams, there allowed to deliver, were weighed on gestation days 0, 7, 13 and 20, and on lactation days 0, 7, 14 and 21. Body weights recorded on lactation day 21 were obtained following an overnight fast prior to blood collection.

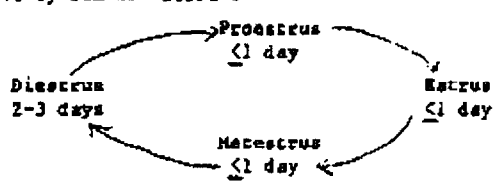
3. Food Consumption

Individual 24-hour food consumption was measured on the first day of each week for males and females up to the mating period, and after the mating period for males and nonbred females. Food consumption was not measured during the mating period as the animals were cohabited at that time. Maternal food consumption was measured during gestation and lactation on the specified body weight days.

4. Estrous Cycle Determinations

Ten days prior to test article administration, vaginal smears of all females were made daily to establish estrous cycles. This examination continued through the 14-day premating treatment period and until evidence of copulation was observed during the mating period.

The following figure depicts normal estrous cycling in rats as described by Fox and Laird[1].



In the proestrus phase of the cycle, the smear is composed of nucleated epithelial cells. During the estrus phase of the cycle, the smear contains cornified epithelial cells. Smears during metestrus contain some cornified cells with leukocytes and mucus appearing later. Diestrus smears are characterized by the presence of leukocytes and nucleated epithelial cells entangled in mucus.

Abnormalities of cycle duration or sequence are considered to be as follows:

Proestrus >1 day
Estrus >1 day
Metestrus >1 day
Diestrus <2 or >3 days

E. MATING PROCEDURE

Each male was cohabited with one female rat of the same strain, source and treatment group in a wire-mesh cage. The occurrence of copulation was determined by daily inspection for a copulatory plug or vaginal inspection for sperm. The day that evidence of mating was detected was designated day 0 of gestation; the female was placed in an individual plastic cage with wood chip (Beta-Chip®) bedding. Any female failing to show evidence of copulation after the initial 10-day mating period was housed for an additional 10 days with a different male which was sperm positive during the initial 10 days. Copulatory intervals were calculated for females with evidence of copulation during the mating period. At the end of the mating period, females with no evidence of copulation were transferred to individual plastic cages containing wood chip bedding until sacrifice.

F. GESTATION DAY 13 UTERINE EXAMINATION

Prior to sacrifice on the 13th day of gestation, a blood sample was collected from the females randomly selected for the 13-day uterine examination. These animals were not fasted prior to blood collection to avoid placing additional stress on the animals. Blood samples were analyzed for the parameters specified in Section IV.A.1. In addition, the following parameters were also analyzed: glucose, creatinine, cholesterol, urea nitrogen, triglycerides, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, albumin, total protein, calcium, phosphorus, sodium, potassium and iron. Immediately following sacrifice by

carbon dioxide inhalation, the uterus and ovaries were exposed by an abdominal incision. The location of viable and nonviable embryos, early resorptions, and the numbers of total implantations and corpora lutea were recorded. The abdominal and thoracic cavities of the rats were examined for grossly evident morphological changes and the carcasses discarded. Maternal tissues were preserved in 10% neutral buffered formalin for possible histopathological examination. Uteri from females that appeared nongravid were opened and placed in 10% ammonium sulfide solution for detection of implantations[2].

C. F_0 PARTURITION AND LITTER OBSERVATIONS

During the period of expected parturition, the remaining F_0 females (25 per group) were observed twice daily for newborn litters. The duration of gestation was calculated and any difficulties occurring at parturition were recorded. Lactation day 0 was defined as the day the entire litter was found and delivery was judged complete. On lactation day 0, the litters were examined for litter size, stillbirths, live births and any gross anomalies.

Litter size was reduced to 10 pups, of equal sex distribution whenever possible, after weighing on lactation day 4 by use of a random numbers table. Litter size was reduced in order to provide a homogeneous group size for evaluation of nursing, survival and pup growth. The culled pups were examined externally, sacrificed and discarded.

Litters were caged with their dams for three weeks following birth. Throughout lactation, the dams and their pups were observed daily for survival and behavioral abnormalities in nesting and nursing. Any intact pups found dead were necropsied, examined for anomalies and discarded. The heart was dissected by a modification of the method described by Staples[3]. Pups were individually weighed on lactation days 0, 4, 7, 14 and 21; the number of pups per sex was recorded on lactation day 21.

H. DISPOSITION OF ANIMALS

1. F_0 Males

The males were externally examined, sacrificed and necropsied (Section IV.I.) following completion of the gestation day 13 uterine examination. Prior to sacrifice, a blood sample was collected and the parameters measured during acclimation were determined at this time.

2. F_0 Females

On lactation day 21, the females allowed to deliver were sacrificed and subjected to gross necropsy. The number and location of uterine implantation sites were recorded. Any tissues appearing macroscopically abnormal and those listed in Section IV.I. were retained in 10% neutral buffered formalin. Blood samples were also collected from those females prior to sacrifice and evaluated as described in Section IV.A.1.

On the 25th day following separation from the male, any female that did not deliver was sacrificed and a gross necropsy (Section IV.I.) was performed. Any condition which could have prevented pregnancy was recorded. Uteri that appeared nongravid were opened and placed in 10% ammonium sulfide solution for detection of implantations[2].

3. F_1 Pups

On lactation day 21, the F_1 pups were externally examined, sacrificed and discarded.

I. HEMATOLOGY AND BIOCHEMISTRY

Hematological evaluations were conducted on all animals within five days of receipt of the animals.

Prior to gestation day 13, blood samples were analyzed for hematology and biochemical analysis on 10 previously randomly selected females chosen for uterine examination.

Hematological parameters were conducted on blood samples obtained from all animals prior to the terminal sacrifice.

At pretest and gestation day 13 collection intervals, animals were allowed free access to food and water. Diet was removed at the terminal sacrifice. Blood samples were obtained from the orbital sinus. The hematologic and biochemical parameters listed below were determined using the instrument listed in accordance with the reference cited.

Summary of Clinical Pathology Determinations

Hematology Parameters	Sample Type	Instrument Used	Reference
Leukocyte Count	WB	Ortho ELT-8®	4
Erythrocyte Count	WB	Ortho ELT-8®	4
Hemoglobin	WB	Ortho ELT-8®	4
Hematocrit	WB	Ortho ELT-8®	4
MCV, MCH, MCHC	WB	Ortho ELT-8®	4
Platelets	WB	Ortho ELT-8®	4
Differential Leukocyte Count	WB	Light Microscope	5
Biochemistry Parameters:			
Sodium	S	Beckman EAA® Electrolyte Analyzer	6
Potassium	S	Beckman EAA® Electrolyte Analyzer	6
Calcium	S	DACOS® Analyzer	7
Alkaline Phosphatase	S	DACOS® Analyzer	8
Aspartate Amino-transferase (AST)	S	DACOS® Analyzer	9
Alanine Amino-transferase (ALT)	S	DACOS® Analyzer	10
Urea Nitrogen	S	DACOS® Analyzer	11
Creatinine	S	DACOS® Analyzer	12
Total Protein	S	DACOS® Analyzer	13
Albumin	S	DACOS® Analyzer	14
Triglycerides	S	DACOS® Analyzer	15
Cholesterol	S	DACOS® Analyzer	16
Glucose	S	DACOS® Analyzer	17
Iron	S	DACOS® Analyzer	18
Phosphorus	S	DACOS® Analyzer	19

S = Serum; WB = Whole Blood
MCV = Mean corpuscular volume
MCH = Mean corpuscular hemoglobin
MCHC = Mean corpuscular hemoglobin concentration

J. ANATOMIC PATHOLOGY

1. Macroscopic

All animals from the F_0 generation received a complete post-mortem examination under the direct supervision of a pathologist. All survivors and all animals sacrificed *in extremis* were euthanized by carbon dioxide asphyxiation and exsanguinated prior to cessation of the heart beat.

After a thorough external examination, each animal was opened and the contents of the abdominal, thoracic and cranial cavities were examined both *in situ* and after removal and dissection. All macroscopic abnormalities were recorded on the Pathology Record sheet.

Representative samples of protocol designated organs and tissues were collected and placed in phosphate-buffered neutral formalin where appropriate. A full complement of organs and tissues was collected from all animals.

The following organs and tissues were collected and saved for possible future histopathological examination:

- Adrenal (2)
- Aorta (thoracic)
- Brain
- Cecum
- Colon
- Duodenum
- Esophagus
- Eye (2)
- Gross lesions
- Heart
- Ileocecolic lymph node
- Ileum
- Jejunum
- Kidney (2)
- Liver
- Lung with mainstem bronchi (2)*
- Rectum
- Rib, bone marrow (left and right, 5th costochondral junction)
- Sciatic nerve (left)
- Seminal vesicle (2)
- Spleen
- Stomach (cardiac, fundic, pyloric)
- Submandibular lymph node
- Submandibular salivary gland
- Testis with epididymis (2)
- Thoracolumbar spinal cord
- Thymic region
- Thyroid/parathyroid complex
- Tongue
- Trachea

*Lungs were perfused with formalin through the trachea.

- Ovary (2)
- Pancreas
- Pituitary
- Prostate
- Psoas muscle (left)
- Urinary bladder
- Uterus (cross section of each horn)
- Vagina

2. Organ Weights

Protocol designated organs were trimmed free of fat and connective tissue and weighed. Organ weights from all animals from the F_0 generation surviving until Day 13 uterine examination and the scheduled terminal sacrifice as well as all animals that died on study or were sacrificed in extremis were recorded along with post-mortem body weights.

The following organs were weighed:

- Kidney (2)
- Liver

X. DATA RETENTION

Raw data, a sample of the test article and copies of the final report are retained in the Archives of International Research and Development Corporation, 500 N. Main, Mattawan, Michigan 49071. Fetal skeletons, wet tissues, blocks and slides prepared for histopathological examination were sent to the Sponsor following acceptance of the final report.

L. STATISTICAL ANALYSIS

All statistical analyses compared the treatment groups with the control, with the levels of significance at $p<0.05$ and $p<0.01$. Body weight gain, hematology and biochemical results, and organ weights (terminal sacrifice) were compared to determine the significance of differences.

Male and female fertility indices were compared using the Chi-square test criterion with Yates' correction for 2 x 2 contingency tables and/or Fisher's exact probability test as described by Siegel[20] to determine the significance of differences.

The proportions of resorbed and nonviable embryos, postimplantation loss and pup survival indices were compared by the Mann-Whitney U-test as described by Siegel[20] and Weil[21] to determine the significance of differences.

Parental body weights, numbers of corpora lutea, total implantations, viable embryos, live pups per litter at birth and mean pup weights on lactation days 0, 4, 7, 14 and 21 were compared by analysis of variance (one-way classification), Bartlett's test for homogeneity of variance and the appropriate t-test (for equal and unequal variance) as described by Steel and Torrie[22] using Dunnett's[23] multiple comparison tables to determine the significance of differences.

Beatrice A. Thierjung
Manager of Data Processing

5/8/89
Date

191-1395

V. RESULTS

A. GENERAL OBSERVATIONS

1. Survival, Appearance and Behavior (Tables 1 and 2)

Seven animals failed to survive to scheduled sacrifice; one control male, two low-dose (10 mg/kg/day) males, one mid-dose (100 mg/kg/day) male and three high-dose (250 mg/kg/day) males. The control male was found dead on study day 70. No visible abnormalities were noted prior to death. One of the low-dose males was found dead on study day 57. This animal died as a result of gavage error. The other male from this group was found dead on study day 112. Localized abrasion and hair loss were seen during the observation period; however, visible abnormalities were not observed for approximately eight weeks prior to death; the cause of death could not be determined. The mid-dose male was sacrificed in extremis on study day 52. Clinical signs that resulted in sacrifice included emaciation and labored breathing. Other findings noted were reduced motor activity, material around nose and eyes, scabbed area and nasal malalignment. One of the high-dose males died on study day 103. On the day prior to death, the animal was pale, had pale eyes, brown material around the mouth and brown anogenital staining. Rales were noted for 4 days, approximately 3 weeks prior to death. The cause of death could not be determined. One high-dose male was sacrificed in extremis on study day 83. Hair loss was the only abnormality noted prior to the day of sacrifice. On the day of sacrifice, the animal had red material around the nose, soft stool, eyes and skin areas were pale, the animal was cold to touch, had decreased defecation, reduced motor activity, labored breathing, thick red anogenital staining, and was emaciated and moribund. No abnormalities were seen during the six weeks immediately prior to

sacrifice. The remaining high-dose male died on study day 42 due to probable gavage error. None of the deaths in the treated groups was considered treatment-induced.

Most of the clinical signs seen among the treated animals were not thought to be induced by the test article. Four high-dose males had rales at some time during the observation period that may have been related to treatment. Although comparable incidence was not documented for the high-dose females, it should be noted that the males were treated for a longer period than the females.

2. Body Weights (Tables 3-5)

Mean body weight values for the mid- and high-dose males were slightly to significantly less ($p<0.05$ or 0.01) than the corresponding control values from study day 13 (approximately study week 2) through study week 17. Several weight gain values for these groups from study day 7 through 29 were also significantly less ($p<0.05$ or 0.01) than the control values. These reduced values were considered related to the test article. The weight change values from study weeks 9 to 17 were generally comparable with the control values at all dosage levels tested. Some values for the low- and mid-dose groups were significantly different ($p<0.05$ or 0.01) from the control values; however, these differences either did not suggest an adverse effect or there was no relationship to dosage level.

Mean weekly body weight and weight gain values for the females from treated groups did not indicate the presence of a toxicological effect. However, again it should be noted that the females were not dosed for as long as the males.

Maternal body weight changes for the treated groups were not affected by the test article at any dosage level tested during gestation or lactation. Two values for the mid-dose group (gestation days 7 to 13 and lactation day 0) were significantly less

($p<0.05$) than the corresponding control values. These discrepancies were not considered meaningful as similar decreases were not seen at the high-dose level. The lactation day 21 values for the high-dose group was significantly greater ($p<0.05$) than the control group value. This was not attributed to treatment as it was not considered an adverse effect.

3. Food Consumption (Tables 6-8)

Weekly food consumption values for males from the mid- and high-dose groups were less than the control values and indicated a possible adverse effect from treatment initiation to study week 7. However, from study weeks 8 through 17, the values for these groups were generally comparable with the control group values.

Mean weekly food consumption values for the treated females were comparable with the control values at weeks 1 and 2.

Treatment with the test material did not adversely affect maternal food consumption at any dosage level tested. Values for the treated groups calculated as g/animal/day and g/kg/day were comparable with the corresponding control values.

4. Estrous Cycle Observations (Table 9)

The test material did not appear to affect the estrous cycles of the females in the treated groups. Types and incidences of estrous cycle abnormalities seen among the treated groups were not markedly different from those in the control group.

5. Gestation Day 13 Uterine Examination Observations (Table 10)

Developmental toxicity was not evident at any dosage level tested. Mean values for viable embryos and total implantations for the mid- and high-dose groups, and corpora lutea for the high-dose group were reduced when compared with the control values. These discrepancies were not considered induced by treatment as the values were well within the range of the historical control data.

B. REPRODUCTIVE AND LITTER PARAMETERS

1. Reproductive Parameters (Table 11)

Treatment with the test material affected neither mating behavior nor fertility of the males and females in the treated groups. Values for the treated males and females of mating and fertility indices, and mean copulatory interval and gestation length were comparable with those of the control.

2. Offspring Viability (Table 12)

Treatment of the F_0 parental animals did not affect offspring viability at any level tested. Mean numbers of viable and nonviable pups at birth for the treated groups were not markedly different from those of the control. Pup survival indices for all groups were generally comparable with the corresponding control values throughout the lactation period (lactation days 0, 4, 7, 14 and 21). The pup survival index value for the high-dose group on lactation day 4 was significantly less ($p<0.05$) than the control group value. This discrepancy was not considered indicative of a treatment effect as the value (97.5%) was within the range of the historical control (96.8% to 99.5%).

3. Offspring Growth (Table 13)

Treatment of the parental animals adversely affected pup growth at the high-dose level. The mean body weight values for the high-dose group were significantly less ($p<0.05$ or 0.01) than the corresponding control group values at birth and on days 4, 7, 14 and 21 of lactation; these discrepancies were considered treatment related.

Mean pup body weight values for the low- and mid-dose groups were not markedly different from those of the control.

4. Offspring Assessment

Twenty-nine F_1 pups were found dead between lactation days 0 and 19; seven, five, six and eleven in the control, low-, mid- and

high-dose groups, respectively. Most of these pups were found to be morphologically normal, or too autolysed or cannibalized to completely examine. One pup each from the low- and high-dose groups had hydronephrosis. No relevance was attributed to these findings due to low incidence. One pup each from the control and mid-dose groups died as a result of mechanical injuries. These pups had necropsy findings consistent with the types of injuries sustained. Ten pups, two each from the control and mid-dose groups, one from the low-dose group and five from the high-dose group were missing and presumed completely cannibalized.

The most commonly observed clinical sign was small appearance. This finding was noted most frequently at the high-dose level and considered due to significantly reduced body weights for this group. Ten pups from one high-dose litter noted to be small in size were also pale.

The remaining findings seen among pups from treated groups occurred in low incidence and were not thought to be related to treatment. One control and one mid-dose pup each had a black distal tail; the control pup eventually lost this portion of its tail. One mid-dose pup had red material (presumably blood) on one shoulder. Another pup from this group was noted to have a short, bent tail and another was observed to be pale.

C. UTERINE OBSERVATIONS AT LACTATION DAY 21 (Table 14)

No indication of treatment-related adverse effects were noted at uterine observations from the delivered dams. Mean numbers of implantation sites, pups delivered and remaining sites (postimplantation loss and/or complete cannibalization) for the treated groups were comparable with those of the control.

D. HEMATOLOGICAL AND BIOCHEMICAL PARAMETERS

1. Hematology (Tables 15-17)

Several hematology parameter values for the high-dose males were significantly less ($p<0.01$) than the corresponding control values. These included hemoglobin concentration, percent hematocrit, MCV and MCH. For the high-dose females sacrificed at lactation day 21, a decrease of similar magnitude was also noted for the MCV value when compared with the control. These decreases were considered induced by the test article. Significant differences ($p<0.05$) were noted incidentally in males at the low- and mid-dose levels, but were not considered to be toxicologically significant as relationships to dosage levels were generally absent.

The remaining hematological parameters for the males and females did not appear to be adversely affected by the test article.

2. Biochemistry (Table 18)

The biochemical parameter values for the treated females sacrificed at gestation day 13 were not markedly different from those of the control group.

E. ANATOMIC PATHOLOGY

1. Macroscopic

Macroscopic observations are summarized in Table 19. Individual macroscopic observations are presented in Appendix F.

No test article related lesions were observed in F_0 females at the day 13 uterine examination or in F_0 males and females at terminal sacrifice. Additionally, males that died prior to termination of the study showed no significant macroscopic lesions. All lesions observed in all control and test groups were considered spontaneous and incidental.

2. Organ Weights

Mean absolute and mean relative organ weights are summarized in Table 20. Individual organ weights are presented in Appendix E.

Statistically significant decreases in absolute and relative liver weights were observed in males of the 100 mg/kg/day and 250 mg/kg/day groups at terminal sacrifice. Corresponding changes were not seen in females at the day 13 uterine examination or terminal sacrifices. A statistically significant increase in absolute body weight and absolute kidney weight was noted in females of the 250 mg/kg/day group at terminal sacrifice. Males of the corresponding group and females at day 13 uterine examination showed no changes in body or kidney weights. The toxicologic significance of these changes is unclear at this time.

Patrick B. Lappin, D.V.M.
Necropsy Pathologist

5/11/94
Date

Robert G. Geil, D.V.M., A.C.V.P. Diplomate
Scientific Director of Pathology Division

5/4/94
Date

191-1395

VI. **SIGNATURES**

Prepared by: Jacqueline M. Miller 5/5/89
Jacqueline M. Miller, B.S.
Technical Writer
Department of Report Writing
Date

Reviewed by: James L. Schardein 5/8/89
James L. Schardein, M.S., D.A.T.S.
Scientific Director
Reproductive and Developmental
Toxicology Division
Date

191-1395

VII. DISCUSSION AND CONCLUSION

Treatment-related effects were apparent at both the mid- and high-dose levels among the parental males. Rales was present among several high-dose males, and reduced body weight and food intake were noted for both the mid- and high-dose males. Similar indications of toxicity were not seen among the females; however, it should be noted that the males were treated for a longer period of time than were the females. Hematological parameters were adversely affected by treatment for both the males and females at the high-dose level.

No apparent effects were seen with respect to estrous cycling, mating behavior, fertility, embryolethality, or offspring survival and appearance. Treatment of the parental animals at the high-dose level did affect growth of the offspring as evidenced by significantly reduced body weights throughout the lactation period.

In conclusion, the no observable effect level of G0539.03 with respect to general toxicity was 10 mg/kg/day; neonatal growth was not affected at 100 mg/kg/day or less and the no observable effect level with respect to reproductive parameters was 250 mg/kg/day.

To the best of my knowledge, there were no significant deviations from the Good Laboratory Practice Regulations which affected the quality or integrity of the study. This study was conducted in conformance with Good Laboratory Practice Regulations. This report accurately reflects the raw data obtained during the performance of the study.

James L. Schardein, M.S., D.A.T.S.
Scientific Director, Reproductive and
Developmental Toxicology Division
Study Director

5/7/89
Date

191-1395

VIII. REFERENCES

1. Fox, R. R. and Laird, C. W. (1970). Sexual Cycles. In: Reproduction and Breeding Techniques for Laboratory Animals, E. S. E. Hafez, ed., Lea and Febiger, Philadelphia, PA, pp 107-122.

2. Kopf, R., Lorenz, D. and Salewski, E. (1964). The effects of thalidomide on the fertility of rats studied in two generations. Naunyn Schmiedebergs Arch. Pharmacol., 247: 121-135.

3. Staples, R. E. (1974). Detection of visceral alterations in mammalian fetuses. Teratology, 9: A37-A38.

4. Ortho ELT-8 Operator Reference Manual. Ortho Diagnostic Systems, Westwood, MA. 1979.

5. Miale, J. B. (1977). Laboratory Medicine Hematology. The C. V. Mosby Company, St. Louis, MO.

6. Systems E-4A Electrolyte Analyzer Operating Manual. Beckman Instruments, Incorporated, Brea, CA. 1984.

7. Coulter Procedure for Calcium Determination using DART Reagents on the DACOS, Cat. #7546838, Coulter Electronics, Inc., Hialeah, FL. 1984.

8. Coulter Procedure for Alkaline Phosphatase Determination using DART Reagents on the DACOS, Cat. #7546681, Coulter Electronics, Inc., Hialeah, FL. 1983.

9. Coulter Procedure for AST Determination using DART Reagents on the DACOS, Cat. #7546049, Coulter Electronics, Inc., Hialeah, FL. 1984.

10. Coulter Procedure for Alanine Aminotransferase Determination using DART Reagents on the DACOS, Cat. #7546051, Coulter Electronics, Inc., Hialeah, FL. 1984.

11. Coulter Procedure for Blood Urea Nitrogen Determination using DART Reagents on the DACOS, Cat. #7546773, Coulter Electronics, Inc., Hialeah, FL. 1986.

191-1395

12. Coulter Procedure for Creatinine using DART Reagents on the DACOS, Cat. #7546058, Coulter Electronics, Inc., Hialeah, FL. 1986.

13. Coulter Procedure for Total Protein Determination using DART Reagents on the DACOS, Cat. #7546016, Coulter Electronics, Inc., Hialeah, FL. 1984.

14. Coulter Procedure for Albumin Determination using DART Reagents on the DACOS, Cat. #7546056, Coulter Electronics, Inc., Hialeah, FL. 1984.

15. Coulter Procedure for Triglycerides Determination using DART Reagents on the DACOS, Cat. #7546848, Coulter Electronics, Inc., Hialeah, FL. 1987.

16. Coulter Procedure for Cholesterol Determination using DART Reagents on the DACOS, Cat. #7546047, Coulter Electronics, Inc., Hialeah, FL. 1985.

17. Coulter Procedure for Glucose Determination using DART Reagents on the DACOS, Cat. #7546800, Coulter Electronics, Inc., Hialeah, FL. 1987.

18. Sigma Procedure for Iron using Sigma Reagents on the DACOS®, CAT #565, Sigma Chemical Company, St. Louis, MO. 1986.

19. Coulter Procedure of Phosphorus Determination using DART Reagents on the DACOS, Cat. #7546687, Coulter Electronics, Inc., Hialeah, FL. 1984.

20. Siegel, S. (1956). Nonparametric Statistics for the Behavioral Sciences, McGraw-Hill, New York, N.Y.

21. Weil, C. S. (1970). Selection of the valid number of sampling units and a consideration of their combination in toxicological studies involving reproduction, teratogenesis or carcinogenesis. Food Cosmet. Toxicol., 8: 177-182.

22. Steel, R. G. D. and Torrie, J. H., (1960). Principles and Procedures of Statistics, McGraw-Hill, New York, N.Y.

23. Dunnett, C. W. (1964). New tables for multiple comparisons with a control. Biometrics, 20: 482-491.

191-1395

TABLE 1. Summary of Antemortem Observations - Males

	0 mg/kg/day (Control)		10 mg/kg/day		100 mg/kg/day		250 mg/kg/day	
	No.	%	No.	%	No.	%	No.	%
Number of animals observed:	35	-	35	-	35	-	35	-
Antemortem Observations								
No visible abnormalities[a]:	11	(31)	13	(37)	21	(60)	17	(49)
Died/sacrificed in extremis:	1	(3)	2	(6)			3	(9)
Moribund:							1	(3)
Cold to touch:							1	(3)
Paleness:							2	(6)
Reduced motor activity:					1	(3)		
Labored breathing:	1	(3)			1	(3)	1	(3)
Rales:					1	(3)	4	(11)
Eye partially closed:					1	(3)		
Emaciated:					1	(3)	1	(3)
Decreased defecation:							1	(3)
Soft stool:			1	(3)			2	(6)
Protruding eye:			1	(3)				
Nodule:			1	(3)				
Swelling:							2	(6)
Discoloring:			1	(3)				
Hole in palate:	1	(3)					2	(6)
Abrasion:			1	(3)				
Anogenital staining:							2	(6)
Staining:	1	(3)			2	(6)		
Scabbed area:	4	(11)	3	(9)	1	(3)		
Material around eyes:	6	(17)	4	(11)	3	(9)	7	(20)
Material around mouth:							2	(6)
Material around nose:	11	(31)	6	(17)	3	(9)	5	(14)
Nasal malalignment:	2	(6)			1	(3)		
Malocclusion:	7	(20)	2	(6)	3	(9)	7	(20)
Incisor missing:	2	(6)	2	(6)	2	(6)	2	(6)
Hair loss:	11	(31)	10	(29)	5	(14)	4	(11)

[a]Includes animals with no visible abnormalities throughout the observation period
No. - Number
- - Not applicable

191-1995

TABLE 2. Summary of Antemortem Observations - Females

	0 mg/kg/day (Control)		10 mg/kg/day		100 mg/kg/day		250 mg/kg/day	
	No.	%	No.	%	No.	%	No.	%
Number of animals observed:	35	-	35	-	35	-	35	-
Antemortem Observations								
No visible abnormalities[a]:	23	(66)	21	(60)	18	(51)	18	(51)
Pain:							1	(3)
Rales:			1	(3)				
Eye appears small:	1	(3)						
Internal eye white:					2	(6)	1	(3)
Eye discolored:							1	(3)
Ulceration:					1	(3)		
Scabbed area:	1	(3)	3	(9)	2	(6)		
Anogenital staining:					1	(3)	3	(9)
Staining:	3	(9)						
Material around mouth/anogenital region/nose/eye:	4	(11)	1	(3)	1	(3)	2	(6)
Hair loss:	6	(17)	11	(31)	13	(37)	13	(37)
Incisor missing:			1	(3)				
Malocclusion:					1	(3)		

[a]Includes animals with no visible abnormalities throughout the observation period

No. = Number

- = Not applicable

191-1395

TABLE 3. Males: Summary of Body Weight Values

Parameters Measured	DAY OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	10 MG/KG/DAY MEAN	S.D.	N	100 MG/KG/DAY MEAN	S.D.	N	250 MG/KG/DAY MEAN	S.D.	N
Body Weight grams	1	218	11.4	35	214	12.1	35	214	10.7	35	213	11.7	35
	4	244	13.0	35	240	13.9	35	240	13.9	35	239	13.0	35
	7	260	13.3	35	256	14.8	35	258	11.8	35	256	13.8	35
	10	285	17.6	35	279	17.1	35	277	17.3	35	276	15.7	35
	13	304	20.5	35	296	1 .8	35	292[1]	18.3	35	291[1]	18.2	35
	16	327	22.9	35	318	21.4	35	312[2]	21.9	35	310[2]	18.7	35
	19	346	24.4	35	337	23.3	35	330[2]	23.9	35	329[2]	19.2	35
	22	356	27.2	35	348	26.5	35	340[1]	24.2	35	341[1]	20.3	35
	29	396	30.6	35	388	27.2	35	375[2]	28.8	35	370[2]	23.2	35
	36	420	32.7	35	414	29.4	35	398[2]	32.2	35	393[2]	23.7	35
	43	441	37.7	35	437	32.0	35	416[2]	38.1	35	413[2]	27.3	34
	50	459	39.6	35	456	32.6	35	432[2]	46.8	36	429[2]	30.2	34

191-1395

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from the Control group; p<0.05 [2]Significantly different from the Control group; p<0.01

TABLE 3. Cont.

Males: Summary of Body Weight Values

Parameters Measured	DAY OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	10 MG/KG/DAY MEAN	S.D.	N	100 MG/KG/DAY MEAN	S.D.	N	250 MG/KG/DAY MEAN	S.D.	N
Body Weight Change grams	1-4	27	3.6	35	27	3.5	35	27	8.6	35	26	3.7	35
	4-7	15	7.0	35	15	5.4	35	17	8.1	35	16	4.3	35
	7-10	26	8.7	35	23	7.7	35	19[2]	10.2	35	21[1]	6.0	35
	10-13	18	4.3	35	17	3.6	35	15[2]	3.8	35	15[2]	2.6	35
	13-16	24	4.3	35	23	5.4	35	20[2]	5.1	35	18[2]	5.7	35[4]
	16-19	19	3.6	35	19	4.8	35	18	4.8	35	20	4.7	35[4]
	19-22	10	9.9	35	11	7.6	35	10	3.3	35	11	3.9	35
	22-29	40	6.0	35	40	9.0	35	35[2]	7.1	35	29[2]	10.7	35
	29-36	24	4.9	35	26	5.6	35	23	6.7	35	22	7.3	35
	36-43	21	8.6	35	23	7.4	35	18	20.0	35	21	13.2	34
	43-50	19	6.0	35	20	5.3	35	15	12.7	35	17	8.8	34

191-1395

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from the Control group; p<0.05 [2]Significantly different from the Control group; p<0.01

TABLE 3. Cont-

Males: Summary of Body Weight Values

Parameters Measured	WEEK OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	10 MG/KG/DAY MEAN	S.D.	N	100 MG/KG/DAY MEAN	S.D.	N	250 MG/KG/DAY MEAN	S.D.	N
Body Weight grams	9	482	40.8	35	476	36.3	35	454[1]	41.1	34	447[2]	30.2	34
	10	495	43.4	35	491	37.6	34	467[1]	42.8	34	458[2]	36.5	34
	11	501	44.8	34	499	35.9	34	477[1]	43.5	34	469[2]	36.1	34
	12	511	44.3	34	508	39.2	34	487[1]	45.3	34	477[2]	35.9	34
	13	525	46.1	34	522	40.4	34	498[1]	45.9	34	489[2]	39.2	34
	14	535	51.8	34	536	44.0	34	511	46.7	34	502[1]	40.0	33
	15	544	55.3	34	547	44.2	34	520	48.0	34	511[1]	42.7	33
	16	555	55.2	34	555	45.8	34	529	49.8	34	522[1]	43.9	32
	17	526	56.9	34	540	45.1	33	514	49.9	34	494[2]	43.1	32

191-1395

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from the Control group; p<0.05

[2]Significantly different from the Control group; p<0.01

TABLE 3. Cont.

Males: Summary of Body Weight Values

Parameters Measured	WEEK OF STUDY	0 MG/KG/DAY (CONTROL)			10 MG/KG/DAY			100 MG/KG/DAY			250 MG/KG/DAY		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Body Weight Change grams	9-10	13	17.9	35	15	5.8	34	13	6.1	34	12	16.3	34
	10-11	5	7.4	34	8	6.0	34	10[2]	7.3	34	11	16.4	34
	11-12	10	8.2	34	10	6.7	34	10	4.8	34	8	9.4	34
	12-13	14	6.0	34	14	9.8	34	11[1]	5.9	34	13	9.1	33
	13-14	9	11.4	34	13	8.9	34	12	7.7	34	13	18.1	33
	14-15	10	9.6	34	11	4.9	34	9	6.6	34	9	8.4	33
	15-16	11	5.7	34	9[1]	5.6	34	10	5.2	34	9	10.9	32
	16-17	-30	18.5	34	-14[2]	5.9	33	-15[2]	4.9	34	-28	6.1	32

191-1395

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from the Control group; $p<0.05$

[2]Significantly different from the Control group; $p<0.01$

TABLE 4. Females: Summary of Body Weight Values

Parameters Measured	WEEK OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	10 MG/KG/DAY MEAN	S.D.	N	100 MG/KG/DAY MEAN	S.D.	N	250 MG/KG/DAY MEAN	S.D.	N
Body Weight grams	0	260	11.4	35	260	14.7	35	259	11.8	35	260	15.2	35
	1	269	12.8	35	269	16.7	35	268	12.5	35	267	18.1	35
	2	280	16.2	35	280	17.7	35	279	14.4	35	278	19.0	35
	3	320	24.0	2	310	18.4	2	297	-	1	327	-	1
	4	352	33.9	2	322	4.9	2	325	-	1	346	-	1
	5	429	44.5	2	383	-	1	403	-	1			

191-1395

S.D. - Standard Deviation
N - Number of Animals
- - Not applicable

Values of the treated groups were not significantly different from those of the control; p>0.05

TABLE 4. Cont.

Females: Summary of Body Weight Values

Parameters Measured	WEEK OF STUDY	0 MG/KG/DAY (CONTROL)			10 MG/KG/DAY			100 MG/KG/DAY			250 MG/KG/DAY		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Body Weight Change grams	0-1	10	7.8	35	9	7.4	35	9	7.9	35	7	7.7	35
	1-2	10	9.0	35	11	6.1	35	11	7.6	35	11	6.1	35
	2-3	37	2.8	2	35	0.7	2	25	-	1	20	-	1
	3-4	24	9.9	2	12	13.4	2	28	-	1	19	-	1
	4-5	77	10.6	2	65	-	1	70	-	1			

191-1395

S.D. - Standard Deviation
N - Number of Animals
- - Not applicable

Values of the treated groups were not significantly different from those of the control; p>0.05

TABLE 5. Summary of Maternal Body Weights and Body Weight Changes During Gestation and Lactation - F_0 Does

Day of Gestation	Group Mean Maternal Body Weights (grams)							
	0 mg/kg/day (Control)		10 mg/kg/day		100 mg/kg/day		250 mg/kg/day	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
0	280	15.2	283	20.0	279	19.1	279	17.2
7	315	13.1	316	21.3	310	16.1	315	20.9
13	347	15.0	345	24.7	337	18.2	346	21.3
20	420	24.6	428	34.8	412	21.1	427	26.1
Day of Lactation								
0	330	17.2	335	27.9	320*	14.5	340	18.9
7	353	17.0	366	24.7	348	18.4	356	21.4
14	365	15.5	373	24.7	362	17.7	380	23.4
21	303	18.4	306	18.8	304	15.0	318*	18.8
Days of Gestation	Group Mean Maternal Body Weight Changes (grams)[a]							
0 to 7	35	10.3	33	7.1	31	7.7	35	9.8
7 to 13	32	6.3	29	7.2	27*	9.4	31	7.3
13 to 20	75	17.4	79	14.4	76	15.6	79	12.5
0 to 20	140	24.0	142	20.2	136	17.1	145	17.1
Days of Lactation								
0 to 7	22	11.5	31	13.6	28	18.0	25	12.2
7 to 14	12	15.9	7	18.2	19	24.9	14	13.4
14 to 21	-62	16.4	-67	13.1	-63	18.8	-62	16.2
0 to 21	-27	17.8	-29	15.0	-16	14.1	-23	17.5

[a]Values represent the mean of the individual changes in maternal body weight for these intervals

S.D. - Standard deviation

*Significantly different from the control group; $p<0.05$

191-1395

TABLE 6. Males: Summary of Food Consumption Values

Parameters Measured	WEEK OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	10 MG/KG/DAY MEAN	S.D.	N	100 MG/KG/DAY MEAN	S.D.	N	250 MG/KG/DAY MEAN	S.D.	N
Food Consumption g/animal/day	1	19.9	2.03	35	19.0	2.06	34	15.8	2.59	35	16.6	1.63	34
	2	25.1	2.30	35	23.7	2.39	35	23.5	3.82	35	24.2	2.20	35
	3	26.3	13.70	35	23.5	2.24	35	23.3	2.63	35	23.7	3.04	35
	4	25.5	4.31	35	24.5	2.56	35	22.4	3.04	35	24.6	2.28	35
	5	27.2	2.88	35	26.3	2.61	35	24.1	2.97	35	25.0	1.17	35
	6	29.1	17.34	35	25.9	3.06	35	22.3	2.65	35	25.7	2.38	35
	7	25.9	3.39	35	24.9	3.12	35	24.7	5.04	34	23.3	4.25	34
	8	27.5	5.22	35	27.0	6.27	35	27.6	10.66	34	26.1	3.07	34
	9	25.4	4.17	35	25.2	3.12	34	23.4	3.79	34	24.0	5.30	33
	10	31.3	4.13	35	31.2	2.66	34	31.4	11.00	34	30.5	5.31	34
	13	27.4	3.53	34	29.9	10.92	34	29.1	6.94	34	28.9	4.92	33
	14	26.6	4.53	34	25.7	2.41	34	25.9	3.60	34	29.5	16.43	33
	15	25.3	4.71	34	25.4	2.58	34	25.1	3.32	34	26.2	4.03	33
	16	29.3	16.85	34	23.6	6.82	34	26.2	13.03	34	23.6	8.55	32
	17	28.5	6.06	34	24.1	5.47	33	27.6	4.06	34	31.4	13.17	31

191-1395

S.D. - Standard Deviation
N - Number of Animals

TABLE 7. Females: Summary of Food Consumption Values

Parameters Measured	WEEK OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	10 MG/KG/DAY MEAN	S.D.	N	100 MG/KG/DAY MEAN	S.D.	N	250 MG/KG/DAY MEAN	S.D.	N
Food Consumption g/day	1	14.6	3.60	35	17.8	3.10	35	13.8	4.10	35	14.6	3.01	35
	2	15.8	3.62	35	17.5	3.07	35	16.0	4.08	35	17.2	2.95	35
	6	26.0	1.41	2	18.0	-	1	21.0	-	1			

191-3385

S.D. - Standard Deviation
N - Number of Animals

TABLE 8. Summary of Maternal Food Consumption Values - F_0 Dams

Gestation Days	0 mg/kg/day (Control) Mean	S.D.	N	10 mg/kg/day Mean	S.D.	N	100 mg/kg/day Mean	S.D.	N	250 mg/kg/day Mean	S.D.	N
	g/animal/day											
0 - 7	21.9	1.89	28	21.7	2.01	29	22.2	2.18	28	22.8	2.41	31
7 - 13	24.5	2.38	28	24.4	2.70	29	24.1	2.02	28	25.7	2.09	30
13 - 20	24.8	2.85	19	25.8	1.86	20	25.2	2.34	20	27.2	1.91	20
0 - 20	23.6	1.43	28	23.6	2.16	29	23.7	1.58	28	24.8	2.00	31
Lactation Days												
0 - 7	37.4	7.00	22	43.4	3.91	21	43.0	6.81	18	43.5	6.12	23
7 - 14	60.5	7.27	20	65.1	8.97	21	64.5	15.00	18	67.0	13.91	22
14 - 20	82.6	11.22	21	85.4	9.08	21	80.6	15.65	21	84.1	14.88	22
0 - 20	58.6	7.17	22	63.6	4.86	21	63.6	12.39	21	63.6	10.40	23
	g/kg/day											
0 - 7	69.5	4.79	28	68.9	3.65	29	71.4	5.47	28	87.8	86.15	31
7 - 13	70.6	6.20	28	70.5	4.13	29	71.7	5.00	28	74.6	3.19	30
13 - 20	59.2	7.64	19	60.5	4.05	20	61.2	5.32	20	63.7	3.27	20
0 - 20	56.3	4.47	20	56.6	2.41	20	57.2	3.04	20	59.0	2.83	22
Lactation Days												
0 - 7	105.7	18.35	22	118.9	11.48	21	122.5	19.65	18	119.0	19.42	23
7 - 14	165.8	17.46	20	134.4	20.16	21	179.6	32.93	18	179.4	35.69	22
14 - 20	271.8	30.11	21	279.5	27.14	21	266.2	51.19	21	266.4	47.20	22
0 - 20	193.8	21.98	22	208.2	14.93	21	209.6	40.12	21	200.6	52.99	23

S.D. = Standard deviation
N = Number of animals

191-1399

TABLE 9. Summary of Estrous Cycle Abnormalities

Study Period Estrous Abnormality	0 mg/kg/day (Control) No.	(%)	10 mg/kg/day No.	(%)	100 mg/kg/day No.	(%)	250 mg/kg/day No.	(%)
	Number and Percentage[a] of Animals with Abnormalities							
Untreated Premating								
Long Diestrus	2	(5.7)	1	(2.9)	1	(2.9)	3	(8.6)
Short Diestrus	20	(57.1)	12	(34.3)	11	(31.4)	15	(42.9)
Long Estrus	34	(97.1)	29	(82.9)	33	(94.3)	32	(91.4)
Irregular Cycle	1	(2.9)	1	(2.9)	3	(8.6)	1	(2.9)
Treated Premating								
Long Diestrus	13	(37.1)	22	(62.9)	22	(62.9)	18	(51.4)
Short Diestrus	19	(54.3)	14	(40.0)	13	(37.1)	16	(45.7)
Long Estrus	31	(88.6)	31	(88.6)	27	(77.1)	31	(88.6)
Treated Mating								
Long Diestrus	9	(25.7)	6	(17.1)	7	(20)	4	(11.4)
Short Diestrus			1	(2.9)			1	(2.9)
Long Estrus	1	(2.9)	1	(2.9)				

[a]Based on 35 animals per group

Long diestrus - Diestrus occurring for more than 3 consecutive days
Short diestrus - Diestrus occurring for less than 2 consecutive days
Long estrus - Estrus occurring for 2 or more consecutive days

191-1395

TABLE 10. Summary of Maternal and Embryonic Observations at 13-Day Uterine Examination - F_0 Dams

	0 mg/kg/day (Control)			30 mg/kg/day			100 mg/kg/day			350 mg/kg/day		
	No.	%	S.D.	No.	%	S.D.	No.	%	S.D.	No.	%	S.D.
Animals examined at uterine examination:	10	-	-	10	-	-	10	-	-	10	-	-
Nongravid:	2	-	-	1	-	-	2	-	-	2	-	-
Gravid:	8	-	-	9	-	-	8	-	-	8	-	-
Dams with resorptions only:	0	-	-	0	-	-	1	-	-	0	-	-
Dams with viable fetuses:	8	-	-	9	-	-	7	-	-	8	-	-
Viable embryos/dam:	16.0	-	3.16	16.2	-	1.30	14.3	-	5.90	14.4	-	4.21
Postimplantation loss/dam:	0.6	-	0.74	0.9	-	1.36	0.9	-	1.13	0.6	-	1.06
Total implantations/dam:	16.6	-	3.34	17.1	-	1.05	15.1	-	5.14	15.0	-	3.34
Corpora lutea/dam:	18.8	-	2.96	17.9	-	1.27	18.1	-	2.61	16.8	-	2.12
Group mean preimplantation loss (%)[a]:	-	11.5	-	-	4.3	-	-	7.1[c]	-	-	10.6	-
Group mean postimplantation loss (%)[b]:	-	3.8	-	-	5.2	-	-	5.8	-	-	4.2	-

391-1399

[a]Total No. Corpora Lutea - Total No. Implantations / Total No. Corpora Lutea x 100

[b]Total No. Implantations - Total No. Viable Fetuses / Total No. Implantations x 100

[c]Does not include dam with regressing corpora lutea

Values of the treated groups were not significantly different from those of the control; $p<0.05$

- - Not applicable

S.D. - Standard deviation

No. - Number

TABLE 11. Summary of Reproductive Parameters - F_0 Parents

Dosage Level (mg/kg/day)	Female Mating Index[a] No. of Females Mated / Total Number of Females Paired		Female[a] Fertility Index Gravid Females / Total Females Paired		Male Mating Index Mated Males / Total Males Paired		Male Fertility Index Fertile Males / Total Males Paired		Copulatory Interval (days) Mean	S.D.	Gestation Length (days) Mean	S.D.
		%		%		%		%				
0 (Control):	35/35	100	30/35	85.7	35/35	100	30/35	85.7	2.7	1.57	22.3	0.44
10:	35/35	100	30/35	85.7	33/34	97.1	30/34	88.2	3.0	2.65	22.4	0.49
100:	35/35	100	29/35	82.9	34/34	100	29/34	85.3	2.1	1.17	22.1	0.31
250:	35/35	100	31/35	88.6	34/34	100	30/34	88.2	2.4	1.44	22.2	0.50

[a]Includes animals scheduled for gestation day 13 uterine examination as well as those allowed to deliver
[b]Mated is defined as having had evidence of copulation either by presence of sperm, copulatory plug or delivery of a litter
Values of the treated groups were not significantly different from those of the control; $p>0.05$
S.D. - Standard deviation
No. - Number

191-1395

TABLE 12. Summary of Offspring Viability - F_1 Offspring

Dosage Level (mg/kg/day)	No. Live Pups at Lactation Day 0 Mean	S.D.	No. Dead Pups at Lactation Day 0 Mean	S.D.	Pup Survival Index (Lactation Days) 0: No. Live Pups at Day 0 Total Born	%	4: No. Live Pups at Day 4 BR / No. Live Pups at Day 0	%	7: No. Live Pups at Day 7 / No. Live Pups at Day 4 AR	%	14: No. Live Pups at Day 14 / No. Live Pups at Day 7	%	21: No. Live Pups at Day 21 / No. Live Pups at Day 14	
0 (Control):	13.9	3.04	0.3	0.77	306/312	98.1	305/306	99.7	213/213	100	213/213	100	211/213	99.1
10:	14.4	3.09	0.1	0.30	302/304	99.3	299/302	99.0	205/205	100	205/205	100	205/205	100
100:	13.6	3.23	0.2	0.54	286/291	98.3	284/286	99.3	201/201	100	200/201	99.5	200/200	100
250:	14.0	3.23	0.2	0.74	320/325	98.5	312/320*	97.5	221/222	99.5	221/221	100	221/221	100

BR - Before reduction
AR - After reduction
S.D. - Standard deviation
No. - Number
*Significantly different from the control group: $p<0.05$

191-1395

TABLE 13. Summary of Offspring Growth Data - F_1 Offspring

Dosage Level (mg/kg/day)	Group Mean Body Weight (grams) of Live Pups During Lactation (Lactation Days)													
	0		4BR		4AR		7		14		21			
											Male		Female	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
0 (Control):	6.9	0.53	11.5	1.23	11.5	1.24	17.9	1.71	35.1	2.77	59.7	4.47	56.0	4.13
10:	6.7	0.63	11.5	1.64	11.5	1.67	18.2	2.47	36.4	3.52	60.3	5.78	56.9	4.96
100:	6.6	0.51	10.5	1.18	10.6	1.23	16.8	2.23	34.3	2.08	57.5	3.94	53.9	3.70
250:	6.3*	0.69	10.3*	1.52	10.4*	1.53	16.5*	2.18	32.2*	4.41	53.6**	6.45	50.4**	6.75

BR - Before reduction
AR - After reduction
S.D. - Standard deviation
*Significantly different from the control group; $p<0.05$
**Significantly different from the control group; $p<0.01$

191-1399

TABLE 14. Summary of Uterine Observations on Lactation Day 21 - F_0 Dams

Dosage Level (mg/kg/day)	Number of Implantation Sites		Number of Pups Delivered		Number of Remaining Sites*	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
0 (Control):	15.5	3.07	14.2	2.99	1.3	1.39
10:	15.5	2.75	14.5	3.17	1.0	1.22
100:	15.1	3.45	13.9	3.32	1.2	1.26
250:	15.6	3.53	14.2	3.25	1.3	1.23

*Implantation sites not corresponding to delivered pups; values represent postimplantation loss and/or complete cannibalization.

S.D. - Standard deviation

191-1395

TABLE 19. Males: Summary of Hematological Values

Parameters Measured	DAY OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	10 MG/KG/DAY MEAN	S.D.	N	100 MG/KG/DAY MEAN	S.D.	N	250 MG/KG/DAY MEAN	S.D.	N
Leukocytes $\times 10^3$/cmm	Pretest	11.8	2.29	35	11.7	1.90	35	11.3	2.16	36	11.7	2.38	35
	Terminal	12.0	3.17	34	12.4	2.51	33	10.9	3.33	34	11.6	2.94	32
Erythrocytes $\times 10^6$/cmm	Pretest	5.26	0.279	35	5.21	0.223	35	5.34	0.291	35	5.33	0.286	35
	Terminal	7.49	0.391	34	7.34	0.403	33	7.40	0.625	34	7.39	0.524	32
Hemoglobin g/dl	Pretest	12.8	0.56	36	12.7	0.56	35	12.8	0.61	35	12.9	0.58	35
	Terminal	15.5	0.80	34	15.3	1.08	33	15.6	0.78	34	14.7[2]	1.28	32
Hematocrit %	Pretest	39.5	1.75	35	39.1	1.54	35	39.8	1.84	35	39.9	1.90	35
	Terminal	50.4	7.26	34	49.1[1]	2.99	33	49.0	4.33	34	47.6[2]	3.33	32

IRI-1395

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from the Control group; $p<0.05$ [2]Significantly different from the Control group; $p<0.01$

TABLE 15. Cont.

Males: Summary of Hematological Values

Parameters Measured	DAY OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	10 MG/KG/DAY MEAN	S.D.	N	100 MG/KG/DAY MEAN	S.D.	N	250 MG/KG/DAY MEAN	S.D.	N
MCV	Pretest	75	1.7	35	75	1.6	35	75	1.3	35	75	1.5	35
microns[3]	Terminal	67	1.9	34	67	1.9	33	66	2.1	34	65[2]	2.4	32
MCH	Pretest	24.3	0.87	35	24.3	0.84	35	24.1	0.63	35	24.2	0.78	35
pg	Terminal	20.7	0.91	34	20.9	0.95	33	21.2	1.91	34	19.8[2]	1.00	32
MCHC	Pretest	32.3	0.54	35	32.3	0.61	35	32.2	0.45	35	32.3	0.50	35
g/dl	Terminal	30.7	0.92	34	31.2	1.12	33	32.0[1]	2.85	34	30.8	1.26	32
Platelets	Pretest	576	107.5	35	582	101.9	35	576	75.9	35	579	130.4	35
$\times 10^3$/cmm	Terminal	585	57.4	34	585	67.0	33	636	274.0	34	607	84.0	32

191-1395

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from the Control group; $p<0.05$

[2]Significantly different from the Control group; $p<0.01$

TABLE 15. Cont.

Males: Summary of Hematological Values*

Parameters Measured	DAY OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	30 MG/KG/DAY MEAN	S.D.	N	100 MG/KG/DAY MEAN	S.D.	N	200 MG/KG/DAY MEAN	S.D.	N
Segmented Neutrophils $x10^3$/cmm	Pretest	2.6	0.89	35	2.6	0.78	35	2.4	0.76	35	2.6	0.86	35
	Terminal	3.2	1.92	34	3.6	2.18	33	3.0	2.09	34	3.1	1.84	30
Lymphocytes $x10^3$/cmm	Pretest	8.4	1.94	35	8.2	1.63	35	8.2	1.91	35	8.3	1.66	35
	Terminal	8.5	2.32	34	8.5	2.10	33	7.6	1.99	34	8.3	1.85	32

191-1395

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

TABLE 16. Females; Summary of Hematological Values*

Parameters Measured	DAY OF STUDY	0 MG/KG/DAY (CONTROL)			10 MG/KG/DAY			100 MG/KG/DAY			250 MG/KG/DAY		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Leukocytes	Pretest	11.5	2.99	25	11.4	2.70	25	12.0	2.64	25	11.6	2.49	25
$\times 10^3$/cmm	Terminal	9.3	3.54	22	9.0	3.81	21	10.1	3.08	21	8.5	3.16	23
Erythrocytes	Pretest	6.44	0.334	25	6.38	0.315	25	6.49	0.332	25	6.38	0.331	25
$\times 10^6$/cmm	Terminal	6.73	0.286	22	6.82	0.195	21	6.87	0.369	21	6.94	0.449	23
Hemoglobin	Pretest	15.0	0.67	25	14.9	0.67	25	15.2	0.77	25	14.8	0.82	25
g/dl	Terminal	15.9	0.83	22	16.1	0.66	21	16.3	0.77	21	16.1	0.81	21
Hematocrit	Pretest	47.5	2.30	25	46.8	1.88	25	48.1	2.62	25	47.0	2.44	25
%	Terminal	48.6	1.94	22	49.1	1.54	21	49.3	2.31	21	49.3	2.93	23

191 1395

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

TABLE 16. Cont.

Females: Summary of Hematological Values

Parameters Measured	Day of Study	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	10 MG/KG/DAY MEAN	S.D.	N	100 MG/KG/DAY MEAN	S.D.	N	250 MG/KG/DAY MEAN	S.D.	N
MCV	Pretest	74	1.6	25	73	1.5	25	74	2.2	25	74	1.6	25
microns[3]	Terminal	72	1.6	22	72	1.1	21	72	1.1	21	71[2]	1.3	23
MCH	Pretest	23.3	0.83	25	23.4	0.91	25	23.4	0.79	25	23.2	1.19	25
pg	Terminal	23.7	1.09	22	23.6	0.84	21	23.8	1.02	21	23.3	0.80	23
MCHC	Pretest	31.5	1.00	25	31.9	0.98	25	31.5	0.97	25	31.4	1.21	25
g/dl	Terminal	32.8	0.86	22	32.7	0.89	21	33.2	1.12	21	32.7	0.83	23
Platelets	Pretest	595	96.1	25	609	61.4	25	619	84.6	25	596	96.6	25
$\times 10^3$/cmm	Terminal	714	91.8	22	659	144.2	21	756	227.7	21	714	190.5	23

191-1385

S.D. - Standard Deviation
N - Number of Animals

[2]Significantly different from the Control group; $p<0.01$

TABLE 1a. Cont.

Females: Summary of Hematological Values*

Parameters Measured	DAY OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	10 MG/KG/DAY MEAN	S.D.	N	100 MG/KG/DAY MEAN	S.D.	N	250 MG/KG/DAY MEAN	S.D.	N
Segmented Neutrophils $\times 10^3$/cmm	Pretest	2.1	0.89	25	1.8	0.99	25	2.2	0.98	25	2.4	1.56	25
	Terminal	2.9	1.97	22	2.8	1.82	21	3.6	2.06	21	2.5	1.62	23
Lymphocytes $\times 10^3$/cmm	Pretest	9.2	2.66	25	9.5	2.21	25	9.6	2.00	25	8.8	2.29	25
	Terminal	6.1	2.56	22	6.0	2.26	21	6.2	1.89	21	5.7	1.78	23

191-1395

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

TABLE 17. Females: Summary of Hematological Values* - Animals scheduled for 13 day Uterine Examination

Parameters Measured	DAY OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	10 MG/KG/DAY MEAN	S.D.	N	100 MG/KG/DAY MEAN	S.D.	N	250 MG/KG/DAY MEAN	S.D.	N
Leukocytes	Pretest	11.9	2.66	10	12.1	2.05	10	12.2	4.55	10	11.0	2.66	10
$\times 10^3$/cmm	Terminal	12.0	3.38	10	14.3	2.21	9	11.9	2.99	10	12.2	2.56	10
Erythrocytes	Pretest	6.38	0.315	10	6.52	.338	10	6.48	0.363	10	6.32	0.145	10
$\times 10^6$/cmm	Terminal	6.12	0.424	10	6.15	0.323	9	6.26	0.401	10	6.16	0.509	10
Hemoglobin	Pretest	14.6	0.82	10	14.9	0.64	10	14.0	0.91	10	14.9	0.39	10
g/dl	Terminal	14.0	1.10	10	14.2	0.74	9	14.1	0.84	10	14.0	1.19	10
Hematocrit	Pretest	46.5	2.37	10	47.6	2.02	10	47.4	2.78	10	46.5	0.66	10
%	Terminal	43.2	3.05	10	43.4	2.13	9	43.9	2.63	10	43.3	3.53	10

191-1395

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

TABLE 17. Cont.

Females: Summary of Hematological Values* - Animals scheduled for 13 day Uterine examination

Parameters Measured	DAY OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	10 MG/KG/DAY MEAN	S.D.	N	100 MG/KG/DAY MEAN	S.D.	N	250 MG/KG/DAY MEAN	S.D.	N
MCV	Pretest	73	1.8	10	73	1.5	10	73	1.4	10	74	1.9	10
microns^3	Terminal	71	0.8	10	70	0.7	9	70	0.9	10	70	0.8	10
MCH	Pretest	22.9	0.76	10	22.9	0.92	10	22.8	0.57	10	23.6	0.61	10
pg	Terminal	22.8	0.61	10	23.1	0.63	9	22.6	0.44	10	22.7	0.55	10
MCHC	Pretest	31.4	0.93	10	31.3	1.13	10	31.2	0.47	10	32.0	0.87	10
g/dl	Terminal	32.4	0.73	10	32.7	0.85	9	32.2	0.40	10	32.3	0.90	10
Platelets	Pretest	562	56.3	10	608	134.2	10	625	79.7	10	638	199.1	10
x10^3/cmm	Terminal	672	113.9	10	717	171.2	9	807	159.1	10	692	93.1	10

191-1395

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

TABLE 17, Cont.

Females: Summary of Hematological Values - Animals scheduled for 13 day Uterine examination

Parameters Measured	DAY OF STUDY	0 MG/KG/DAY (CONTROL)			10 MG/KG/DAY			100 MG/KG/DAY			250 MG/KG/DAY		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Segmented Neutrophils $\times 10^3$/cmm	Pretest	2.2	1.85	10	2.5	0.88	10	2.9	2.23	10	1.8	0.90	10
	Terminal	2.7	0.93	10	4.0[1]	1.09	9	3.3	1.10	10	3.2	0.83	10
Lymphocytes $\times 10^3$/cmm	Pretest	9.5	2.14	10	9.5	1.54	10	9.0	2.73	10	9.0	2.40	10
	Terminal	8.5	2.97	10	9.6	1.84	9	8.2	2.17	10	8.2	2.40	10

191-1385

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from the Control group; $p<0.05$

TABLE 16. Females: Summary of Biochemical Values* - Animals scheduled for 13 day Uterine examination

Parameters Measured	DAY OF STUDY	0 MG/KG/DAY (CONTROL)			10 MG/KG/DAY			100 MG/KG/DAY			750 MG/KG/DAY		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Phosphorus mg/dl	Terminal	7.7	0.76	10	8.5	0.84	10	7.7	0.43	10	7.7	0.75	10
Calcium mg/dl	Terminal	13.3	1.50	10	13.1	.36	10	13.0	0.39	10	13.1	0.79	10
Sodium mEq/l	Terminal	140	6.9	10	140	3.1	10	140	3.6	10	141	5.1	10
Potassium mEq/l	Terminal	5.8	0.80	10	6.1	0.33	10	5.7	0.49	10	6.0	0.63	10

191-1305

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

TABLE 18. Cont. Females: Summary of Biochemical Values* - Animals scheduled for 13 day Uterine examination

Parameters Measured	DAY OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	10 MG/KG/DAY MEAN	S.D.	N	100 MG/KG/DAY MEAN	S.D.	N	250 MG/KG/DAY MEAN	S.D.	N
Alkaline Phosphatase IU/l	Terminal	239	75.7	10	247	111.1	10	209	56.0	10	202	73.7	10
Aspartate Aminotransferase IU/l	Terminal	100	13.2	10	101	24.2	10	94	14.0	10	84	9.9	10
Alanine Aminotransferase IU/l	Terminal	56	14.0	10	66	24.0	10	58	15.1	10	55	14.3	10
Triglycerides mg/dl	Terminal	57	15.0	10	82	23.2	10	66	20.4	10	77	20.4	10

191-1395

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

TABLE 16. Cont.

Females: Summary of Biochemical Values* - Animals scheduled for 13 day Uterine examination

Parameters Measured	DAY OF STUDY	0 MG/KG/DAY (CONTROL)			10 MG/KG/DAY			100 MG/KG/DAY			250 MG/KG/DAY		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Urea Nitrogen mg/dl	Terminal	15.2	2.10	10	14.7	2.36	10	16.5	2.42	10	17.8	3.36	10
Creatinine mg/dl	Terminal	0.7	0.09	10	0.7	0.09	10	0.7	0.07	10	0.7	0.16	10
Cholesterol mg/dl	Terminal	52	11.9	10	57	9.0	10	69	17.6	10	57	9.6	10
Glucose mg/dl	Terminal	110	16.5	10	111	13.4	10	115	18.3	10	124	19.6	10
Iron ug/dl	Terminal	286	138.1	10	255	122.2	10	166	68.4	10	181	58.0	10

191-1395

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

TABLE 18. Cont. Females; Summary of Biochemical Values* - Animals scheduled for 13 day Uterine examination

Parameters Measured	DAY OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	10 MG/KG/DAY MEAN	S.D.	N	300 MG/KG/DAY MEAN	S.D.	N	250 MG/KG/DAY MEAN	S.D.	N
Total Protein g/dl	Terminal	6.9	0.33	10	6.9	0.74	10	6.6	0.31	10	6.8	0.71	10
Albumin g/dl	Terminal	3.0	0.20	10	3.0	0.08	10	2.9	0.30	10	3.0	0.32	10

191-1395

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

TABLE 19.

INCIDENCE OF MACROSCOPIC OBSERVATIONS
Deaths and Unscheduled Sacrifices, 0 to Termination
Terminal Sacrifice, F_0 Males

SITE - Observation	0 mg/kg/day (Control) DOS	0 mg/kg/day (Control) TS	10 mg/kg/day DOS	10 mg/kg/day TS	100 mg/kg/day DOS	100 mg/kg/day TS	250 mg/kg/day DOS	250 mg/kg/day TS
NUMBER OF ANIMALS EXAMINED	1	34	2	33	1	34	3	32
NUMBER WITHIN NORMAL LIMITS	0	27	0	28	0	30	1	21
CAVITY, ABDOMINAL								
- Fluid, clear, moderate	1							
EPIDIDYMIS								
- Abscess, moderate				1				
EYE								
- Cornea, cloudy, mild		1				1		
KIDNEY								
- Hydronephrosis, mild	1	1				1		2
- Small, severe				1				
LIVER								
- Pale, mild							1	
LUNG								
- Dark red area, moderate								1
- Fibrin, fluid-filled, moderate			1					
- Focus/foci, red, mild		1	1					
- Hemorrhage, ecchymotic, severe							1	
LYMPH NODE, MANDIBULAR								
- Enlarged, mild								1
ORAL TISSUES								
- Malalignment/malocclusion		1			1			1
- Teeth broken/missing, no grade		3		2		1		4

DOS - Deaths and unscheduled sacrifices
TS - Terminal sacrifice

191-1399

TABLE 19. Cont.

INCIDENCE OF MACROSCOPIC OBSERVATIONS
Deaths and Unscheduled Sacrifices, 0 to Termination
Terminal Sacrifice, F_0 Males

SITE - Observation		0 mg/kg/day (Control) DOS	0 mg/kg/day (Control) TS	10 mg/kg/day DOS	10 mg/kg/day TS	100 mg/kg/day DOS	100 mg/kg/day TS	250 mg/kg/day DOS	250 mg/kg/day TS
SKIN									
- Nodule					1				
- Scabbed, mild			1						
SKIN, TAIL									
- Black, moderate					1				
SOFT TISSUE, LEG									
- Swollen, mild					1				
STOMACH									
- Foci, red, trace									1
STOMACH, GLANDULAR									
- Erosions, mild						1			
- Focus/foci, red/dark red, mild								1	1
STOMACH, NONGLANDULAR									
- Erosions, mild						1			
TRACHEA									
- Fluid, frothy.	- moderate			1					
	- severe							1	
THYMUS									
- Enlarged, moderate									1
- Focus/foci, red/dark red, mild									2
URINARY BLADDER									
- Dark red, severe							1		
- Distended with blood colored urine, moderate							1		
- Filled with red fluid		1							

DOS - Deaths and unscheduled sacrifices
TS - Terminal sacrifice

191-1395

TABLE 19. Cont.

INCIDENCE OF MACROSCOPIC OBSERVATIONS
Deaths and Unscheduled Sacrifices, 0 to Termination
Terminal Sacrifice, F_0 Females

SITE - Observation		0 mg/kg/day (Control)	10 mg/kg/day	100 mg/kg/day	250 mg/kg/day
NUMBER OF ANIMALS EXAMINED		25	25	25	25
NUMBER WITHIN NORMAL LIMITS		17	17	17	14
EYE					
- Cornea, cloudy, severe					1
- Lens opacity, severe				1	
KIDNEY					
- Mottled, mild					1
LIVER					
- Adhesions, mild					1
- Focus/foci, tan/white, mild		2			1
- Foci, red, mild					1
LUNG					
- Congestion, moderate					1
- Focus/foci, red, mild		4	1	2	2
LYMPH NODE					
- Iliac, enlarged, mild				1	
SKIN					
- Hair thinned,	- mild				1
	- moderate			1	
STOMACH, GLANDULAR					
- Erosions,	- mild	4	2	1	1
	- moderate		4		
- Focus/foci, red/black	- mild	2	1	1	
	- moderate				1
- Thickened, mucosa,	- mild			1	
	- moderate		1		1
- Ulcer, mild				1	2
UTERUS					
- Cyst, mild					1

191-1395

TABLE 19. Cont.

INCIDENCE OF MACROSCOPIC OBSERVATIONS
13 Day Uterine Examination, Females

SITE - Observation	0 mg/kg/day (Control)	10 mg/kg/day	100 mg/kg/day	250 mg/kg/day
NUMBER OF ANIMALS EXAMINED	10	10	10	10
NUMBER WITHIN NORMAL LIMITS	10	8	9	8
EYE				
- Cataract, severe			1	
KIDNEY				
- Hydronephrosis, mild				1
LIVER				
- Foci, white, mild		1		
LUNG				
- Foci, red, mild				1
SKIN				
- Scab, mild		1		
- Hair loss, mild				1

191-1399

TABLE 20. Males: Summary of Organ Weight Values - FO Terminal Sacrifice

Parameters Measured	0 mg/kg/day (Control)			10 mg/kg/day			100 mg/kg/day			250 mg/kg/day		
	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Body Weight g	564	54.1	34	549	48.0	33	523	50.8	34	519	48.5	32
Kidney g	4.00	0.508	34	3.99	0.364	33	3.94	0.362	34	3.99	0.416	32
Kidney/Body Weight %x10	7.37	0.769	34	7.32	0.921	33	7.57	0.569	34	7.73	0.727	31
Liver g	19.67	2.727	34	19.24	2.214	32	17.93[2]	2.526	34	17.65[2]	1.821	31
Liver/Body Weight %	3.61	0.291	34	3.52	0.358	32	3.43[1]	0.285	34	3.40[1]	0.272	31

191-1395

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from the Control group; $p<0.05$

[2]Significantly different from the Control group; $p<0.01$

TABLE 20. Cont.

Females: Summary of Organ Weight Values - F0 Terminal Sacrifice

Parameters Measured	0 mg/kg/day (Control)			10 mg/kg/day			100 mg/kg/day			250 mg/kg/day		
	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Body Weight g	294	16.8	21	300	19.1	21	296	15.3	20	309[1]	18.6	22
Kidney g	2.75	0.198	22	2.87	0.164	21	2.75	0.170	21	2.91[1]	0.243	21
Kidney/Body Weight %x10	9.33	0.595	21	9.60	0.470	21	9.34	0.589	20	9.41	0.827	20
Liver g	15.42	1.632	22	15.51	1.470	21	15.15	1.729	21	16.06	2.264	21
Liver/Body Weight %	5.23	0.467	21	5.18	0.371	21	5.18	0.471	20	5.15	0.701	22

191-1395

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from the Control group; $p<0.05$

TABLE 20. Cont.

Females: Summary of Organ Weight Values - 13 Day Uterine Examination, F0 Female*

Parameters Measured	0 mg/kg/day (Control)			10 mg/kg/day			100 mg/kg/day			250 mg/kg/day		
	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Body Weight g	326	17.6	8	319	20.8	9	320	26.0	10	320	18.5	10
Kidney g	2.51	0.212	10	2.61	0.202	10	2.48	0.158	10	2.55	0.302	10
Kidney/Body Weight %x10	7.78	0.450	8	8.14	0.566	9	7.78	0.659	10	7.99	0.946	10
Liver g	14.09	1.556	10	14.29	1.621	10	13.47	2.035	10	14.42	1.681	10
Liver/Body Weight %	4.36	0.374	8	4.44	0.341	9	4.20	0.415	10	4.51	0.402	10

191-1395

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

International Research
and Development Corporation
MATTAWAN, MICHIGAN, U.S.A. 49071 TELEPHONE (616) 668-3336

Segment I Study of Fertility in Rats

G0539.03

May 8, 1989

Volume 2 of 2

RECEIVED BY
MAY 17 1989
OPERATIONS SECTION

191-1395

"credence through research"

APPENDIX A

Quality Assurance Inspections

191-1395

Quality Assurance Inspections

Dates of Inspections	Dates of Reports to Management	Dates of Reports to Study Director
3-21-88	6-29-88	6-29-88
4-06-88	7-25-88	7-25-88
4-11-88	2-06-89	2-06-89
4-20-88	2-09-89	2-09-89
4-28-88	3-02-89	3-02-89
5-02-88		
5-23-88		
6-14-88		
6-15-88		
6-27-88		
6-28-88		
6-29-88		
7-08-88		
7-15-88		
7-25-88		
7-28-88		
2-06-89		
2-09-89		
3-02-89		

APPENDIX B

Individual Experimental Data

Individual Antemortem Observations - Males

Dosage Level, Animal Number	Study Day	Antemortem	Study Day at Sacrifice
0 mg/kg/day (Control):			
47380	1-15,40-57,63-114	No visible abnormalities	114
	16-21,38-39,58-62	Hair loss, focal	
	22-37	Hair loss, generalized	
47381	1-17,86-94,105-106,114	No visible abnormalities	114
	18,49-53,63-85,95-104,107-113	Hair loss, focal	
	19-48,54-62	Hair loss, generalized	
47382	1-14,74-77,114	No visible abnormalities	114
	15-18,49-50,65-73,78-92,95-97,105-110	Hair loss, focal	
	19-48,51-64,93-94,98-104,111-113	Hair loss, generalized	
	15-26	Scabbed area, both limbs	
	36-37	Scabbed area, left forelimb	
	87	Material around nose, red	
47383	1-44,49-61,67-72	No visible abnormalities	114
	45-48,62-66,73-114	Malocclusion	
	43	Material around eye, black, both	
	46-48	Material around eye, black, left	
	113	Material around eye, black, right	
47384	1-91,103-112,114	No visible abnormalities	114
	113	Material around eye, black, right	
	92-102	Hair loss, generalized	
47385	1,9-76	No visible abnormalities	114
	2-8	Hair loss, focal	
	77-114	Body surface stained, both forelimbs, yellow	
	109-111	Material around nose, black	
	110-114	Malocclusion	
47386	1-114	No visible abnormalities	114
47387	1-88	No visible abnormalities	114
	89-92,95	Hair loss, focal	
	93-94,96-114	Hair loss, generalized	
47388	1-67,71-114	No visible abnormalities	114
	68-70	Material around nose, black	

191-1395

Individual Antemortem Observations - Males

Dosage Level, Animal Number	Study Day	Antemortem	Study Day at Sacrifice
0 mg/kg/day (Control):			
47389	1-14,22-37,62-114	No visible abnormalities	114
	15-21,38-61	Hair loss, focal	
47390	1-89,105-114	No visible abnormalities	114
	90-104	Malocclusion	
	91-99	Incisor missing	
47391	1-114	No visible abnormalities	114
47392	1-92,94-114	No visible abnormalities	114
	93	Material around nose, red	
47393	1-86,90-114	No visible abnormalities	114
	87-89	Material around nose, red	
47394	1-21	No visible abnormalities	114
	22-26,113-114	Material around eye, right, black	
	23-104	Nasal malalignment	
	29-76,79-114	Material around eye, left, black	
	29-50	Hair loss, focal	
	29,33-35,73-76,79-114	Malocclusion	
	78	Material around eye	
47395	1-51,54-99	No visible abnormalities	114
	52-53,100-103	Material around nose, red	
	104-113	Material around nose, black	
	114	Scabbed area, nasal region	
47396	1-28,40-114	No visible abnormalities	114
	29-39	Hair loss, focal	
47397	1-104,112-114	No visible abnormalities	114
	105-111	Material around nose, black	
47398	1-90	No visible abnormalities	115
	91-93	Material around eye, black, right	
	91-115	Malocclusion	
	93-115	Incisor missing	
	114	Material around eye, black, left	
47399	1-23,32-115	No visible abnormalities	115
	24-31	Malocclusion	

191-1389

Individual Antemortem Observations - Males

Dosage Level, Animal Number	Study Day	Antemortem	Study Day at Sacrifice/Death
0 mg/kg/day (Control):			
47400	1-115	No visible abnormalities	115
47401	1-76,79-104,115	No visible abnormalities	115
	77-78	Scabbed area, lip, upper, right	
	105-110	Material around nose, black	
	111-114	Hair loss, focal	
47402	1-115	No visible abnormalities	115
47403	1-115	No visible abnormalities	115
47404	1-115	No visible abnormalities	115
47405	1-115	No visible abnormalities	115
47406	1-91	No visible abnormalities	115
	92-96	Material around eye, black, both	
	92-115	Malocclusion	
	92-101	Material around nose, black	
	93-115	Nasal malalignment	
	94-103	Hole in palate	
	96-97,98-104	Labored breathing	
	96	Material around eye, black, right	
	99-100	Material around eye, black, left	
47407	1-70	No visible abnormalities	70
	70 (later in day)	Died	
47408	1-15,27-115	No visible abnormalities	115
	16-18	Scabbed area, forehead, left	
	19-26	Hair loss, focal	
47409	1-103,106-115	No visible abnormalities	115
	104-105	Material around nose, red	
47410	1-32,34-113,115	No visible abnormalities	115
	33	Material around nose, black	
	114	Material around eye, red, right	
47411	1-115	No visible abnormalities	115

191-1395

Individual Antemortem Observations - Males

Dosage Level, Animal Number	Study Day	Antemortem	Study Day at Sacrifice/Death
0 mg/kg/day (Control):			
47412	1-115	No visible abnormalities	115
47413	1-115	No visible abnormalities	115
47414	1-115	No visible abnormalities	115

191-1595

Individual Antemortem Observations - Males

Dosage Level, Animal Number	Study Day	Antemortem	Study Day at Sacrifice/Death
30 mg/kg/day:			
47415	1-93,95-99,100-114	No visible abnormalities	114
	94	Material around nose, red	
	100-107	Incisor missing	
47416	1-57	No visible abnormalities	57
	57 (later in day)	Died	
47417	1-14,16-43,53-112	No visible abnormalities	112
	15-17	Abrasion, lip, lower, right	
	44-52	Hair loss, focal	
	112 (later in day)	Died	
47418	1-79,96-114	No visible abnormalities	114
	80-95	Hair loss, generalized	
47419	1-25,29-114	No visible abnormalities	114
	26-31	Scabbed area, forehead, left	
	32-57,63-78	Hair loss, foc 1	
	58-62	Hair loss, generalized	
47420	1-114	No visible abnormalities	114
47421	1-112,114	No visible abnormalities	114
	113	Material around eye, black, right	
47422	1-106,111-114	No visible abnormalities	114
	107-110	Material around nose, black	
47423	1-113	No visible abnormalities	114
	114	Material around eye, black, right	
47424	1-10	No visible abnormalities	114
	11-13,49-50,76-77	Hair loss, focal	
	14-48,51-75,78-114	Hair loss, generalized	
47425	1-114	No visible abnormalities	114
47426	1-114	No visible abnormalities	114
47427	1-113	No visible abnormalities	114
	114	Body surface stained, ventral abdomen, brown	

191-1395

Individual Antemortem Observations - Males

Dosage Level, Animal Number	Study Day	Antemortem	Study Day at Sacrifice
10 mg/kg/day:			
47428	1-114	No visible abnormalities	114
47429	1-13,66-72,74-91,112-114	No visible abnormalities	114
	14,47-65,92-111	Hair loss, focal	
	15-46	Hair loss, generalized	
	73	Material around nose, black	
47430	1-114	No visible abnormalities	114
47431	1-114	No visible abnormalities	114
47432	1-114	No visible abnormalities	114
47433	1-10,66-85,88-91,98-99,105-111,114	No visible abnormalities	114
	11-13,53-65,86-87,92-97,100-104	Hair loss, focal	
	14-52	Hair loss, generalized	
	15-29	Scabbed area, forelimbs, both	
	94	Material around nose, red	
	112-113	Hair loss	
47434	1-16,115	No visible abnormalities	115
	17-29	Scabbed area, forelimb, right	
	30-33,39-55,63-85,98-104	Hair loss, focal	
	34-38,56-62,86-97,105-114	Hair loss, generalized	
47435	1-115	No visible abnormalities	115
47436	1-55	No visible abnormalities	115
	56-61,79-84	Material around eye, left, black	
	56-115	Malocclusion	
47437	1-32,34-115	No visible abnormalities	115
	33	Material around nose, moist, red	
47438	1-99	No visible abnormalities	115
	100-103	Tail discolored, blue	
	104-115	Tail discolored, black	
	114-115	Swelling, focal, left hindlimb	

191-1395

Individual Antemortem Observations - Males

Dosage Level, Animal Number	Study Day	Antemortem	Study Day at Sacrifice
10 mg/kg/day:			
47439	1-8,63-115 9-16,34-41,47-62 17-33,42-46	No visible abnormalities Hair loss, focal Hair loss, generalized	115
47440	1-115	No visible abnormalities	115
47441	1-115	No visible abnormalities	115
47442	1-115	No visible abnormalities	115
47443	1-8,40-53 9-39,59-115 54-52 63-78,80-85 90-91	No visible abnormalities Malocclusion Material around eye, right, black Material around eye, right, red Material around eye, right, [illegible]	115
47444	1-31,92-94,112-115 32-46,58-62,72-78 47-57,63-71,79-91,95-111	No visible abnormalities Hair loss, generalized Hair loss, focal	115
47445	1-115	No visible abnormalities	115
47446	1-55,62-84,86-87,90-112,115 56-61 85 88-89 113-114	No visible abnormalities Soft stool Material around nose, black Incisors missing Protruding eye	115
47447	1-91 92-115	No visible abnormalities Nodule, posterior, dorsal region	115
47448	1-94,105-115 95-104	No visible abnormalities Hair loss, focal	
47449	1-115	No visible abnormalities	115

[a]Color of material inadvertently not recorded

191-1395

Individual Antemortem Observations - Males

Dosage Level, Animal Number	Study Day	Antemortem	Study Day at Sacrifice
100 mg/kg/day:			
47450	1-84,90-91,93-114	No visible abnormalities	114
	85-89,92	Incisors missing	
47451	1-114	No visible abnormalities	114
47452	1-114	No visible abnormalities	114
47453	1-33,56-96,101-111	No visible abnormalities	114
	34-52	Body surface stained, both forelimbs, yellow	
	53-55	Body surface stained, right forelimb, yellow	
	97-100	Hair loss, focal	
	112-114	Rales	
47454	1-104,106-112	No visible abnormalities	114
	106	Material around nose, red	
	113-114	Material around right nose, black	
	114	Body surface s'in, entire ventral surface, moist, red	
47455	1-44,52-114	No visible abnormalities	114
	45-51	Malocclusion	
	47-51	Incisor missing	
47456	1-114	No visible abnormalities	114
47457	1-114	No visible abnormalities	114
47458	1-114	No visible abnormalities	114
47459	1-114	No visible abnormalities	114
47460	1-38	No visible abnormalities	52
	39-43,45	Material around both eyes, dark red	
	39-41,45	Material around nose, dark red	
	39-52	Nasal malalignment	
	40-42	Reduced motor activity	
	43-52	Emaciated	
	45-52	Labored breathing	
	46-50	Material around eye, left, black	
	51-52	Scabbed area, forelimb, right	
	51-52	Material around eye, left, red	
	52	Sacrificed in extremis	

(91-1395

Individual Antemortem Observations - Males

Dosage Level, Animal Number	Study Day	Antemortem	Study Day at Sacrifice
100 mg/kg/day:			
47461	1-68 69-114	No visible abnormalities Eye partially closed, right	114
47462	1-114	No visible abnormalities	114
47463	1-114	No visible abnormalities	114
47464	1-114	No visible abnormalities	114
47465	1-114	No visible abnormalities	114
47466	1-8 9-114 62-114	No visible abnormalities Malocclusion Material around eye, left, black	114
47467	1-114	No visible abnormalities	114
47468	1-114	No visible abnormalities	114
47469	1-115	No visible abnormalities	115
47470	1-17,34-115 18-33	No visible abnormalities Hair loss, facial	115
47471	1-92,95-106,111-115 93-94,107-110	No visible abnormalities Material around nose, red	115
47472	1-115	No visible abnormalities	115
47473	1-115	No visible abnormalities	115
47474	1-115	No visible abnormalities	115
47475	1-115	No visible abnormalities	115
47476	1-115	No visible abnormalities	115
47477	1-115	No visible abnormalities	115
47478	1-115	No visible abnormalities	115
47479	1-115	No visible abnormalities	115

191-1395

Individual Antemortem Observations - Males

Dosage Level, Animal Number	Study Day	Antemortem	Study Day at Sacrifice
100 mg/kg/day:			
47480	1-32,33-115 33-92	No visible abnormalities Malocclusion	115
47481	1-8,14-115 9-13	No visible abnormalities Hair loss, focal	115
47482	1-91 92-101,115 102-114	No visible abnormalities Hair loss, focal Hair loss, generalized	115
47483	1-60,62-112 61 113-114 115	No visible abnormalities Material around eye, left, black Protruding eye Material around eye, right, black	115
47484	1-55,74-91,105-115 56-73,92-104	No visible abnormalities Hair loss, focal	115

Individual Antemortem Observations - Males

Dosage Level, Animal Number	Study Day	Antemortem	Study Day at Sacrifice
250 mg/kg/day:			
47485	1-114	No visible abnormalities	114
47486	1-48	No visible abnormalities	114
	49-114	Malocclusion	
	50-55,68-87	Material around eye, left, black	
	56-59	Material around eye, both, black	
	65-67	Material around eye, both, red	
	88-89	Material around eye, left, red	
47487	1-36,53-63,65-81,83-84,86-87,92-106, 113-114	No visible abnormalities	114
	37-52,82,85,88-91,107-112	Rales	
	64-65	Soft stool	
47488	1-112	No visible abnormalities	114
	113-114	Material around eye, right, black	
47489	1-14,34-113	No visible abnormalities	114
	15-33	Hair loss, focal	
		Swelling, ears, both	
47490	1-114	No visible abnormalities	114
47491	1-55	No visible abnormalities	114
	56-114	Malocclusion	
	56-59,88-89	Material around eye, right, black	
47492	1-114	No visible abnormalities	114
47493	1-87,90-114	No visible abnormalities	114
	88-89	Rales	
47494	1-114	No visible abnormalities	114
47495	1-39	No visible abnormalities	114
	40-114	Malocclusion	
	40-42	Material around nose, black	
	40-44	Swelling, focal, nasal region	

191-1395

Individual Antemortem Observations - Males

Dosage Level, Animal Number	Study Day	Antemortem	Study Day of Sacrifice/Death
250 mg/kg/day			
47496	1-25	No visible abnormalities	114
	24-114	Malocclusion	
	26-29	Material around eyes, both, black	
	26-29,105-106	Material around nose, black	
	32	Material around eye, right, red	
	33-36,42-43,54-61,113	Material around eye, right, black	
	100-114	Incisor missing	
47497	1-114	No visible abnormalities	114
47498	1-114	No visible abnormalities	114
47499	1-114	No visible abnormalities	114
47500	1-80,85-101	No visible abnormalities	103
	81-84	Males	
	102	Pale in color	
	102	Eyes pale in color	
	102	Material around mouth, brown	
	102	Anogenital staining, brown	
	103	Died	
47501	1-9,40-82	No visible abnormalities	83
	10-13,19-39	Hair loss, focal	
	14-18	Hair loss, generalized	
	83	Material around nose, red	
	83	Soft stool	
	83	Exposed skin area, pale	
	83	Eye discolored, both, pale	
	83	Cold to touch	
	83	Decreased defecation	
	83	Reduced motor activity	
	83	Labored breathing	
	83	Anogenital staining, thick red	
	83	Emaciated	
	83	Moribund	
	83	Sacrificed in extremis	

191-1395

Individual Antemortem Observations - Males

Dosage Level, Animal Number	Study Day	Antemortem	Study Day at Sacrifice/Death
250 mg/kg/day:			
47502	1-29,44-55,68-85,88-91,95-99,104-106,124	No visible abnormalities	114
	30-43,56-67,86-87,92-94,100-103,107-111	Hair loss, focal	
	112-113	Hair loss, generalized	
47503	1-94,97-114	No visible abnormalities	114
	95-96	Material around nose, red	
47504	1-115	No visible abnormalities	115
47505	1-115	No visible abnormalities	115
47506	1-112,115	No visible abnormalities	115
	113-114	Material around eye, right, black	
47507	1-115	No visible abnormalities	115
47508	1-84,86-91,93-115	No visible abnormalities	115
	85	Rales	
	92-94	Malocclusion	
47509	1-115	No visible abnormalities	115
47510	1-31,53	No visible abnormalities	115
	32-45,49-52,54-57,113	Hair loss, focal	
	46-48,58-114	Hair loss, generalized	
47511	1-115	No visible abnormalities	115
47512	1-115	No visible abnormalities	115
47513	1-115	No visible abnormalities	115
47514	1-115	No visible abnormalities	115
47515	1-115	No visible abnormalities	115
47516	1-42	No visible abnormalities	42
	42 (later in day)	Died	
47517	1-115	No visible abnormalities	115

Individual Antemortem Observations - Males

Dosage Level, Animal Number	Study Day	Antemortem	Study Day at Sacrifice
250 mg/kg/day:			
47518	1-89	No visible abnormalities	115
	90-115	Malocclusion	
	90-92,115	Material around eyes, both, black	
	93-103	Material around eye, left, brown	
	93-114	Material around eye, right, black	
	90-94	Material around nose, black	
	101	Material around nose, red	
	93-103	Hole in palate	
47519	1-55	No visible abnormalities	115
	56-106	Malocclusion	
	56-57	Material around eye, both, black	
	62	Material around eye, left, red	
	63-64	Material around eye, left, black	
	56-62	Hole in palate	
	57-115	Incisor missing	
	63-65	Material around mouth, black	

Individual Maternal Antemortem Observations - Females

Dosage Level, Dam Number	Study Day	Antemortem	Study Day at Sacrifice
0 mg/kg/day (Control):			
50206	1-29	No visible abnormalities	29
50207	1-52,54-62 53	No visible abnormalities Hair loss, focal	62
50208	1-54,56-62 55	No visible abnormalities Material around eye, right, black	62
50209	1-52,54-60 53	No visible abnormalities Hair loss, focal	60
50210	1-29	No visible abnormalities	29
50211	1-31	No visible abnormalities	31
50212	1-59	No visible abnormalities	59
50213	1-30	No visible abnormalities	30
50214	1-52 53-62	No visible abnormalities Body surface stained, both forelimbs, brown	62
50215	1-33 34-65 48	No visible abnormalities Hair loss, generalized Scabbed area, forelimbs	65
50216	1-63	No visible abnormalities	63
50217	1-59	No visible abnormalities	59
50218	1-63	No visible abnormalities	63
50219	1-62	No visible abnormalities	62

191-1395

Individual Maternal Antemortem Observations - Females

Dosage Level, Dam Number	Study Day	Antemortem	Study Day at Sacrifice
0 mg/kg/day (Control):			
50220	1-61	No visible abnormalities	61
50221	1-61	No visible abnormalities	61
50222	1-24 25-29,32 30-31	No visible abnormalities Hair loss, generalized Hair loss, focal	32
50223	1-60	No visible abnormalities	60
50224	1-16,18-22 17 23-31 24-31	No visible abnormalities Material around nose, black Body surface stained, left forelimb, yellow Hair loss, focal	31
50225	1-29	No visible abnormalities	29
50226	1-43	No visible abnormalities	43
50227	1-46	No visible abnormalities	46
50228	1-54,56-63 55	No visible abnormalities Material around nose, brown	63
50229	1-29	No visible abnormalities	29
50230	1-60	No visible abnormalities	60
50231	1-59	No visible abnormalities	59
50232	1-29	No visible abnormalities	29
50235	1-42	No visible abnormalities	42

191-t305

Individual Maternal Antemortem Observations - Females

Dosage Level, Dam Number	Study Day	Antemortem	Study Day at Sacrifice
0 mg/kg/day (Control):			
50234	1-52 53-59	No visible abnormalities Body surface stained, abdomen, brown	59
50235	1-27,30 28-29	No visible abnormalities Eye appears small in size, right	30
50236	1-16 17-23,32-35 24-31,36-61	No visible abnormalities Hair loss, local Hair loss, generalized	61
50237	1-63	No visible abnormalities	63
50238	1-60	No visible abnormalities	60
50239	1-62	No visible abnormalities	62
50240	1-27,29-60 28	No visible abnormalities Material around nose, red, moist	60

191-1395

Individual Maternal Antemortem Observations - Females

Dosage Level, Dam Number	Study Day	Antemortem	Study Day at Sacrifice
10 mg/kg/day:			
50241	1-24 25-62	No visible abnormalities Hair loss, generalized	62
50242	1-59	No visible abnormalities	59
50243	1-29	No visible abnormalities	29
50244	1-62	No visible abnormalities	62
50245	1-60	No visible abnormalities	60
50246	1-22 23,30-47 24-29,48-62 24-29	No visible abnormalities Hair loss, focal Hair loss, generalized Scabbed area, forelimbs	62
50247	1-55 56-63	No visible abnormalities Hair loss, focal	63
50248	1-60	No visible abnormalities	60
50249	1-31 32-33	No visible abnormalities Hair loss, generalized	33
50250	1-63	No visible abnormalities	63
50251	1-28 29	No visible abnormalities Scabbed area, dorsal head	29
50252	1-61	No visible abnormalities	61
50253	1-10 11,42 12-41	No visible abnormalities Hair loss, focal Hair loss, generalized	42
50254	1-29	No visible abnormalities	29

691-1395

Individual Maternal Antemortem Observations - Females

Dosage Level, Dam Number	Study Day	Antemortem
10 mg/kg/day:		
50255	1-61	No visible abnormalities
50256	1-30	No visible abnormalities
50257	1-43 44-47,56-63 48-55	No visible abnormalities Hair loss, focal Hair loss, generalized
50258	1-31	No visible abnormalities
50259	1-29	No visible abnormalities
50260	1-16,40 17-24,30-39,56-60 25-29,41-55	No visible abnormalities Hair loss, focal Hair loss, generalized
50261	1-30,55-59 31-54 32-58	No visible abnormalities Hair loss, focal Rales
50262	1-61	No visible abnormalities
50263	1-62	No visible abnormalities
50264	1-56	No visible abnormalities
50265	1-42,48-63 43-47	No visible abnormalities Material around eye, right, black
50266	1-30,42-47,55 31-41,48-54,56-61 35-40 62	No visible abnormalities Hair loss, focal Scabbed area, left forelimb Hair loss, generalized

191-1399

(Individual) Maternal Antemortem Observations - Females

Dosage Level, * Dam Number	Study Day	Antemortem
10 mg/kg/day:		
50267	1-59	No visible abnormalities
50268	1-62	No visible abnormalities
50269	1-40 41-60 61	No visible abnormalities Hair loss, focal Hair loss, generalized
50270	1-42	No visible abnormalities
50271	1-51	No visible abnormalities
50272	1-41,49-59 42-48	No visible abnormalities Incisor missing
50273	1-32	No visible abnormalities
50274	1-30	No visible abnormalities
50275	1-10,27 11-16 17-26,28-45	No visible abnormalities Hair loss, focal Hair loss, generalized

191-4395

Individual Maternal Antemortem Observations - Females

Dosage Level, Dam Number	Study Day	Antemortem	Study Day at Sacrifice
100 mg/kg/day:			
50276	1-42 43-61	No visible abnormalities Internal eye white, right	61
50277	1-60	No visible abnormalities	60
50278	1-63	No visible abnormalities	63
50279	1-62	No visible abnormalities	62
50280	1-35,56-59 36-46,53-55 47-52	No visible abnormalities Hair loss, focal Hair loss, generalized	59
50281	1-62	No visible abnormalities	62
50282	1-59	No visible abnormalities	59
50283	1-47,56 48-55 57-62	No visible abnormalities Hair loss, focal Hair loss	62
50284	1-41 42-46 47-60	No visible abnormalities Hair loss, focal Hair loss, generalized	60
50285	1-29	No visible abnormalities	29
50286	1-21 22-30	No visible abnormalities Internal eye white, right	30
50287	1-46 47-59 60	No visible abnormalities Hair loss, focal Hair loss, generalized	60
50288	1-6 7-14 15-60	No visible abnormalities Hair loss, focal Hair loss, generalized	60

191-1395

Individual Maternal Antemortem Observations - Females

Dosage Level, Dam Number	Study Day	Antemortem	Study Day at Sacrifice
100 mg/kg/day:			
50289	1-14 15-30	Ulceration, right posterior dorsal region No visible abnormalities	30
50290	1-30	No visible abnormalities	30
50291	1-42	Hair loss, generalized	42
50292	1-21,59 22-46,52-58 47-51	No visible abnormalities Hair loss, focal Hair loss, generalized	59
50293	1-61 23-27	Hair loss, generalized Scabbed area, left shoulder	61
50294	1-31	No visible abnormalities	31
50295	1-61	No visible abnormalities	61
50296	1-59	No visible abnormalities	59
50297	1-31	No visible abnormalities	31
50298	1-23 24-30 30	No visible abnormalities Hair loss, focal Scabbed area, left forelimb	30
50299	1-59	No visible abnormalities	59
50300	1-60	No visible abnormalities	60
50301	1-29	No visible abnormalities	29
50302	1-62	No visible abnormalities	62
50303	1-34 34,41-42 40 40-42	No visible abnormalities Material around eye, black, left Material around eye, black Malocclusion	42

191-1395