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December 12, 1997

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Document Control Office (7407)
Office of Pollution Prevention and Toxics
Environmental Protection Agency
401 M St., S.W.
Washington, D.C. 20460

8EHQ-97-14025

Subject: TSCA Section 8(e) Submission

Dear Sir/Madam:

Elf Atochem North America, Inc. (Elf Atochem) has received the final reports of three toxicology studies in rats and is submitting the results to the Environmental Protection Agency (EPA) pursuant to Toxic Substances Control Act (TSCA) Section 8(e). The three studies, all entitled *A Study to Evaluate Early Embryonic Development in Rats*, provide information on t-butylaminoethanol (CAS No. 4620-70-6), n-propylaminoethanol (CAS No. 16369-21-4) and diethylaminoethanol (CAS No. 100-37-8). Preliminary results from these studies were submitted to the Agency by Elf Atochem on September 23, 1997. These studies do not involve effects in humans.

Nothing in this letter or the enclosed study reports is considered to be confidential business information of Elf Atochem.

Further questions regarding this submission may be directed to me at (215) 419-5890.

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Sincerely,

Debra Randall

Debra Randall, DABT
Product Safety Manager

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# FINAL REPORT

## STUDY TITLE

A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS

## STUDY DIRECTOR

Donald G. Stump, Ph.D.

## STUDY INITIATED ON

April 23, 1997

## STUDY COMPLETED ON

November 12, 1997

## PERFORMING LABORATORY

WIL Research Laboratories, Inc.
1407 George Road
Ashland, OH 44805-9281

## LABORATORY STUDY NUMBER

WIL-160079

## SPONSOR

Elf Atochem North America, Inc.
2000 Market Street
Philadelphia, PA 19103-3222

A Study to Evaluate Early Embryonic Development in Rats

## COMPLIANCE STATEMENT

This study, designated WIL-160079, was conducted in general compliance with the United States Environmental Protection Agency (EPA) Good Laboratory Practice Regulations (40 CFR Part 792), September 18, 1989, the Standard Operating Procedures of WIL Research Laboratories, Inc., and the protocol as approved by the sponsor.

Donald G. Stump

Donald G. Stump, Ph.D.
Study Director

11/12/97
Date

A Study to Evaluate Early Embryonic Development in Rats

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# A Study to Evaluate Early Embryonic Development in Rats

## I. SUMMARY

The potential maternal toxicity and adverse effects on the pre-implantation stages of the embryo through implantation and early development of the embryo resulting from oral administration of the test article were evaluated. The test article in deionized water was administered to four groups of five bred female Crl:CD®(SD)BR rats once daily, from gestation days 0 through 11. Dosage levels were 10, 30, 100 and 300 mg/kg/day administered at dose volumes of 1, 3, 3.3 and 10 ml/kg, respectively. A concurrent control group, composed of five bred females, received the vehicle, deionized water, on a comparable regimen at 10 ml/kg. The route of administration was oral by gastric intubation. Throughout gestation all females were observed twice daily for appearance and behavior. Clinical observations, body weights and food consumption were recorded. On gestation day 12, all females were euthanized for a scheduled uterine examination. The uteri and ovaries were examined and the numbers of embryos, early and late resorptions, total implantations and corpora lutea were recorded. Individual maternal kidney and liver weights were recorded. Kidney and liver tissues were examined microscopically from all animals in the control and 300 mg/kg/day groups.

All females survived to the scheduled euthanization on gestation day 12. No treatment-related clinical signs were observed at any dose level. None of the females in the 300 mg/kg/day group were gravid; therefore, body weight and food consumption data for this group could not be evaluated. Slight mean body weight losses were noted in the 100 mg/kg/day group during gestation days 9-11 and 11-12. In the 10 and 30 mg/kg/day groups, mean body weights were similar to the control group values throughout the study. Food consumption was unaffected by treatment at dose levels of 10, 30 and 100 mg/kg/day. No treatment-related internal findings were noted during the macroscopic examination. No treatment-related microscopic findings were observed in the livers and kidneys from the 300 mg/kg/day group. No effects were observed on liver and kidney weights that could be clearly attributed to treatment.

All of the females in the 300 mg/kg/day group and three of the females in the 100 mg/kg/day group were nongravid; this dose-related effect was attributed to treatment. In the 100 mg/kg/day group, pre-implantation loss was increased, and the mean numbers

of implantation sites and viable embryos were reduced. In the 10 and 30 mg/kg/day groups, intrauterine parameters were unaffected by treatment.

In conclusion, maternal toxicity was expressed at a dose level of 100 mg/kg/day by slight mean body weight losses during the last three days of treatment. A toxic effect on pre-implantational events occurred in the 100 and 300 mg/kg/day groups, as evidenced by dose-related increases in the number of nongravid females (all females in the 300 mg/kg/day group and three females in the 100 mg/kg/day group were nongravid) and an increase in pre-implantation loss (100 mg/kg/day group only).

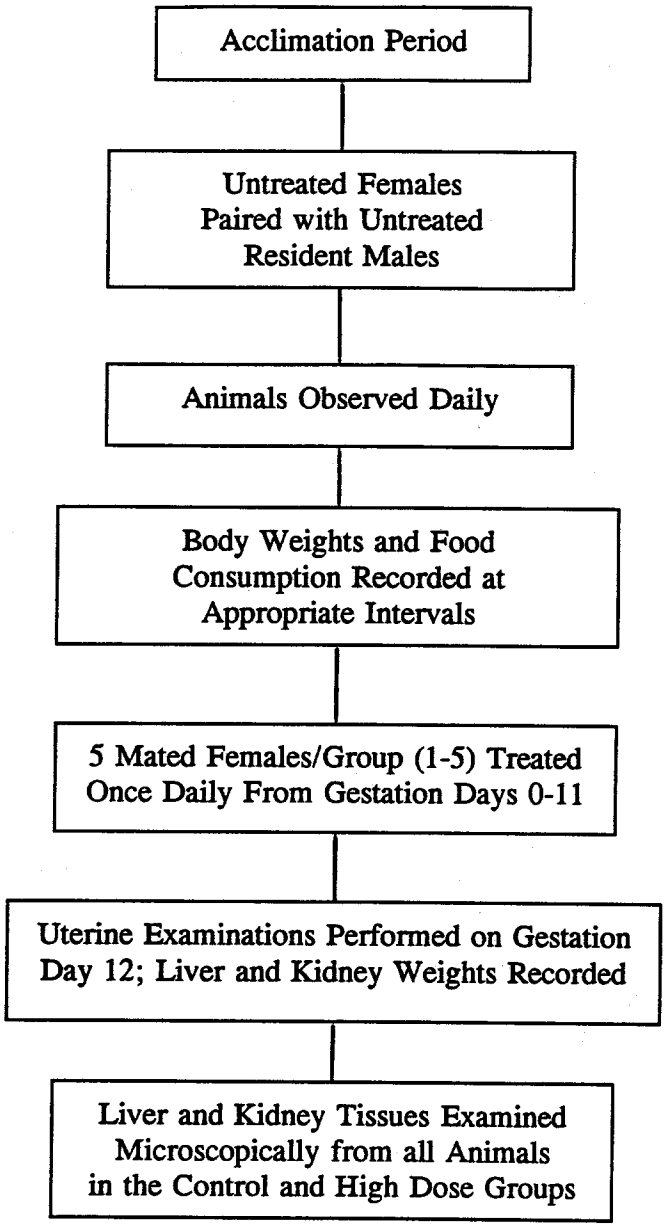
Based on the results of this study, the no observed effect level (NOEL) was 30 mg/kg/day for maternal toxicity and embryonic development.

## II. OBJECTIVE

This study was designed to investigate the potential maternal toxicity and adverse effects on the pre-implantation stages of the embryo through implantation and early development of the embryo resulting from oral (gavage) administration of the test article to pregnant rats during early gestation.

The selected route of administration was oral to assure bioavailability of the test article. The animal model, the Crl:CD®(SD)BR rat, was selected on the basis of availability of historical control data and susceptibility of the species to known developmental toxicants.

## III. STUDY DESIGN



# IV. EXPERIMENTAL PROCEDURES

## A. INTRODUCTION

The experimental phase of the study was initiated with the assignment of mated rats to treatment groups on May 28, 1997, and concluded with the last histopathological examination on August 5, 1997. The dosing period was from May 28, 1997 to June 11, 1997. Dose levels were selected based on the results of a preliminary seven-day toxicity study using non-mated females. These results are presented separately in Appendix A (designated WIL-160079A for computer entry).

## B. TEST AND CONTROL ARTICLES

### 1. TEST ARTICLE IDENTIFICATION

The test article was received from the sponsor on April 17, 1997, as follows:

| Identification | No. of Containers Received | Physical Description |
|---|---|---|
| Name/Code:<br>t-Butylaminoethanol 0153<br>Product: PF153<br>CAS Number: 4620-70-6<br>Concentration: 99.6%<br>Lot No.: Tank 3560<br>on 3/22/97<br>Exp. Date: 10/15/97<br>[WIL Log No. 3338A] | 1 Bottle<br>Gross Weight:<br>631.5 g | Water<br>white<br>liquid |

Stability and purity data were the responsibility of the sponsor. The bulk test article was 99.6% pure. For purposes of dose calculations, the test article was assumed to be 100% pure. The test article was stored at room temperature and was considered stable under this condition. A reserve sample (1.2 g) of the bulk test article was taken on April 26, 1997, and stored in the Archives at WIL Research Laboratories, Inc.

### 2. VEHICLE CONTROL ARTICLE IDENTIFICATION

The vehicle control article utilized in preparation of the test mixtures was deionized water (prepared on-site).

3. PREPARATION

An appropriate amount of the vehicle, deionized water, was dispensed into a properly labeled storage container for administration to the control group. A stir bar was added, and the vehicle was stirred continuously throughout the dosing procedures. A sufficient volume of the vehicle was dispensed daily for administration to the control group.

The container of test article was heated to 45-50°C in a water bath to liquify the contents prior to preparation of the formulations. The test article formulations were then prepared as follows. An appropriate amount of test article was weighed for each group into a labeled, precalibrated storage container. A sufficient amount of the vehicle was added to bring the volume of each formulation to the calibration mark. A stir bar was added to each preparation, and the formulations were stirred on a magnetic stir plate throughout the dosing procedures.

The formulations for all dose groups were prepared three times during the study, on May 28, June 4 and June 11, 1997. The preparations were visually inspected by the study director for homogeneity prior to the initiation of dosing and were found to be acceptable for use. Due to the limited scope of this study, analytical verification of the dose formulations for homogeneity, stability and concentration was not performed.

4. ADMINISTRATION

The test mixtures were administered orally by gavage, via a 16-gauge stainless steel gavage cannula (Popper and Sons, Inc., New Hyde Park, New York), once daily for 12 consecutive days initiating on gestation day 0 and continuing up to and including day 11 of gestation. Dosage volumes of 1, 3, 3.3 and 10 ml/kg were used for the 10, 30, 100 and 300 mg/kg/day dosage levels, respectively. The control animals received deionized water on a comparable regimen of 10 ml/kg. Individual dosages were based on the most recently recorded body weight to provide the correct mg/kg/day dose. All rats were dosed at approximately the same time each day. The following diagram presents the study group assignment:

| Group Number | Group Name | Dosage Level (mg/kg/day) | Dosage Concentration (mg/ml) | Dosage Volume (ml/kg) | Number of Females |
|---|---|---|---|---|---|
| 1 | Vehicle Control | 0 | 0 | 10 | 5 |
| 2 | Low Dose | 10 | 10 | 1 | 5 |
| 2 | Intermediate Dose-1 | 30 | 10 | 3 | 5 |
| 3 | Intermediate Dose-2 | 100 | 30 | 3.3 | 5 |
| 5 | High Dose | 300 | 30 | 10 | 5 |

C. ANIMAL RECEIPT AND ACCLIMATION

One hundred twenty-six sexually mature, virgin female Crl:CD®(SD)BR rats, were received in good health on May 15, 1997, from Charles River Laboratories, Inc., Portage, Michigan, to be used for WIL-160079, WIL-160080[1], WIL-160081[2] and WIL-160082[3]. The animals were approximately 70 days old. Upon receipt, each animal was observed by a qualified technician. The animals were initially weighed on the day of receipt. All animals were uniquely identified by a Monel metal eartag displaying the animal number and housed for 13 days for acclimation purposes. During this time, the animals were observed twice daily for changes in general appearance and behavior, as well as for mortality and moribundity. The animals were weighed again at pairing on May 27, 1997.

D. ANIMAL HOUSING

Upon arrival and until pairing, all animals were individually housed in clean, wire-mesh cages suspended above cage-board. The animals were paired for mating in the home cage of the male. Following positive identification of mating, each female was returned to an individual suspended wire-mesh cage; nesting material was not required as the females were euthanized prior to the date of expected parturition. All animals were maintained in accordance with the "Guide for the Care and Use of Laboratory Animals[4]." The animal facilities at WIL Research Laboratories, Inc., are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International).

E. DIET, DRINKING WATER AND MAINTENANCE

The basal diet used in this study was PMI Feeds, Inc.© Certified Rodent LabDiet© 5002. This diet is a certified feed with appropriate analyses performed

by the manufacturer and provided to WIL Research Laboratories, Inc., Ashland, Ohio. Municipal water supplying the facility is sampled for contaminants according to Standard Operating Procedures. The results of these analyses are maintained at WIL Research Laboratories, Inc. Contaminants were not present in animal feed or water at concentrations expected to interfere with the objectives of this study. Drinking water delivered by an automatic watering system and the basal diet were provided *ad libitum* throughout the acclimation period and during the study.

F. ENVIRONMENTAL CONDITIONS

All animals were housed throughout the acclimation period and during the study in an environmentally controlled room. Controls were set to maintain a temperature of 72° ± 4°F and a relative humidity of 30% to 70%. Room temperature and relative humidity were recorded daily. Temperature ranged from 71.2°F to 72.7°F and relative humidity ranged from 30.6% to 47.3% during the study period. Light timers were calibrated to provide a 12-hour light/12-hour dark photoperiod. Air handling units were set to provide approximately 10 fresh air changes per hour.

G. ASSIGNMENT OF ANIMALS TO TREATMENT GROUPS AND BREEDING PROCEDURES

At the conclusion of the acclimation period, all available females were weighed and examined in detail for physical abnormalities. At the discretion of the study director, animals judged to be in good health and meeting acceptable body weight requirements (a minimum of 220 g) were placed in a suspended wire-mesh cage with a resident male from the same strain and source for breeding. Resident males were untreated, sexually mature rats utilized exclusively for breeding. These rats were maintained under similar laboratory conditions as the females. A breeding record containing the male and female identification numbers and the dates of cohabitation was prepared. The selected females were approximately 12 weeks old when paired for breeding.

Positive evidence of mating was confirmed by the presence of a copulatory plug or the presence of sperm in a vaginal smear. Each mating pair was examined

daily. The day on which evidence of mating was identified was termed day 0 of gestation and the animals were separated.

The experimental design for WIL-160079 consisted of four treated groups (Groups 2-5) and one vehicle control group (Group 1). The bred females were consecutively assigned in a block design to groups containing five rats each by the following randomization procedure. The first mated female and the appropriate gestation day 0 designation were recorded and the female was assigned to group 1, the second mated female was assigned to group 2, and the third to group 3, etc. This process was continued daily until five females were placed into each group. Body weight values ranged from 228 g to 268 g on day 0 of gestation.

H. MATERNAL OBSERVATIONS DURING GESTATION

1. CLINICAL OBSERVATIONS AND SURVIVAL

All rats were observed twice daily for moribundity and mortality. Individual detailed clinical observations were recorded from gestation days 0 through 12 (prior to test article administration during the dosing period). The animals were also observed for signs of toxicity approximately one hour following dosing.

2. BODY WEIGHTS

Individual maternal body weights were recorded on gestation days 0, 1, 3, 7, 9, 11 and 12. A group mean body weight was calculated for each of these days. Mean body weight changes were calculated for each corresponding interval and also for gestation days 0-12.

3. FOOD CONSUMPTION

Individual food consumption was recorded on gestation days 0, 1, 3, 7, 9, 11 and 12. Food intake was reported as g/animal/day and g/kg/day for the corresponding body weight change intervals.

I. GESTATION DAY 12 UTERINE EXAMINATION

All maternal animals were euthanized by carbon dioxide inhalation on gestation day 12. The thoracic, abdominal and pelvic cavities were opened by a ventral midline incision, and the contents were examined. In all instances, the *post mortem* findings were correlated with the *ante mortem* comments and any abnormalities

were recorded. The uterus and ovaries were then exposed and examined. The number of corpora lutea on each ovary was recorded. The uterus was opened and the number of all embryos, early and late resorptions and the total number of implantation sites were recorded. The liver, kidneys and gross lesions from all maternal animals were preserved in 10% neutral buffered formalin.

Uteri with no macroscopic evidence of nidation were excised, opened and subsequently placed in 10% ammonium sulfide solution for detection of early implantation loss as described by Salewski[5].

Intrauterine data were summarized using two methods of calculation. An example of each method of calculation follows:

1. Group Mean Litter Basis:

$$\text{Postimplantation Loss/Litter} = \frac{\text{No. Dead Embryos, Resorptions (Early/Late)/Group}}{\text{No. Gravid Females/Group}}$$

2. Proportional Litter Basis:

$$\text{Summation per Group (\%)} = \frac{\text{Postimplantation Loss/Litter (\%)}^{a}}{\text{No. of Litters/Group}}$$

$$a = \frac{\text{No. Dead Embryos, Resorptions (Early/Late)/Litter}}{\text{No. Implantation Sites/Litter}} \times 100$$

J. ORGAN WEIGHTS - SCHEDULED NECROPSY

The liver and kidneys from each animal were excised and weighed at the scheduled necropsy. Paired organs were weighed collectively. Absolute organ weights were recorded.

K. MICROSCOPIC EXAMINATION

The liver and kidneys from all females in the control and high dose groups were examined microscopically. The following procedure was used for the preparation of all tissues. After fixation, the tissues were trimmed as described by Thompson[6]. Trimmed specimens were placed into properly labeled and numbered cassettes. The fixed tissue samples were then processed into paraffin

blocks. The paraffin blocks were sectioned at 5-8 microns, and the paraffin ribbons of the sectioned tissues were placed on clean glass microscope slides labeled with the appropriate study, animal, group and cassette numbers.

Upon completion of staining with hematoxylin and eosin (AFIP Manual of Histologic Staining Methods[7]), coverslips were placed on the slides. Microscopic examinations were performed by Chandikumar S. Elangbam, M.V.Sc., Ph.D., D.A.C.V.P., D.A.B.T., Senior Pathologist, WIL Research Laboratories, Inc.

L. STATISTICAL ANALYSES

All analyses were conducted using two-tailed tests for a minimum significance level of 5%, comparing each treated group to the vehicle control group. Each mean was presented with the standard deviation (S.D.) and the number of animals (N) used to calculate the mean. Statistical analyses were not performed when the number of animals was two or less. The following statistical tests were performed by a Digital® MicroVAX® 3400 computer (with appropriate programming) in this laboratory and are referenced on the report tables:

| STATISTICAL TEST | PARAMETER |
|---|---|
| - One-way ANOVA with Dunnett's test[8] | Corpora Lutea, Total Implantations, Viable Embryos, Maternal Body Weights and Weight Changes, Maternal Food Consumption, Organ Weights |
| - Kruskal-Wallis test with Mann-Whitney U test[8] | Litter Proportions of Intrauterine Data (Considering the Litter, Rather than the Embryo, as the Experimental Unit) |

M. DATA RETENTION

The sponsor will have title to all documentation records, raw data, specimens or other work product generated during the performance of the study. All work product including raw paper data and specimens will be retained in the Archives at WIL Research Laboratories, Inc., as specified in the protocol.

Raw data in magnetic form, a retention sample of the test article and the original final report will be retained at WIL Research Laboratories, Inc., Ashland, Ohio, in compliance with regulatory requirements.

# V. RESULTS

## A. CLINICAL OBSERVATIONS AND SURVIVAL

Summary Data: Tables 1, 2, 3

Individual Data: Tables 11, 12

All females survived to the scheduled necropsy. Clinical signs noted in the treated groups, including exophthalmic eyes, rales and wet clear matting around the mouth, were noted infrequently and were not attributed to treatment.

## B. BODY WEIGHTS

Summary Data: Tables 4, 5

Individual Data: Tables 13, 14

None of the females in the 300 mg/kg/day group were gravid; therefore, body weight data could not be assessed for this group. In the 100 mg/kg/day group, mean body weight gains were similar to the control group values during gestation days 0-1, 1-3, 3-7 and 7-9. During gestation days 9-11 and 11-12, slight mean body weight losses were observed in this group (it should be noted that only two females in this group were gravid). When the entire treatment period (gestation days 0-12) was evaluated, the mean body weight gain in the 100 mg/kg/day group was slightly reduced relative to the control group value. Mean body weights in this group were slightly reduced relative to the control group values on gestation days 11 and 12.

In the 10 and 30 mg/kg/day groups, mean body weights and body weight gains were similar to the control group values throughout the study; differences were slight and were not statistically significant.

## C. FOOD CONSUMPTION

Summary Data: Tables 6, 7

Individual Data: Tables 15, 16

None of the females in the 300 mg/kg/day group were gravid; therefore, food consumption data could not be assessed for this group. Food consumption, evaluated as g/animal/day and g/kg/day, was unaffected by treatment at dose levels of 10, 30 and 100 mg/kg/day. Differences from the control group values were slight and were not statistically significant.

D. NECROPSY DATA

Individual Data: Table 17

At the scheduled euthanization on gestation day 12, no internal findings were noted at any dose level.

E. ORGAN WEIGHTS

Summary Data: Table 8

Individual Data: Table 18

None of the females in the 300 mg/kg/day group were gravid; therefore, organ weight data could not be assessed for this group. In the 100 mg/kg/day group, the mean liver weight was slightly reduced relative to the control group value. However, only two of the females in this group were gravid, making it difficult to establish a clear relationship to treatment. The mean kidney weight in this group was similar to the control group value.

In the 10 and 30 mg/kg/day groups, mean liver and kidney weights were similar to the control group values; differences were slight and were not statistically significant.

F. MICROSCOPIC EXAMINATION

Individual Data: Table 19

No treatment-related microscopic findings were noted in the kidneys and livers from females in the 300 mg/kg/day group. Findings observed in the 300 mg/kg/day group, including nonsuppurative inflammation in the liver and tubular mineralization and congestion in the kidneys, were noted infrequently and/or at a similar frequency in the control group.

G. GESTATION DAY 12 UTERINE EXAMINATION

Summary Data: Tables 9, 10

Individual Data: Tables 20, 21

Historical Control Data: Appendices B, C

None of the females in the 300 mg/kg/day group were gravid. In the 100 mg/kg/day group, three of five females were nongravid; this dose-related effect was attributed to treatment, as all females in the control, 10 and 30 mg/kg/day groups were gravid.

Pre-implantation loss in the 100 mg/kg/day group was increased relative to the control group value (78.2 percent per litter in the 100 mg/kg/day group [93.8 percent per litter in one dam, 62.5 percent per litter in the second dam], as compared to a control group value of 4.4 percent per litter). This resulted in reduced mean numbers of implantation sites and viable embryos in this group (2.0 implantation sites/dam [3 in one dam, 1 in the second dam] in the 100 mg/kg/day group, as compared to a mean value of 16.4 implantation sites/dam in the concurrent control group and a minimum mean value of 11.5 implantation sites/dam in the WIL historical control data; and 1.5 viable embryos/dam [3 in one dam, 0 in the second dam] in the 100 mg/kg/day group, as compared to a value of 16.0 viable embryos/dam in the concurrent control group and a minimum mean value of 10.7 viable embryos/dam in the WIL historical control data). A reduction in the mean number of corpora lutea was also observed in the 100 mg/kg/day group; this reduction was due to one of the two gravid females (no. 69483) in this group. Evaluation of postimplantation events could not be adequately assessed in this group based on the limited number of implantation sites in the group.

In the 10 and 30 mg/kg/day groups, intrauterine parameters (pre- and postimplantation losses, viable embryos and numbers of implantation sites and corpora lutea) were unaffected by treatment. Differences between the control and treated groups were slight and were not statistically significant.

## VI. DISCUSSION AND CONCLUSIONS

All females survived to the scheduled euthanization on gestation day 12. No treatment-related clinical signs were observed at any dose level.

None of the females in the 300 mg/kg/day group were gravid; therefore, body weight and food consumption data for this group could not be evaluated. Mean body weight gains in the two gravid 100 mg/kg/day group females were similar to the control group values during gestation days 0-1, 1-3, 3-7 and 7-9. Slight mean body weight losses were noted in this group during gestation days 9-11 and 11-12. In the 10 and 30 mg/kg/day groups, mean body weights and body weight gains were similar to the control group values throughout the study. Food consumption, evaluated as g/animal/day and g/kg/day, was unaffected by treatment at dose levels of 10, 30 and 100 mg/kg/day.

No treatment-related internal findings were noted during the macroscopic examination. Microscopic examinations of the livers and kidneys in the 300 mg/kg/day group revealed no treatment-related findings. Liver and kidney weights in the treated groups were generally similar to the control group values; no clear relationship to treatment was evident.

All of the females in the 300 mg/kg/day group and three of the females in the 100 mg/kg/day group were nongravid; this dose-related effect was attributed to treatment. In the 100 mg/kg/day group, pre-implantation loss was increased, and the mean number of implantation sites was reduced relative to the concurrent control group values and the respective values in the WIL historical control data. The mean number of viable embryos was also reduced in this group. In the 10 and 30 mg/kg/day groups, intrauterine parameters were unaffected by treatment.

In conclusion, maternal toxicity was expressed at a dose level of 100 mg/kg/day by slight mean body weight losses during the last three days of treatment. A toxic effect on pre-implantational events occurred in the 100 and 300 mg/kg/day groups, as evidenced by dose-related increases in the number of nongravid females (all females

in the 300 mg/kg/day group and three females in the 100 mg/kg/day group were nongravid) and an increase in pre-implantation loss (100 mg/kg/day group only).

Based on the results of this study, the no observed effect level (NOEL) was 30 mg/kg/day for maternal toxicity and embryonic development.

Donald G. Stump, Ph.D.
Study Director

11/12/97
Date

## VII. KEY STUDY PERSONNEL AND REPORT SUBMISSION

Key Personnel:

| | |
|---|---|
| Sally A. Keets, A.S. | Manager of Vivarium |
| Daniel W. Sved, Ph.D. | Director of Metabolism and Analytical Chemistry |
| Tammye L. Fleeman, B.S. | Group Supervisor of Gross Pathology and Developmental Toxicology Laboratory |

Report Prepared By:

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President, Director
Date

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VII. KEY STUDY PERSONNEL AND REPORT SUBMISSION (continued)

Approved and Submitted By:

Donald G. Stump

Donald G. Stump, Ph.D.
Staff Toxicologist, Developmental,
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11/12/97
Date

## VIII. QUALITY ASSURANCE UNIT STATEMENT

| Date(s) of Inspection(s) | Phase Inspected | Date(s) Findings Reported to Study Director | Date(s) Findings Reported to Management |
|---|---|---|---|
| 5/27, 29/97 | Cohabitation/ Confirmation of Breeding | 5/29/97 | 6/27/97 |
| 7/14-16, 25/97 | Study Records (I-1) | 7/25/97 | 8/29/97 |
| 7/16/97 | Study Records (N-1) | 7/25/97 | 8/29/97 |
| 8/6/97 | Study Records (H-1/P-1) | 8/6/97 | 9/30/97 |
| 7/23, 8/7,8/97 | Draft Report (without Histology) | 8/8/97 | 9/30/97 |
| 8/20/97 | Draft Report (Table 19) | 8/20/97 | 9/30/97 |

The study was conducted and inspected in general accordance with the United States Environmental Protection Agency (EPA) Good Laboratory Practice Regulations, the Standard Operating Procedures of WIL Research Laboratories, Inc., and the protocol as approved by the sponsor. Quality Assurance findings, derived from inspections during the conduct of the study and inspections of the raw data and the draft report, are documented and have been reported to the study director. A status report is submitted to management monthly.

The raw data, retention sample(s), if applicable, and the original final report will be stored in the Archives at WIL Research Laboratories, Inc.

Deborah L Little

Deborah L. Little
Manager of Quality Assurance

11/12/97
Date

## IX. REFERENCES


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A Study to Evaluate Early Embryonic Development in Rats

TABLES 1-21

PROJECT NO.:WIL-160079

TABLE 1
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
SUMMARY OF MATERNAL SURVIVAL AND PREGNANCY STATUS



| DOSE GROUP : | 1 | | 2 | | 3 | | 4 | | 5 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | NO. | % | NO. | % | NO. | % | NO. | % | NO. | % |
| FEMALES ON STUDY | 5 | | 5 | | 5 | | 5 | | 5 | |
| FEMALES THAT ABORTED OR DELIVERED | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| FEMALES THAT DIED | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| FEMALES THAT ABORTED | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| NONGRAVID | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| GRAVID | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| FEMALES THAT WERE EUTHANIZED | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| NONGRAVID | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| GRAVID | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| FEMALES EXAMINED AT SCHEDULED NECROPSY | 5 | 100.0 | 5 | 100.0 | 5 | 100.0 | 5 | 100.0 | 5 | 100.0 |
| NONGRAVID | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 3 | 60.0 | 5 | 100.0 |
| GRAVID | 5 | 100.0 | 5 | 100.0 | 5 | 100.0 | 2 | 40.0 | 0 | 0.0 |
| WITH RESORPTIONS ONLY | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 50.0 | 0 | 0.0 |
| WITH VIABLE FETUSES | 5 | 100.0 | 5 | 100.0 | 5 | 100.0 | 1 | 50.0 | 0 | 0.0 |
| TOTAL FEMALES GRAVID | 5 | 100.0 | 5 | 100.0 | 5 | 100.0 | 2 | 40.0 | 0 | 0.0 |

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 30 MG/KG/DAY 4- 100 MG/KG/DAY 5- 300 MG/KG/DAY

TABLE 2 (DAILY EXAMINATIONS)
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS



----- F E M A L E -----

| TABLE RANGE: | 05-28-97 TO 06-12-97 | | | | |
|---|---|---|---|---|---|
| GROUP: | 1 | 2 | 3 | 4 | 5 |
| NORMAL | | | | | |
| -NO SIGNIFICANT CLINICAL OBSERVATIONS | 64/ 5 | 65/ 5 | 61/ 5 | 59/ 5 | 60/ 5 |
| DISPOSITION | | | | | |
| -SENT TO LAB FOR SCHEDULED NECROPSY;GESTATION DAY 12 | 5/ 5 | 5/ 5 | 5/ 5 | 5/ 5 | 5/ 5 |
| BODY/INTEGUMENT | | | | | |
| -HAIR LOSS RIGHT FORELIMB | 0/ 0 | 0/ 0 | 0/ 0 | 6/ 1 | 0/ 0 |
| -HAIR LOSS LEFT FORELIMB | 0/ 0 | 0/ 0 | 0/ 0 | 6/ 1 | 0/ 0 |
| -HAIR LOSS RIGHT HINDLIMB | 0/ 0 | 0/ 0 | 4/ 1 | 0/ 0 | 0/ 0 |
| -RIGHT HINDLIMB RED AND SWOLLEN | 1/ 1 | 0/ 0 | 0/ 0 | 0/ 0 | 0/ 0 |
| CARDIO-PULMONARY | | | | | |
| -RALES | 0/ 0 | 0/ 0 | 0/ 0 | 0/ 0 | 4/ 1 |
| EYES/EARS/NOSE | | | | | |
| -RIGHT EYE EXOPHTHALMIC | 0/ 0 | 0/ 0 | 0/ 0 | 0/ 0 | 2/ 2 |
| -LEFT EYE EXOPHTHALMIC | 0/ 0 | 0/ 0 | 0/ 0 | 0/ 0 | 2/ 2 |
| EXCRETA | | | | | |
| -SOFT STOOL | 1/ 1 | 0/ 0 | 0/ 0 | 0/ 0 | 0/ 0 |

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 30 MG/KG/DAY 4- 100 MG/KG/DAY 5- 300 MG/KG/DAY

TABLE 3 (1-HOUR POST-DOSING)
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS



----- F E M A L E -----

| TABLE RANGE: | 05-28-97 TO 06-11-97 | | | | |
|---|---|---|---|---|---|
| GROUP: | 1 | 2 | 3 | 4 | 5 |
| EYES/EARS/NOSE | | | | | |
| -RIGHT EYE EXOPHTHALMIC | 0/ 0 | 0/ 0 | 0/ 0 | 0/ 0 | 2/ 1 |
| -LEFT EYE EXOPHTHALMIC | 0/ 0 | 0/ 0 | 0/ 0 | 0/ 0 | 2/ 1 |
| ORAL/DENTAL | | | | | |
| -WET CLEAR MATTING AROUND MOUTH | 0/ 0 | 0/ 0 | 0/ 0 | 0/ 0 | 1/ 1 |

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 30 MG/KG/DAY 4- 100 MG/KG/DAY 5- 300 MG/KG/DAY

PROJECT NO.:WIL-160079

TABLE 4
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
MEAN BODY WEIGHTS (GRAMS) DURING GESTATION



| GROUP : | | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| DAY 0 | MEAN | 244. | 253. | 248. | 246. | 0. |
| | S.D./N | 3.8/ 5 | 10.5/ 5 | 11.5/ 5 | 17.0/ 2 | 0.0/ 0 |
| DAY 1 | MEAN | 250. | 260. | 251. | 252. | 0. |
| | S.D./N | 2.8/ 5 | 11.4/ 5 | 17.2/ 5 | 12.0/ 2 | 0.0/ 0 |
| DAY 3 | MEAN | 256. | 270. | 258. | 261. | 0. |
| | S.D./N | 6.1/ 5 | 11.1/ 5 | 18.2/ 5 | 12.0/ 2 | 0.0/ 0 |
| DAY 7 | MEAN | 272. | 286. | 277. | 272. | 0. |
| | S.D./N | 6.2/ 5 | 18.1/ 5 | 16.7/ 5 | 12.7/ 2 | 0.0/ 0 |
| DAY 9 | MEAN | 278. | 293. | 284. | 277. | 0. |
| | S.D./N | 4.7/ 5 | 20.2/ 5 | 17.3/ 5 | 13.4/ 2 | 0.0/ 0 |
| DAY 11 | MEAN | 291. | 305. | 297. | 276. | 0. |
| | S.D./N | 7.1/ 5 | 23.7/ 5 | 20.1/ 5 | 9.2/ 2 | 0.0/ 0 |
| DAY 12 | MEAN | 298. | 310. | 302. | 274. | 0. |
| | S.D./N | 10.1/ 5 | 23.9/ 5 | 18.6/ 5 | 4.2/ 2 | 0.0/ 0 |

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 30 MG/KG/DAY 4- 100 MG/KG/DAY 5- 300 MG/KG/DAY
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING A TWO-TAILED DUNNETT'S TEST
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 5
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
MEAN BODY WEIGHT CHANGES (GRAMS) DURING GESTATION



| GROUP : | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| DAY 0- 1 MEAN | 6. | 7. | 2. | 6. | 0. |
| S.D./N | 2.4/ 5 | 3.3/ 5 | 8.2/ 5 | 4.9/ 2 | 0.0/ 0 |
| DAY 1- 3 MEAN | 6. | 10. | 7. | 9. | 0. |
| S.D./N | 4.6/ 5 | 1.5/ 5 | 6.4/ 5 | 0.0/ 2 | 0.0/ 0 |
| DAY 3- 7 MEAN | 16. | 16. | 19. | 12. | 0. |
| S.D./N | 2.3/ 5 | 9.7/ 5 | 5.5/ 5 | 0.7/ 2 | 0.0/ 0 |
| DAY 7- 9 MEAN | 6. | 8. | 7. | 5. | 0. |
| S.D./N | 5.3/ 5 | 4.2/ 5 | 4.1/ 5 | 0.7/ 2 | 0.0/ 0 |
| DAY 9- 11 MEAN | 13. | 12. | 13. | -1. | 0. |
| S.D./N | 8.0/ 5 | 6.4/ 5 | 4.8/ 5 | 4.2/ 2 | 0.0/ 0 |
| DAY 11- 12 MEAN | 7. | 4. | 5. | -2. | 0. |
| S.D./N | 6.1/ 5 | 1.9/ 5 | 3.4/ 5 | 4.9/ 2 | 0.0/ 0 |
| DAY 0- 12 MEAN | 54. | 57. | 54. | 28. | 0. |
| S.D./N | 7.0/ 5 | 18.6/ 5 | 8.2/ 5 | 12.7/ 2 | 0.0/ 0 |

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 30 MG/KG/DAY 4- 100 MG/KG/DAY 5- 300 MG/KG/DAY
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING A TWO-TAILED DUNNETT'S TEST
MEAN DIFFERENCES CALCULATED FROM INDIVIDUAL DIFFERENCES
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 6
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY)



| GROUP : | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| DAY 0- 1 MEAN | 20. | 21. | 18. | 21. | 0. |
| S.D./N | 2.1/ 5 | 2.4/ 5 | 5.0/ 5 | 0.0/ 2 | 0.0/ 0 |
| DAY 1- 3 MEAN | 20. | 23. | 19. | 21. | 0. |
| S.D./N | 2.2/ 5 | 2.7/ 5 | 3.7/ 5 | 0.0/ 2 | 0.0/ 0 |
| DAY 3- 7 MEAN | 21. | 23. | 23. | 22. | 0. |
| S.D./N | 1.2/ 5 | 3.9/ 5 | 1.8/ 5 | 0.7/ 2 | 0.0/ 0 |
| DAY 7- 9 MEAN | 21. | 24. | 24. | 21. | 0. |
| S.D./N | 1.5/ 5 | 2.7/ 5 | 5.8/ 5 | 1.4/ 2 | 0.0/ 0 |
| DAY 9- 11 MEAN | 23. | 25. | 24. | 20. | 0. |
| S.D./N | 1.3/ 5 | 4.5/ 5 | 2.1/ 5 | 0.7/ 2 | 0.0/ 0 |
| DAY 11- 12 MEAN | 24. | 24. | 23. | 29. | 0. |
| S.D./N | 2.0/ 5 | 4.6/ 5 | 2.8/ 5 | 15.6/ 2 | 0.0/ 0 |
| DAY 0- 12 MEAN | 21. | 23. | 22. | 22. | 0. |
| S.D./N | 0.9/ 5 | 3.4/ 5 | 2.8/ 5 | 0.7/ 2 | 0.0/ 0 |

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 30 MG/KG/DAY 4- 100 MG/KG/DAY 5- 300 MG/KG/DAY
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING A TWO-TAILED DUNNETT'S TEST
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

PROJECT NO.:WIL-160079

TABLE 7
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/KG/DAY)



| GROUP : | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| DAY 0- 1 MEAN | 79. | 83. | 72. | 85. | 0. |
| S.D./N | 8.6/ 5 | 9.6/ 5 | 15.7/ 5 | 4.9/ 2 | 0.0/ 0 |
| DAY 1- 3 MEAN | 78. | 85. | 74. | 82. | 0. |
| S.D./N | 8.1/ 5 | 7.8/ 5 | 10.6/ 5 | 4.2/ 2 | 0.0/ 0 |
| DAY 3- 7 MEAN | 80. | 82. | 85. | 81. | 0. |
| S.D./N | 3.6/ 5 | 11.3/ 5 | 3.1/ 5 | 0.7/ 2 | 0.0/ 0 |
| DAY 7- 9 MEAN | 78. | 83. | 84. | 76. | 0. |
| S.D./N | 5.1/ 5 | 4.3/ 5 | 15.7/ 5 | 1.4/ 2 | 0.0/ 0 |
| DAY 9- 11 MEAN | 80. | 83. | 81. | 71. | 0. |
| S.D./N | 4.2/ 5 | 9.9/ 5 | 2.1/ 5 | 5.7/ 2 | 0.0/ 0 |
| DAY 11- 12 MEAN | 81. | 76. | 78. | 106. | 0. |
| S.D./N | 6.5/ 5 | 10.8/ 5 | 6.6/ 5 | 59.4/ 2 | 0.0/ 0 |
| DAY 0- 12 MEAN | 79. | 83. | 81. | 82. | 0. |
| S.D./N | 2.9/ 5 | 8.6/ 5 | 5.3/ 5 | 6.4/ 2 | 0.0/ 0 |

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 30 MG/KG/DAY 4- 100 MG/KG/DAY 5- 300 MG/KG/DAY
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING A TWO-TAILED DUNNETT'S TEST
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

PROJECT NO.:WIL-160079

TABLE 8
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
ORGAN WEIGHTS (GRAMS) - SUMMARY OF MEANS



| | | ----- F E M A L E ----- | | | | |
|---|---|---|---|---|---|---|
| GROUP: | | 0 MG/KG/DAY | 10 MG/KG/DAY | 30 MG/KG/DAY | 100 MG/KG/DAY | 300 MG/KG/DAY |
| KIDNEYS | | | | | | |
| | MEAN | 2.33 | 2.45 | 2.46 | 2.17 | NA |
| | S.D. | 0.161 | 0.218 | 0.107 | 0.049 | |
| | N | 5 | 5 | 5 | 2 | |
| LIVER | | | | | | |
| | MEAN | 13.69 | 13.65 | 13.20 | 11.65 | NA |
| | S.D. | 1.145 | 2.467 | 1.127 | 0.028 | |
| | N | 5 | 5 | 5 | 2 | |

NONE SIGNIFICANTLY DIFFERENT USING DUNNETT'S TEST
NA = NOT APPLICABLE
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

PROJECT NO.:WIL-160079

TABLE 9
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
SUMMARY OF MEAN FETAL DATA AT THE SCHEDULED NECROPSY



| GROUP | | VIABLE FETUSES | DEAD FETUSES | RESORPTIONS EARLY | RESORPTIONS LATE | POST IMPLANTATION LOSS | IMPLANTATION SITES | CORPORA LUTEA | PRE IMPLANTATION LOSS | NO. OF GRAVID FEMALES |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | TOTAL | 80 | 0 | 2 | 0 | 2 | 82 | 86 | 4 | 5 |
| | MEAN | 16.0 | 0.0 | 0.4 | 0.0 | 0.4 | 16.4 | 17.2 | 0.8 | |
| | S.D. | 2.00 | 0.00 | 0.55 | 0.00 | 0.55 | 1.95 | 2.28 | 0.84 | |
| 2 | TOTAL | 79 | 0 | 0 | 0 | 0 | 79 | 88 | 9 | 5 |
| | MEAN | 15.8 | 0.0 | 0.0 | 0.0 | 0.0 | 15.8 | 17.6 | 1.8 | |
| | S.D. | 1.30 | 0.00 | 0.00 | 0.00 | 0.00 | 1.30 | 2.70 | 1.64 | |
| 3 | TOTAL | 73 | 0 | 0 | 0 | 0 | 73 | 80 | 7 | 5 |
| | MEAN | 14.6 | 0.0 | 0.0 | 0.0 | 0.0 | 14.6 | 16.0 | 1.4 | |
| | S.D. | 4.16 | 0.00 | 0.00 | 0.00 | 0.00 | 4.16 | 4.64 | 2.07 | |
| 4 | TOTAL | 3 | 0 | 1 | 0 | 1 | 4 | 24 | 20 | 2 |
| | MEAN | 1.5 | 0.0 | 0.5 | 0.0 | 0.5 | 2.0 | 12.0 | 10.0 | |
| | S.D. | 2.12 | 0.00 | 0.71 | 0.00 | 0.71 | 1.41 | 5.66 | 7.07 | |
| 5 | THERE WERE NO GRAVID DAMS IN THIS GROUP | | | | | | | | | |

NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP

MEAN NUMBERS OF VIABLE FETUSES, CORPORA LUTEA AND IMPLANTATION SITES COMPARED USING DUNNETT'S TEST

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 30 MG/KG/DAY 4- 100 MG/KG/DAY 5- 300 MG/KG/DAY

PROJECT NO.:WIL-160079

TABLE 10
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
SUMMARY OF MEAN FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)



| GROUP NUMBER: | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| CORPORA LUTEA | | | | | |
| MEAN | 17.2 | 17.6 | 16.0 | 12.0 | NA |
| S.D. | 2.28 | 2.70 | 4.64 | 5.66 | |
| N | 5 | 5 | 5 | 2 | |
| IMPLANTATION SITES | | | | | |
| MEAN | 16.4 | 15.8 | 14.6 | 2.0 | NA |
| S.D. | 1.95 | 1.30 | 4.16 | 1.41 | |
| N | 5 | 5 | 5 | 2 | |
| VIABLE FETUSES (%) | | | | | |
| MEAN | 97.5 | 100.0 | 100.0 | 50.0 | NA |
| S.D. | 3.45 | 0.00 | 0.00 | 70.71 | |
| N | 5 | 5 | 5 | 2 | |
| DEAD FETUSES (%) | | | | | |
| MEAN | 0.0 | 0.0 | 0.0 | 0.0 | NA |
| S.D. | 0.00 | 0.00 | 0.00 | 0.00 | |
| N | 5 | 5 | 5 | 2 | |
| EARLY RESORPTIONS (%) | | | | | |
| MEAN | 2.5 | 0.0 | 0.0 | 50.0 | NA |
| S.D. | 3.45 | 0.00 | 0.00 | 70.71 | |
| N | 5 | 5 | 5 | 2 | |
| LATE RESORPTIONS (%) | | | | | |
| MEAN | 0.0 | 0.0 | 0.0 | 0.0 | NA |
| S.D. | 0.00 | 0.00 | 0.00 | 0.00 | |
| N | 5 | 5 | 5 | 2 | |

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 30 MG/KG/DAY 4- 100 MG/KG/DAY 5- 300 MG/KG/DAY

PROPORTIONAL (%) DATA COMPARED USING THE KRUSKAL-WALLIS TEST
CORPORA LUTEA AND IMPLANTATION SITES COMPARED USING DUNNETT'S TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP
NA = THERE WERE NO GRAVID DAMS IN THIS GROUP

PROJECT NO.:WIL-160079

TABLE 10
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
SUMMARY OF MEAN FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)



| GROUP NUMBER: | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| TOTAL RESORPTIONS (%) | | | | | |
| MEAN | 2.5 | 0.0 | 0.0 | 50.0 | NA |
| S.D. | 3.45 | 0.00 | 0.00 | 70.71 | |
| N | 5 | 5 | 5 | 2 | |
| PRE-IMPLANTATION LOSS (%) | | | | | |
| MEAN | 4.4 | 9.4 | 8.2 | 78.2 | NA |
| S.D. | 4.52 | 7.81 | 10.43 | 22.13 | |
| N | 5 | 5 | 5 | 2 | |
| POST-IMPLANTATION LOSS (%) | | | | | |
| MEAN | 2.5 | 0.0 | 0.0 | 50.0 | NA |
| S.D. | 3.45 | 0.00 | 0.00 | 70.71 | |
| N | 5 | 5 | 5 | 2 | |

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 30 MG/KG/DAY 4- 100 MG/KG/DAY 5- 300 MG/KG/DAY

PROPORTIONAL (%) DATA COMPARED USING THE KRUSKAL-WALLIS TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP
NA = THERE WERE NO GRAVID DAMS IN THIS GROUP

TABLE 11 (DAILY EXAMINATIONS)
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL CLINICAL OBSERVATIONS



| OBSERVATION | ANIMAL | GROUP | GESTATIONAL DAY 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NO SIGNIFICANT CLINICAL OBSERVATIONS | 69467 | 1 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69469 | 1 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69476 | 1 | P | P | P | P | P | P | P | P | P | P | P | P | |
| | 69493 | 1 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69472 | 1 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69480 | 2 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69471 | 2 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69478 | 2 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69465 | 2 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69477 | 2 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69487 | 3 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69473 | 3 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69482 | 3 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69466 | 3 | P | P | P | P | P | P | P | P | P | | | | |
| | 69479 | 3 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69492 | 4 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69474 | 4 | P | P | P | P | P | P | P | | | | | | |
| | 69486 | 4 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69468 | 4 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69483 | 4 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69464 | 5 | P | P | P | P | P | P | | P | P | P | P | P | P |
| | 69475 | 5 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69490 | 5 | P | P | | P | P | P | P | | | | P | P | P |
| | 69470 | 5 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| | 69484 | 5 | P | P | P | P | P | P | P | P | P | P | P | P | P |
| SENT TO LAB FOR SCHEDULED NECROPSY;GESTATION DAY 12 | 69467 | 1 | | | | | | | | | | | | | P |

GRADE CODE: P = PRESENT 1 = SLIGHT 2 = MODERATE 3 = SEVERE

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 30 MG/KG/DAY 4- 100 MG/KG/DAY 5- 300 MG/KG/DAY

TABLE 11 (DAILY EXAMINATIONS)
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL CLINICAL OBSERVATIONS



| OBSERVATION | ANIMAL | GROUP | GESTATIONAL DAY 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 1 0 | 1 1 | 1 2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SENT TO LAB FOR SCHEDULED NECROPSY;GESTATION DAY 12 | 69469 | 1 | | | | | | | | | | | | | P |
| | 69476 | 1 | | | | | | | | | | | | | P |
| | 69493 | 1 | | | | | | | | | | | | | P |
| | 69472 | 1 | | | | | | | | | | | | | P |
| | 69480 | 2 | | | | | | | | | | | | | P |
| | 69471 | 2 | | | | | | | | | | | | | P |
| | 69478 | 2 | | | | | | | | | | | | | P |
| | 69465 | 2 | | | | | | | | | | | | | P |
| | 69477 | 2 | | | | | | | | | | | | | P |
| | 69487 | 3 | | | | | | | | | | | | | P |
| | 69473 | 3 | | | | | | | | | | | | | P |
| | 69482 | 3 | | | | | | | | | | | | | P |
| | 69466 | 3 | | | | | | | | | | | | | P |
| | 69479 | 3 | | | | | | | | | | | | | P |
| | 69492 | 4 | | | | | | | | | | | | | P |
| | 69474 | 4 | | | | | | | | | | | | | P |
| | 69486 | 4 | | | | | | | | | | | | | P |
| | 69468 | 4 | | | | | | | | | | | | | P |
| | 69483 | 4 | | | | | | | | | | | | | P |
| | 69464 | 5 | | | | | | | | | | | | | P |
| | 69475 | 5 | | | | | | | | | | | | | P |
| | 69490 | 5 | | | | | | | | | | | | | P |
| | 69470 | 5 | | | | | | | | | | | | | P |
| | 69484 | 5 | | | | | | | | | | | | | P |
| HAIR LOSS RIGHT FORELIMB | 69474 | 4 | | | | | | | 1 | 2 | 2 | 1 | 1 | 1 | |
| HAIR LOSS LEFT FORELIMB | 69474 | 4 | | | | | | | 1 | 2 | 2 | 1 | 1 | 1 | |

GRADE CODE: P = PRESENT 1 = SLIGHT 2 = MODERATE 3 = SEVERE

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 30 MG/KG/DAY 4- 100 MG/KG/DAY 5- 300 MG/KG/DAY

TABLE 11 (DAILY EXAMINATIONS)
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL CLINICAL OBSERVATIONS



| OBSERVATION | ANIMAL | GROUP | GESTATIONAL DAY 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HAIR LOSS RIGHT HINDLIMB | 69466 | 3 | | | | | | | | | | 1 | 1 | 1 | 1 |
| RIGHT HINDLIMB RED AND SWOLLEN | 69476 | 1 | | | | | | | | | | | | | P |
| RALES | 69490 | 5 | | | P | | | | | P | P | P | | | |
| RIGHT EYE EXOPHTHALMIC | 69464 | 5 | | | | | | | P | | | | | | |
| | 69490 | 5 | | | | | | | | P | | | | | |
| LEFT EYE EXOPHTHALMIC | 69464 | 5 | | | | | | | P | | | | | | |
| | 69490 | 5 | | | | | | | | P | | | | | |
| SOFT STOOL | 69476 | 1 | | | | | | | | | | | | | P |

GRADE CODE: P = PRESENT 1 = SLIGHT 2 = MODERATE 3 = SEVERE

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 30 MG/KG/DAY 4- 100 MG/KG/DAY 5- 300 MG/KG/DAY

PROJECT NO.:WIL-160079

TABLE 12 (1-HOUR POST-DOSING)
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL CLINICAL OBSERVATIONS



| OBSERVATION | ANIMAL | GROUP | GESTATIONAL DAY 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RIGHT EYE EXOPHTHALMIC | 69464 | 5 | | | | P | P | | | | | | | | |
| LEFT EYE EXOPHTHALMIC | 69464 | 5 | | | | P | P | | | | | | | | |
| WET CLEAR MATTING AROUND MOUTH | 69464 | 5 | | | | | | | 1 | | | | | | |

GRADE CODE: P = PRESENT 1 = SLIGHT 2 = MODERATE 3 = SEVERE

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 30 MG/KG/DAY 4- 100 MG/KG/DAY 5- 300 MG/KG/DAY

TABLE 13
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL BODY WEIGHTS (GRAMS) DURING GESTATION



| PREGNANCY STATUS | DAY 0 | 1 | 3 | 7 | 9 | 11 | 12 | |
|---|---|---|---|---|---|---|---|---|
| DAMS FROM GROUP 1: 0 MG/KG/DAY | | | | | | | | |
| 69467 G | 244. | 247. | 256. | 275. | 284. | 287. | 302. | SCHEDULED NECROPSY DAY 12 |
| 69469 G | 247. | 252. | 264. | 278. | 278. | 300. | 309. | SCHEDULED NECROPSY DAY 12 |
| 69476 G | 241. | 250. | 257. | 275. | 275. | 282. | 285. | SCHEDULED NECROPSY DAY 12 |
| 69493 G | 249. | 253. | 257. | 271. | 281. | 296. | 304. | SCHEDULED NECROPSY DAY 12 |
| 69472 G | 240. | 247. | 247. | 262. | 272. | 291. | 290. | SCHEDULED NECROPSY DAY 12 |
| MEAN | 244. | 250. | 256. | 272. | 278. | 291. | 298. | |
| S.D. | 3.8 | 2.8 | 6.1 | 6.2 | 4.7 | 7.1 | 10.1 | |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 13
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL BODY WEIGHTS (GRAMS) DURING GESTATION



| PREGNANCY STATUS | DAY 0 | 1 | 3 | 7 | 9 | 11 | 12 | |
|---|---|---|---|---|---|---|---|---|
| DAMS FROM GROUP 2: 10 MG/KG/DAY | | | | | | | | |
| 69480 G | 250. | 252. | 260. | 272. | 276. | 286. | 291. | SCHEDULED NECROPSY DAY 12 |
| 69471 G | 242. | 251. | 263. | 285. | 288. | 308. | 309. | SCHEDULED NECROPSY DAY 12 |
| 69478 G | 246. | 253. | 263. | 264. | 274. | 278. | 283. | SCHEDULED NECROPSY DAY 12 |
| 69465 G | 268. | 275. | 284. | 301. | 310. | 319. | 325. | SCHEDULED NECROPSY DAY 12 |
| 69477 G | 259. | 270. | 280. | 306. | 319. | 336. | 341. | SCHEDULED NECROPSY DAY 12 |
| MEAN | 253. | 260. | 270. | 286. | 293. | 305. | 310. | |
| S.D. | 10.5 | 11.4 | 11.1 | 18.1 | 20.2 | 23.7 | 23.9 | |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 13
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL BODY WEIGHTS (GRAMS) DURING GESTATION



| PREGNANCY STATUS | DAY 0 | 1 | 3 | 7 | 9 | 11 | 12 | |
|---|---|---|---|---|---|---|---|---|
| DAMS FROM GROUP 3: 30 MG/KG/DAY | | | | | | | | |
| 69487 G | 247. | 247. | 244. | 271. | 278. | 283. | 294. | SCHEDULED NECROPSY DAY 12 |
| 69473 G | 240. | 229. | 243. | 260. | 270. | 283. | 287. | SCHEDULED NECROPSY DAY 12 |
| 69482 G | 266. | 275. | 285. | 304. | 311. | 329. | 333. | SCHEDULED NECROPSY DAY 12 |
| 69466 G | 252. | 259. | 268. | 280. | 290. | 304. | 306. | SCHEDULED NECROPSY DAY 12 |
| 69479 G | 237. | 244. | 249. | 270. | 270. | 285. | 291. | SCHEDULED NECROPSY DAY 12 |
| MEAN | 248. | 251. | 258. | 277. | 284. | 297. | 302. | |
| S.D. | 11.5 | 17.2 | 18.2 | 16.7 | 17.3 | 20.1 | 18.6 | |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 13
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL BODY WEIGHTS (GRAMS) DURING GESTATION



DAMS FROM GROUP 4: 100 MG/KG/DAY

| | PREGNANCY STATUS | DAY 0 | 1 | 3 | 7 | 9 | 11 | 12 | |
|---|---|---|---|---|---|---|---|---|---|
| 69492 | G | 258. | 260. | 269. | 281. | 286. | 282. | 277. | SCHEDULED NECROPSY DAY 12 |
| 69474 | NG | 242. | 247. | 264. | 282. | 286. | 292. | 279. | SCHEDULED NECROPSY DAY 12 |
| 69486 | NG | 255. | 254. | 268. | 282. | 289. | 295. | 300. | SCHEDULED NECROPSY DAY 12 |
| 69468 | NG | 255. | 264. | 274. | 292. | 299. | 305. | 307. | SCHEDULED NECROPSY DAY 12 |
| 69483 | G | 234. | 243. | 252. | 263. | 267. | 269. | 271. | SCHEDULED NECROPSY DAY 12 |
| MEAN | | 246. | 252. | 261. | 272. | 277. | 276. | 274. | |
| S.D. | | 17.0 | 12.0 | 12.0 | 12.7 | 13.4 | 9.2 | 4.2 | |
| N | | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 13
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL BODY WEIGHTS (GRAMS) DURING GESTATION



| | PREGNANCY STATUS | DAY 0 | 1 | 3 | 7 | 9 | 11 | 12 | |
|---|---|---|---|---|---|---|---|---|---|
| DAMS FROM GROUP 5: 300 MG/KG/DAY | | | | | | | | | |
| 69464 | NG | 249. | 254. | 272. | 284. | 289. | 294. | 297. | SCHEDULED NECROPSY DAY 12 |
| 69475 | NG | 264. | 264. | 276. | 287. | 285. | 304. | 300. | SCHEDULED NECROPSY DAY 12 |
| 69490 | NG | 263. | 247. | 264. | 255. | 257. | 272. | 268. | SCHEDULED NECROPSY DAY 12 |
| 69470 | NG | 253. | 248. | 257. | 268. | 265. | 268. | 244. | SCHEDULED NECROPSY DAY 12 |
| 69484 | NG | 228. | 232. | 234. | 240. | 242. | 245. | 249. | SCHEDULED NECROPSY DAY 12 |
| MEAN | | 0. | 0. | 0. | 0. | 0. | 0. | 0. | |
| S.D. | | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | |
| N | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 14
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL BODY WEIGHT CHANGES (GRAMS) DURING GESTATION



| PREGNANCY STATUS | | DAY 0- 1 | 1- 3 | 3- 7 | 7- 9 | 9-11 | 11-12 | 0-12 | |
|---|---|---|---|---|---|---|---|---|---|
| DAMS FROM GROUP 1: 0 MG/KG/DAY | | | | | | | | | |
| 69467 | G | 3. | 9. | 19. | 9. | 3. | 15. | 58. | SCHEDULED NECROPSY DAY 12 |
| 69469 | G | 5. | 12. | 14. | 0. | 22. | 9. | 62. | SCHEDULED NECROPSY DAY 12 |
| 69476 | G | 9. | 7. | 18. | 0. | 7. | 3. | 44. | SCHEDULED NECROPSY DAY 12 |
| 69493 | G | 4. | 4. | 14. | 10. | 15. | 8. | 55. | SCHEDULED NECROPSY DAY 12 |
| 69472 | G | 7. | 0. | 15. | 10. | 19. | -1. | 50. | SCHEDULED NECROPSY DAY 12 |
| MEAN | | 6. | 6. | 16. | 6. | 13. | 7. | 54. | |
| S.D. | | 2.4 | 4.6 | 2.3 | 5.3 | 8.0 | 6.1 | 7.0 | |
| N | | 5 | 5 | 5 | 5 | 5 | 5 | 5 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 14
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL BODY WEIGHT CHANGES (GRAMS) DURING GESTATION



| PREGNANCY STATUS | | DAY 0- 1 | 1- 3 | 3- 7 | 7- 9 | 9-11 | 11-12 | 0-12 | |
|---|---|---|---|---|---|---|---|---|---|
| DAMS FROM GROUP 2: 10 MG/KG/DAY | | | | | | | | | |
| 69480 | G | 2. | 8. | 12. | 4. | 10. | 5. | 41. | SCHEDULED NECROPSY DAY 12 |
| 69471 | G | 9. | 12. | 22. | 3. | 20. | 1. | 67. | SCHEDULED NECROPSY DAY 12 |
| 69478 | G | 7. | 10. | 1. | 10. | 4. | 5. | 37. | SCHEDULED NECROPSY DAY 12 |
| 69465 | G | 7. | 9. | 17. | 9. | 9. | 6. | 57. | SCHEDULED NECROPSY DAY 12 |
| 69477 | G | 11. | 10. | 26. | 13. | 17. | 5. | 82. | SCHEDULED NECROPSY DAY 12 |
| MEAN | | 7. | 10. | 16. | 8. | 12. | 4. | 57. | |
| S.D. | | 3.3 | 1.5 | 9.7 | 4.2 | 6.4 | 1.9 | 18.6 | |
| N | | 5 | 5 | 5 | 5 | 5 | 5 | 5 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 14
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL BODY WEIGHT CHANGES (GRAMS) DURING GESTATION



| | PREGNANCY STATUS | DAY 0- 1 | 1- 3 | 3- 7 | 7- 9 | 9-11 | 11-12 | 0-12 | |
|---|---|---|---|---|---|---|---|---|---|
| DAMS FROM GROUP 3: 30 MG/KG/DAY | | | | | | | | | |
| 69487 | G | 0. | -3. | 27. | 7. | 5. | 11. | 47. | SCHEDULED NECROPSY DAY 12 |
| 69473 | G | -11. | 14. | 17. | 10. | 13. | 4. | 47. | SCHEDULED NECROPSY DAY 12 |
| 69482 | G | 9. | 10. | 19. | 7. | 18. | 4. | 67. | SCHEDULED NECROPSY DAY 12 |
| 69466 | G | 7. | 9. | 12. | 10. | 14. | 2. | 54. | SCHEDULED NECROPSY DAY 12 |
| 69479 | G | 7. | 5. | 21. | 0. | 15. | 6. | 54. | SCHEDULED NECROPSY DAY 12 |
| MEAN | | 2. | 7. | 19. | 7. | 13. | 5. | 54. | |
| S.D. | | 8.2 | 6.4 | 5.5 | 4.1 | 4.8 | 3.4 | 8.2 | |
| N | | 5 | 5 | 5 | 5 | 5 | 5 | 5 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 14
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL BODY WEIGHT CHANGES (GRAMS) DURING GESTATION



DAMS FROM GROUP 4: 100 MG/KG/DAY

| | PREGNANCY STATUS | DAY 0- 1 | 1- 3 | 3- 7 | 7- 9 | 9-11 | 11-12 | 0-12 | |
|---|---|---|---|---|---|---|---|---|---|
| 69492 | G | 2. | 9. | 12. | 5. | -4. | -5. | 19. | SCHEDULED NECROPSY DAY 12 |
| 69474 | NG | 5. | 17. | 18. | 4. | 6. | -13. | 37. | SCHEDULED NECROPSY DAY 12 |
| 69486 | NG | -1. | 14. | 14. | 7. | 6. | 5. | 45. | SCHEDULED NECROPSY DAY 12 |
| 69468 | NG | 9. | 10. | 18. | 7. | 6. | 2. | 52. | SCHEDULED NECROPSY DAY 12 |
| 69483 | G | 9. | 9. | 11. | 4. | 2. | 2. | 37. | SCHEDULED NECROPSY DAY 12 |
| MEAN | | 6. | 9. | 12. | 5. | -1. | -2. | 28. | |
| S.D. | | 4.9 | 0.0 | 0.7 | 0.7 | 4.2 | 4.9 | 12.7 | |
| N | | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 14
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL BODY WEIGHT CHANGES (GRAMS) DURING GESTATION



| | PREGNANCY STATUS | DAY 0- 1 | 1- 3 | 3- 7 | 7- 9 | 9-11 | 11-12 | 0-12 | |
|---|---|---|---|---|---|---|---|---|---|
| DAMS FROM GROUP 5: 300 MG/KG/DAY | | | | | | | | | |
| 69464 | NG | 5. | 18. | 12. | 5. | 5. | 3. | 48. | SCHEDULED NECROPSY DAY 12 |
| 69475 | NG | 0. | 12. | 11. | -2. | 19. | -4. | 36. | SCHEDULED NECROPSY DAY 12 |
| 69490 | NG | -16. | 17. | -9. | 2. | 15. | -4. | 5. | SCHEDULED NECROPSY DAY 12 |
| 69470 | NG | -5. | 9. | 11. | -3. | 3. | -24. | -9. | SCHEDULED NECROPSY DAY 12 |
| 69484 | NG | 4. | 2. | 6. | 2. | 3. | 4. | 21. | SCHEDULED NECROPSY DAY 12 |
| MEAN | | 0. | 0. | 0. | 0. | 0. | 0. | 0. | |
| S.D. | | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | |
| N | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 15
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY)



| PREGNANCY STATUS | DAY | 0- 1 | 1- 3 | 3- 7 | 7- 9 | 9-11 | 11-12 | 0-12 | |
|---|---|---|---|---|---|---|---|---|---|
| DAMS FROM GROUP 1: 0 MG/KG/DAY | | | | | | | | | |
| 69467 | G | 17. | 22. | 22. | 23. | 21. | 24. | 22. | SCHEDULED NECROPSY DAY 12 |
| 69469 | G | 20. | 21. | 21. | 20. | 24. | 27. | 22. | SCHEDULED NECROPSY DAY 12 |
| 69476 | G | 22. | 21. | 22. | 20. | 22. | 24. | 22. | SCHEDULED NECROPSY DAY 12 |
| 69493 | G | 18. | 17. | 21. | 23. | 24. | 22. | 21. | SCHEDULED NECROPSY DAY 12 |
| 69472 | G | 21. | 18. | 19. | 21. | 23. | 22. | 20. | SCHEDULED NECROPSY DAY 12 |
| MEAN | | 20. | 20. | 21. | 21. | 23. | 24. | 21. | |
| S.D. | | 2.1 | 2.2 | 1.2 | 1.5 | 1.3 | 2.0 | 0.9 | |
| N | | 5 | 5 | 5 | 5 | 5 | 5 | 5 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 15

A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS

INDIVIDUAL FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY)



| PREGNANCY STATUS | DAY 0- 1 | 1- 3 | 3- 7 | 7- 9 | 9-11 | 11-12 | 0-12 | |
|---|---|---|---|---|---|---|---|---|
| DAMS FROM GROUP 2: 10 MG/KG/DAY | | | | | | | | |
| 69480 G | 18. | 20. | 20. | 21. | 21. | 20. | 20. | SCHEDULED NECROPSY DAY 12 |
| 69471 G | 23. | 22. | 26. | 24. | 27. | 28. | 25. | SCHEDULED NECROPSY DAY 12 |
| 69478 G | 21. | 21. | 18. | 22. | 20. | 18. | 20. | SCHEDULED NECROPSY DAY 12 |
| 69465 G | 20. | 23. | 24. | 25. | 26. | 24. | 24. | SCHEDULED NECROPSY DAY 12 |
| 69477 G | 24. | 27. | 27. | 28. | 31. | 28. | 28. | SCHEDULED NECROPSY DAY 12 |
| MEAN | 21. | 23. | 23. | 24. | 25. | 24. | 23. | |
| S.D. | 2.4 | 2.7 | 3.9 | 2.7 | 4.5 | 4.6 | 3.4 | |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 15
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY)



| | PREGNANCY STATUS | DAY 0- 1 | 1- 3 | 3- 7 | 7- 9 | 9-11 | 11-12 | 0-12 | |
|---|---|---|---|---|---|---|---|---|---|
| DAMS FROM GROUP 3: 30 MG/KG/DAY | | | | | | | | | |
| 69487 | G | 16. | 14. | 22. | 24. | 23. | 22. | 21. | SCHEDULED NECROPSY DAY 12 |
| 69473 | G | 12. | 17. | 22. | 22. | 22. | 24. | 21. | SCHEDULED NECROPSY DAY 12 |
| 69482 | G | 25. | 23. | 26. | 33. | 27. | 28. | 27. | SCHEDULED NECROPSY DAY 12 |
| 69466 | G | 21. | 22. | 22. | 23. | 24. | 21. | 22. | SCHEDULED NECROPSY DAY 12 |
| 69479 | G | 17. | 19. | 22. | 17. | 22. | 22. | 20. | SCHEDULED NECROPSY DAY 12 |
| MEAN | | 18. | 19. | 23. | 24. | 24. | 23. | 22. | |
| S.D. | | 5.0 | 3.7 | 1.8 | 5.8 | 2.1 | 2.8 | 2.8 | |
| N | | 5 | 5 | 5 | 5 | 5 | 5 | 5 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 15
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY)



| PREGNANCY STATUS | DAY | 0- 1 | 1- 3 | 3- 7 | 7- 9 | 9-11 | 11-12 | 0-12 | |
|---|---|---|---|---|---|---|---|---|---|
| DAMS FROM GROUP 4: 100 MG/KG/DAY | | | | | | | | | |
| 69492 | G | 21. | 21. | 22. | 22. | 19. | 18. | 21. | SCHEDULED NECROPSY DAY 12 |
| 69474 | NG | 18. | 21. | 22. | 21. | 20. | 16. | 21. | SCHEDULED NECROPSY DAY 12 |
| 69486 | NG | 19. | 21. | 37. | 23. | 19. | 35. | 27. | SCHEDULED NECROPSY DAY 12 |
| 69468 | NG | 23. | 24. | 25. | 24. | 23. | 22. | 24. | SCHEDULED NECROPSY DAY 12 |
| 69483 | G | 21. | 21. | 21. | 20. | 20. | 40. | 22. | SCHEDULED NECROPSY DAY 12 |
| MEAN | | 21. | 21. | 22. | 21. | 20. | 29. | 22. | |
| S.D. | | 0.0 | 0.0 | 0.7 | 1.4 | 0.7 | 15.6 | 0.7 | |
| N | | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 15
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY)



| PREGNANCY STATUS | DAY 0- 1 | 1- 3 | 3- 7 | 7- 9 | 9-11 | 11-12 | 0-12 | |
|---|---|---|---|---|---|---|---|---|
| DAMS FROM GROUP 5: 300 MG/KG/DAY | | | | | | | | |
| 69464 NG | 19. | 24. | 25. | 26. | 23. | 28. | 24. | SCHEDULED NECROPSY DAY 12 |
| 69475 NG | 17. | 21. | 22. | 22. | 24. | 24. | 22. | SCHEDULED NECROPSY DAY 12 |
| 69490 NG | 9. | 16. | 17. | 16. | 21. | 28. | 17. | SCHEDULED NECROPSY DAY 12 |
| 69470 NG | 14. | 17. | 18. | 19. | 19. | 2. | 16. | SCHEDULED NECROPSY DAY 12 |
| 69484 NG | 16. | 15. | 18. | 18. | 18. | 17. | 17. | SCHEDULED NECROPSY DAY 12 |
| MEAN | 0. | 0. | 0. | 0. | 0. | 0. | 0. | |
| S.D. | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | |
| N | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 16
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FOOD CONSUMPTION DURING GESTATION (GRAMS/KG/DAY)



| PREGNANCY STATUS | DAY | 0- 1 | 1- 3 | 3- 7 | 7- 9 | 9-11 | 11-12 | 0-12 | |
|---|---|---|---|---|---|---|---|---|---|
| DAMS FROM GROUP 1: 0 MG/KG/DAY | | | | | | | | | |
| 69467 | G | 69. | 87. | 83. | 82. | 73. | 81. | 81. | SCHEDULED NECROPSY DAY 12 |
| 69469 | G | 80. | 81. | 77. | 72. | 83. | 89. | 80. | SCHEDULED NECROPSY DAY 12 |
| 69476 | G | 89. | 83. | 83. | 73. | 79. | 85. | 83. | SCHEDULED NECROPSY DAY 12 |
| 69493 | G | 72. | 67. | 80. | 83. | 83. | 73. | 77. | SCHEDULED NECROPSY DAY 12 |
| 69472 | G | 86. | 73. | 75. | 79. | 82. | 76. | 76. | SCHEDULED NECROPSY DAY 12 |
| MEAN | | 79. | 78. | 80. | 78. | 80. | 81. | 79. | |
| S.D. | | 8.6 | 8.1 | 3.6 | 5.1 | 4.2 | 6.5 | 2.9 | |
| N | | 5 | 5 | 5 | 5 | 5 | 5 | 5 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 16
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FOOD CONSUMPTION DURING GESTATION (GRAMS/KG/DAY)



| PREGNANCY STATUS | DAY | 0- 1 | 1- 3 | 3- 7 | 7- 9 | 9-11 | 11-12 | 0-12 | |
|---|---|---|---|---|---|---|---|---|---|
| DAMS FROM GROUP 2: 10 MG/KG/DAY | | | | | | | | | |
| 69480 | G | 72. | 78. | 75. | 77. | 75. | 69. | 74. | SCHEDULED NECROPSY DAY 12 |
| 69471 | G | 93. | 86. | 95. | 84. | 91. | 91. | 90. | SCHEDULED NECROPSY DAY 12 |
| 69478 | G | 84. | 81. | 68. | 82. | 72. | 64. | 75. | SCHEDULED NECROPSY DAY 12 |
| 69465 | G | 74. | 82. | 82. | 82. | 83. | 75. | 81. | SCHEDULED NECROPSY DAY 12 |
| 69477 | G | 91. | 98. | 92. | 89. | 95. | 83. | 93. | SCHEDULED NECROPSY DAY 12 |
| MEAN | | 83. | 85. | 82. | 83. | 83. | 76. | 83. | |
| S.D. | | 9.6 | 7.8 | 11.3 | 4.3 | 9.9 | 10.8 | 8.6 | |
| N | | 5 | 5 | 5 | 5 | 5 | 5 | 5 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 16
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FOOD CONSUMPTION DURING GESTATION (GRAMS/KG/DAY)



DAMS FROM GROUP 3: 30 MG/KG/DAY

| | PREGNANCY STATUS | DAY 0- 1 | 1- 3 | 3- 7 | 7- 9 | 9-11 | 11-12 | 0-12 | |
|---|---|---|---|---|---|---|---|---|---|
| 69487 | G | 65. | 57. | 85. | 87. | 82. | 76. | 79. | SCHEDULED NECROPSY DAY 12 |
| 69473 | G | 51. | 72. | 87. | 83. | 79. | 84. | 81. | SCHEDULED NECROPSY DAY 12 |
| 69482 | G | 92. | 82. | 88. | 107. | 84. | 85. | 90. | SCHEDULED NECROPSY DAY 12 |
| 69466 | G | 82. | 83. | 80. | 81. | 81. | 69. | 79. | SCHEDULED NECROPSY DAY 12 |
| 69479 | G | 71. | 77. | 85. | 63. | 79. | 76. | 76. | SCHEDULED NECROPSY DAY 12 |
| MEAN | | 72. | 74. | 85. | 84. | 81. | 78. | 81. | |
| S.D. | | 15.7 | 10.6 | 3.1 | 15.7 | 2.1 | 6.6 | 5.3 | |
| N | | 5 | 5 | 5 | 5 | 5 | 5 | 5 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 16
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FOOD CONSUMPTION DURING GESTATION (GRAMS/KG/DAY)



| | PREGNANCY STATUS | DAY 0- 1 | 1- 3 | 3- 7 | 7- 9 | 9-11 | 11-12 | 0-12 | |
|---|---|---|---|---|---|---|---|---|---|
| DAMS FROM GROUP 4: 100 MG/KG/DAY | | | | | | | | | |
| 69492 | G | 81. | 79. | 80. | 77. | 67. | 64. | 77. | SCHEDULED NECROPSY DAY 12 |
| 69474 | NG | 73. | 82. | 81. | 74. | 69. | 56. | 78. | SCHEDULED NECROPSY DAY 12 |
| 69486 | NG | 75. | 80. | 135. | 80. | 65. | 117. | 97. | SCHEDULED NECROPSY DAY 12 |
| 69468 | NG | 88. | 89. | 88. | 81. | 76. | 72. | 84. | SCHEDULED NECROPSY DAY 12 |
| 69483 | G | 88. | 85. | 81. | 75. | 75. | 148. | 86. | SCHEDULED NECROPSY DAY 12 |
| MEAN | | 85. | 82. | 81. | 76. | 71. | 106. | 82. | |
| S.D. | | 4.9 | 4.2 | 0.7 | 1.4 | 5.7 | 59.4 | 6.4 | |
| N | | 2 | 2 | 2 | 2 | 2 | 2 | 2 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 16
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FOOD CONSUMPTION DURING GESTATION (GRAMS/KG/DAY)



| | PREGNANCY STATUS | DAY 0- 1 | 1- 3 | 3- 7 | 7- 9 | 9-11 | 11-12 | 0-12 | |
|---|---|---|---|---|---|---|---|---|---|
| DAMS FROM GROUP 5: 300 MG/KG/DAY | | | | | | | | | |
| 69464 | NG | 75. | 91. | 90. | 91. | 79. | 95. | 87. | SCHEDULED NECROPSY DAY 12 |
| 69475 | NG | 64. | 78. | 78. | 77. | 81. | 79. | 78. | SCHEDULED NECROPSY DAY 12 |
| 69490 | NG | 35. | 63. | 65. | 62. | 79. | 104. | 65. | SCHEDULED NECROPSY DAY 12 |
| 69470 | NG | 56. | 67. | 68. | 71. | 71. | 8. | 62. | SCHEDULED NECROPSY DAY 12 |
| 69484 | NG | 70. | 64. | 76. | 75. | 74. | 69. | 71. | SCHEDULED NECROPSY DAY 12 |
| MEAN | | 0. | 0. | 0. | 0. | 0. | 0. | 0. | |
| S.D. | | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | |
| N | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |

G = GRAVID NG = NONGRAVID - WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 17
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL DAM GROSS NECROPSY EXAMINATIONS



| DAMS FROM GROUP 1: 0 MG/KG/DAY | MATERNAL GROSS OBSERVATION |
|---|---|
| 69467 | NO SIGNIFICANT CHANGES OBSERVED |
| 69469 | NO SIGNIFICANT CHANGES OBSERVED |
| 69476 | NO SIGNIFICANT CHANGES OBSERVED |
| 69493 | NO SIGNIFICANT CHANGES OBSERVED |
| 69472 | NO SIGNIFICANT CHANGES OBSERVED |

TABLE 17
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL DAM GROSS NECROPSY EXAMINATIONS



| DAMS FROM GROUP 2: 10 MG/KG/DAY | MATERNAL GROSS OBSERVATION |
|---|---|
| 69480 | NO SIGNIFICANT CHANGES OBSERVED |
| 69471 | NO SIGNIFICANT CHANGES OBSERVED |
| 69478 | NO SIGNIFICANT CHANGES OBSERVED |
| 69465 | NO SIGNIFICANT CHANGES OBSERVED |
| 69477 | NO SIGNIFICANT CHANGES OBSERVED |

TABLE 17
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL DAM GROSS NECROPSY EXAMINATIONS



| DAMS FROM GROUP 3: 30 MG/KG/DAY | MATERNAL GROSS OBSERVATION |
|---|---|
| 69487 | NO SIGNIFICANT CHANGES OBSERVED |
| 69473 | NO SIGNIFICANT CHANGES OBSERVED |
| 69482 | NO SIGNIFICANT CHANGES OBSERVED |
| 69466 | NO SIGNIFICANT CHANGES OBSERVED |
| 69479 | NO SIGNIFICANT CHANGES OBSERVED |

TABLE 17
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL DAM GROSS NECROPSY EXAMINATIONS



| DAMS FROM GROUP 4: 100 MG/KG/DAY | MATERNAL GROSS OBSERVATION |
|---|---|
| 69492 | NO SIGNIFICANT CHANGES OBSERVED |
| 69474 | NONGRAVID -- AMMONIUM SULFIDE NEGATIVE |
| 69486 | NONGRAVID -- AMMONIUM SULFIDE NEGATIVE |
| 69468 | NONGRAVID -- AMMONIUM SULFIDE NEGATIVE |
| 69483 | NO SIGNIFICANT CHANGES OBSERVED |

TABLE 17
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL DAM GROSS NECROPSY EXAMINATIONS



| DAMS FROM GROUP 5: 300 MG/KG/DAY | MATERNAL GROSS OBSERVATION |
|---|---|
| 69464 | NONGRAVID -- AMMONIUM SULFIDE NEGATIVE |
| 69475 | NONGRAVID -- AMMONIUM SULFIDE NEGATIVE |
| 69490 | NONGRAVID -- AMMONIUM SULFIDE NEGATIVE |
| 69470 | NONGRAVID -- AMMONIUM SULFIDE NEGATIVE |
| 69484 | NONGRAVID -- AMMONIUM SULFIDE NEGATIVE |

TABLE 18
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL ORGAN WEIGHTS (GRAMS)



FEMALE GROUP: 0 MG/KG/DAY

| ANIMAL | PREGNANCY STATUS | KIDNEYS | LIVER |
|---|---|---|---|
| 69467 | G | 2.40 | 13.81 |
| 69469 | G | 2.53 | 15.52 |
| 69476 | G | 2.11 | 12.81 |
| 69493 | G | 2.23 | 13.66 |
| 69472 | G | 2.36 | 12.64 |
| MEAN | | 2.33 | 13.69 |
| S.D. | | 0.161 | 1.145 |
| N | | 5 | 5 |

G = GRAVID NG = NONGRAVID - WEIGHTS NOT INCLUDED IN THE CALCULATION OF THE MEAN

TABLE 18
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL ORGAN WEIGHTS (GRAMS)



FEMALE GROUP: 10 MG/KG/DAY

| ANIMAL | PREGNANCY STATUS | KIDNEYS | LIVER |
|---|---|---|---|
| 69480 | G | 2.26 | 11.66 |
| 69471 | G | 2.54 | 13.72 |
| 69478 | G | 2.22 | 11.04 |
| 69465 | G | 2.50 | 14.60 |
| 69477 | G | 2.75 | 17.21 |
| MEAN | | 2.45 | 13.65 |
| S.D. | | 0.218 | 2.467 |
| N | | 5 | 5 |

G = GRAVID NG = NONGRAVID - WEIGHTS NOT INCLUDED IN THE CALCULATION OF THE MEAN

TABLE 18
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL ORGAN WEIGHTS (GRAMS)



FEMALE GROUP: 30 MG/KG/DAY

| ANIMAL | PREGNANCY STATUS | KIDNEYS | LIVER |
|---|---|---|---|
| 69487 | G | 2.35 | 11.97 |
| 69473 | G | 2.47 | 12.42 |
| 69482 | G | 2.52 | 14.41 |
| 69466 | G | 2.60 | 14.37 |
| 69479 | G | 2.36 | 12.84 |
| MEAN | | 2.46 | 13.20 |
| S.D. | | 0.107 | 1.127 |
| N | | 5 | 5 |

G = GRAVID NG = NONGRAVID - WEIGHTS NOT INCLUDED IN THE CALCULATION OF THE MEAN

TABLE 18
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL ORGAN WEIGHTS (GRAMS)



FEMALE GROUP: 100 MG/KG/DAY

| ANIMAL | PREGNANCY STATUS | KIDNEYS | LIVER |
|---|---|---|---|
| 69492 | G | 2.20 | 11.63 |
| 69474 | NG | 2.45 | 10.46 |
| 69486 | NG | 1.83 | 10.60 |
| 69468 | NG | 2.64 | 13.13 |
| 69483 | G | 2.13 | 11.67 |
| MEAN | | 2.17 | 11.65 |
| S.D. | | 0.049 | 0.028 |
| N | | 2 | 2 |

G = GRAVID NG = NONGRAVID - WEIGHTS NOT INCLUDED IN THE CALCULATION OF THE MEAN

TABLE 18
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL ORGAN WEIGHTS (GRAMS)



FEMALE GROUP: 300 MG/KG/DAY

| ANIMAL | PREGNANCY STATUS | KIDNEYS | LIVER |
|---|---|---|---|
| 69464 | NG | 2.51 | 13.48 |
| 69475 | NG | 2.21 | 11.55 |
| 69490 | NG | 1.86 | 9.52 |
| 69470 | NG | 1.80 | 9.22 |
| 69484 | NG | 1.78 | 9.41 |

G = GRAVID NG = NONGRAVID - WEIGHTS NOT INCLUDED IN THE CALCULATION OF THE MEAN

TABLE 19
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL MICROSCOPIC DESCRIPTION OF ORGANS



ANIMAL NO. 69467 GROUP 1: 0 MG/KG/DAY FEMALE SCHEDULED EUTH 06/09/97 DATE OF DEATH: 06/09/97 STUDY DAY: 12

| ORGAN WEIGHT | ABS.(G) | | | GRADE |
|---|---|---|---|---|
| KIDNEYS | 2.40 | KIDNEYS | MICRO: MINERALIZATION, TUBULAR<br>MULTIFOCAL, MOSTLY CORTICOMEDULLARY TUBULES, BILATERAL | 1 |
| LIVER | 13.81 | LIVER | MICRO: INFLAMMATION, NONSUPPURATIVE<br>MULTIFOCAL | 1 |

MICRO GRADE CODE: 1-MINIMAL, 2-MILD, 3-MODERATE, 4-SEVERE, P-PRESENT

TABLE 19
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL MICROSCOPIC DESCRIPTION OF ORGANS



ANIMAL NO. 69469 GROUP 1: 0 MG/KG/DAY FEMALE SCHEDULED EUTH 06/11/97 DATE OF DEATH: 06/11/97 STUDY DAY: 14

| ORGAN WEIGHT | ABS.(G) | KIDNEYS | MICRO: CONGESTION | GRADE |
|---|---|---|---|---|
| KIDNEYS | 2.53 | LIVER | MICRO: INFLAMMATION, NONSUPPURATIVE MULTIFOCAL | 2 |
| LIVER | 15.52 | | | 1 |

MICRO GRADE CODE: 1-MINIMAL, 2-MILD, 3-MODERATE, 4-SEVERE, P-PRESENT

TABLE 19
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL MICROSCOPIC DESCRIPTION OF ORGANS



ANIMAL NO. 69476 GROUP 1: 0 MG/KG/DAY FEMALE SCHEDULED EUTH 06/11/97 DATE OF DEATH: 06/11/97 STUDY DAY: 14

| ORGAN WEIGHT | ABS.(G) | | | GRADE |
|---|---|---|---|---|
| KIDNEYS | 2.11 | KIDNEYS | MICRO: MINERALIZATION, TUBULAR MULTIFOCAL, MOSTLY CORTICOMEDULLARY TUBULES, UNILATERAL | 1 |
| LIVER | 12.81 | LIVER | MICRO: INFLAMMATION, NONSUPPURATIVE MULTIFOCAL | 1 |

MICRO GRADE CODE: 1-MINIMAL, 2-MILD, 3-MODERATE, 4-SEVERE, P-PRESENT

TABLE 19
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL MICROSCOPIC DESCRIPTION OF ORGANS



ANIMAL NO. 69493 GROUP 1: 0 MG/KG/DAY FEMALE SCHEDULED EUTH 06/11/97 DATE OF DEATH: 06/11/97 STUDY DAY: 14

| ORGAN WEIGHT | ABS.(G) |
|---|---|
| KIDNEYS | 2.23 |
| LIVER | 13.66 |

| | | GRADE |
|---|---|---|
| KIDNEYS | MICRO: MINERALIZATION, TUBULAR<br>MULTIFOCAL, MOSTLY CORTICOMEDULLARY TUBULES, UNILATERAL | 1 |
| LIVER | MICRO: INFLAMMATION, NONSUPPURATIVE<br>MULTIFOCAL | 1 |

MICRO GRADE CODE: 1-MINIMAL, 2-MILD, 3-MODERATE, 4-SEVERE, P-PRESENT

TABLE 19
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL MICROSCOPIC DESCRIPTION OF ORGANS



ANIMAL NO. 69472 GROUP 1: 0 MG/KG/DAY FEMALE SCHEDULED EUTH 06/12/97 DATE OF DEATH: 06/12/97 STUDY DAY: 15

| ORGAN WEIGHT | ABS.(G) | | | GRADE |
|---|---|---|---|---|
| KIDNEYS | 2.36 | KIDNEYS | MICRO: MINERALIZATION, TUBULAR FOCAL, UNILATERAL | 1 |
| LIVER | 12.64 | LIVER | MICRO: INFLAMMATION, NONSUPPURATIVE MULTIFOCAL | 1 |

MICRO GRADE CODE: 1-MINIMAL, 2-MILD, 3-MODERATE, 4-SEVERE, P-PRESENT

TABLE 19
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL MICROSCOPIC DESCRIPTION OF ORGANS



ANIMAL NO. 69464 GROUP 5: 300 MG/KG/DAY FEMALE SCHEDULED EUTH 06/11/97 DATE OF DEATH: 06/11/97 STUDY DAY: 14

| ORGAN WEIGHT | ABS.(G) |
|---|---|
| KIDNEYS | 2.51 |
| LIVER | 13.48 |

| | | GRADE |
|---|---|---|
| KIDNEYS | MICRO: CONGESTION | 2 |
| | MINERALIZATION, TUBULAR | 1 |
| | MULTIFOCAL, MOSTLY CORTICOMEDULLARY TUBULES, UNILATERAL | |
| LIVER | MICRO: INFLAMMATION, NONSUPPURATIVE | 1 |
| | MULTIFOCAL | |

MICRO GRADE CODE: 1-MINIMAL, 2-MILD, 3-MODERATE, 4-SEVERE, P-PRESENT

TABLE 19
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL MICROSCOPIC DESCRIPTION OF ORGANS



ANIMAL NO. 69475 GROUP 5: 300 MG/KG/DAY FEMALE SCHEDULED EUTH 06/11/97 DATE OF DEATH: 06/11/97 STUDY DAY: 14

| ORGAN WEIGHT | ABS.(G) |
|---|---|
| KIDNEYS | 2.21 |
| LIVER | 11.55 |

| | | GRADE |
|---|---|---|
| LIVER | MICRO: INFLAMMATION, NONSUPPURATIVE MULTIFOCAL | 1 |
| NO SIGNIFICANT CHANGES OBSERVED | MICRO:KIDNEYS | |

MICRO GRADE CODE: 1-MINIMAL, 2-MILD, 3-MODERATE, 4-SEVERE, P-PRESENT

TABLE 19
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL MICROSCOPIC DESCRIPTION OF ORGANS



ANIMAL NO. 69490 GROUP 5: 300 MG/KG/DAY FEMALE SCHEDULED EUTH 06/11/97 DATE OF DEATH: 06/11/97 STUDY DAY: 14

| ORGAN WEIGHT | ABS.(G) | | | GRADE |
|---|---|---|---|---|
| KIDNEYS | 1.86 | LIVER | MICRO: INFLAMMATION, NONSUPPURATIVE MULTIFOCAL | 1 |
| LIVER | 9.52 | | | |
| | | NO SIGNIFICANT CHANGES OBSERVED | MICRO:KIDNEYS | |

MICRO GRADE CODE: 1-MINIMAL, 2-MILD, 3-MODERATE, 4-SEVERE, P-PRESENT

TABLE 19
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL MICROSCOPIC DESCRIPTION OF ORGANS



ANIMAL NO. 69470 GROUP 5: 300 MG/KG/DAY FEMALE SCHEDULED EUTH 06/12/97 DATE OF DEATH: 06/12/97 STUDY DAY: 15

| ORGAN WEIGHT | ABS.(G) |
|---|---|
| KIDNEYS | 1.80 |
| LIVER | 9.22 |

| | | GRADE |
|---|---|---|
| KIDNEYS | MICRO: CONGESTION | 1 |
| LIVER | MICRO: INFLAMMATION, NONSUPPURATIVE MULTIFOCAL | 1 |

MICRO GRADE CODE: 1-MINIMAL, 2-MILD, 3-MODERATE, 4-SEVERE, P-PRESENT

TABLE 19
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL MICROSCOPIC DESCRIPTION OF ORGANS



ANIMAL NO. 69484 GROUP 5: 300 MG/KG/DAY FEMALE SCHEDULED EUTH 06/12/97 DATE OF DEATH: 06/12/97 STUDY DAY: 15

| ORGAN WEIGHT | ABS.(G) |
|---|---|
| KIDNEYS | 1.78 |
| LIVER | 9.41 |

| | | GRADE |
|---|---|---|
| LIVER | MICRO: INFLAMMATION, NONSUPPURATIVE MULTIFOCAL | 1 |
| NO SIGNIFICANT CHANGES OBSERVED | MICRO:KIDNEYS | |

MICRO GRADE CODE: 1-MINIMAL, 2-MILD, 3-MODERATE, 4-SEVERE, P-PRESENT

TABLE 20
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FETAL DATA AT THE SCHEDULED NECROPSY



DAMS FROM GROUP 1: 0 MG/KG/DAY

| DAM# | VIABLE FETUSES | | | DEAD FETUSES | | | EARLY RESORPTIONS | | | LATE RESORPTIONS | | | IMPLANTATION SITES | | | CORPORA LUTEA | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT OVARY | RIGHT OVARY | TOTAL |
| 69467 | 7 | 11 | 18 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 7 | 12 | 19 | 8 | 12 | 20 |
| 69469 | 4 | 13 | 17 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 13 | 17 | 4 | 13 | 17 |
| 69476 | 5 | 10 | 15 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 10 | 15 | 5 | 10 | 15 |
| 69493 | 6 | 7 | 13 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 6 | 8 | 14 | 7 | 8 | 15 |
| 69472 | 9 | 8 | 17 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9 | 8 | 17 | 9 | 10 | 19 |
| TOTAL | 31 | 49 | 80 | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 31 | 51 | 82 | 33 | 53 | 86 |
| MEAN | 6.2 | 9.8 | 16.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.4 | 0.4 | 0.0 | 0.0 | 0.0 | 6.2 | 10.2 | 16.4 | 6.6 | 10.6 | 17.2 |
| S.D. | 1.92 | 2.39 | 2.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.55 | 0.55 | 0.00 | 0.00 | 0.00 | 1.92 | 2.28 | 1.95 | 2.07 | 1.95 | 2.28 |
| N = 5 | | | | | | | | | | | | | | | | | | |

TABLE 20
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FETAL DATA AT THE SCHEDULED NECROPSY



DAMS FROM GROUP 2: 10 MG/KG/DAY

| DAM# | VIABLE FETUSES | | | DEAD FETUSES | | | EARLY RESORPTIONS | | | LATE RESORPTIONS | | | IMPLANTATION SITES | | | CORPORA LUTEA | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT OVARY | RIGHT OVARY | TOTAL |
| 69480 | 4 | 11 | 15 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 11 | 15 | 4 | 11 | 15 |
| 69471 | 9 | 7 | 16 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9 | 7 | 16 | 9 | 11 | 20 |
| 69478 | 6 | 12 | 18 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 12 | 18 | 8 | 13 | 21 |
| 69465 | 7 | 8 | 15 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 7 | 8 | 15 | 7 | 9 | 16 |
| 69477 | 3 | 12 | 15 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 12 | 15 | 4 | 12 | 16 |
| TOTAL | 29 | 50 | 79 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 29 | 50 | 79 | 32 | 56 | 88 |
| MEAN | 5.8 | 10.0 | 15.8 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 5.8 | 10.0 | 15.8 | 6.4 | 11.2 | 17.6 |
| S.D. | 2.39 | 2.35 | 1.30 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 2.39 | 2.35 | 1.30 | 2.30 | 1.48 | 2.70 |
| N = 5 | | | | | | | | | | | | | | | | | | |

TABLE 20
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FETAL DATA AT THE SCHEDULED NECROPSY



DAMS FROM GROUP 3: 30 MG/KG/DAY

| DAM# | VIABLE FETUSES | | | DEAD FETUSES | | | EARLY RESORPTIONS | | | LATE RESORPTIONS | | | IMPLANTATION SITES | | | CORPORA LUTEA | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT OVARY | RIGHT OVARY | TOTAL |
| 69487 | 3 | 5 | 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 5 | 8 | 4 | 5 | 9 |
| 69473 | 4 | 10 | 14 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 10 | 14 | 4 | 10 | 14 |
| 69482 | 8 | 11 | 19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 8 | 11 | 19 | 8 | 12 | 20 |
| 69466 | 3 | 12 | 15 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 12 | 15 | 7 | 13 | 20 |
| 69479 | 7 | 10 | 17 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 7 | 10 | 17 | 7 | 10 | 17 |
| TOTAL | 25 | 48 | 73 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 25 | 48 | 73 | 30 | 50 | 80 |
| MEAN | 5.0 | 9.6 | 14.6 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 5.0 | 9.6 | 14.6 | 6.0 | 10.0 | 16.0 |
| S.D. | 2.35 | 2.70 | 4.16 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 2.35 | 2.70 | 4.16 | 1.87 | 3.08 | 4.64 |

N = 5

TABLE 20
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FETAL DATA AT THE SCHEDULED NECROPSY



DAMS FROM GROUP 4: 100 MG/KG/DAY

| DAM# | | VIABLE FETUSES | | | DEAD FETUSES | | | EARLY RESORPTIONS | | | LATE RESORPTIONS | | | IMPLANTATION SITES | | | CORPORA LUTEA | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT OVARY | RIGHT OVARY | TOTAL |
| 69492 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 10 | 6 | 16 |
| 69474 | NONGRAVID | | | | | | | | | | | | | | | | | | |
| 69486 | NONGRAVID | | | | | | | | | | | | | | | | | | |
| 69468 | NONGRAVID | | | | | | | | | | | | | | | | | | |
| 69483 | | 3 | 0 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 3 | 5 | 3 | 8 |
| TOTAL | | 3 | 0 | 3 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 3 | 1 | 4 | 15 | 9 | 24 |
| MEAN | | 1.5 | 0.0 | 1.5 | 0.0 | 0.0 | 0.0 | 0.0 | 0.5 | 0.5 | 0.0 | 0.0 | 0.0 | 1.5 | 0.5 | 2.0 | 7.5 | 4.5 | 12.0 |
| S.D. | | 2.12 | 0.00 | 2.12 | 0.00 | 0.00 | 0.00 | 0.00 | 0.71 | 0.71 | 0.00 | 0.00 | 0.00 | 2.12 | 0.71 | 1.41 | 3.54 | 2.12 | 5.66 |
| N = | 2 | | | | | | | | | | | | | | | | | | |

TABLE 20
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FETAL DATA AT THE SCHEDULED NECROPSY



DAMS FROM GROUP 5: 300 MG/KG/DAY

| | | VIABLE FETUSES | | | DEAD FETUSES | | | EARLY RESORPTIONS | | | LATE RESORPTIONS | | | IMPLANTATION SITES | | | CORPORA LUTEA | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DAM# | | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT HORN | RIGHT HORN | TOTAL | LEFT OVARY | RIGHT OVARY | TOTAL |
| 69464 | NONGRAVID | | | | | | | | | | | | | | | | | | |
| 69475 | NONGRAVID | | | | | | | | | | | | | | | | | | |
| 69490 | NONGRAVID | | | | | | | | | | | | | | | | | | |
| 69470 | NONGRAVID | | | | | | | | | | | | | | | | | | |
| 69484 | NONGRAVID | | | | | | | | | | | | | | | | | | |

THERE WERE NO GRAVID DAMS IN THIS GROUP

TABLE 21
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)



DAMS FROM GROUP 1: 0 MG/KG/DAY

| DAM # | CORPORA LUTEA | IMPLANTATION SITES | FETUSES LIVE | FETUSES DEAD | RESORPTIONS EARLY | RESORPTIONS LATE | RESORPTIONS TOTAL | PRE-IMPLANTATION LOSS | POST-IMPLANTATION LOSS |
|---|---|---|---|---|---|---|---|---|---|
| | # | # | % | % | % | % | % | % | % |
| 69467 | 20.0 | 19.0 | 94.7 | 0.0 | 5.3 | 0.0 | 5.3 | 5.0 | 5.3 |
| 69469 | 17.0 | 17.0 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 69476 | 15.0 | 15.0 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 69493 | 15.0 | 14.0 | 92.9 | 0.0 | 7.1 | 0.0 | 7.1 | 6.7 | 7.1 |
| 69472 | 19.0 | 17.0 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 10.5 | 0.0 |
| MEAN | 17.2 | 16.4 | 97.5 | 0.0 | 2.5 | 0.0 | 2.5 | 4.4 | 2.5 |
| S.D. | 2.28 | 1.95 | 3.45 | 0.00 | 3.45 | 0.00 | 3.45 | 4.52 | 3.45 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

TABLE 21
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)



DAMS FROM GROUP 2: 10 MG/KG/DAY

| DAM # | CORPORA LUTEA | IMPLANTATION SITES | FETUSES LIVE | FETUSES DEAD | RESORPTIONS EARLY | RESORPTIONS LATE | RESORPTIONS TOTAL | PRE-IMPLANTATION LOSS | POST-IMPLANTATION LOSS |
|---|---|---|---|---|---|---|---|---|---|
| | # | # | % | % | % | % | % | % | % |
| 69480 | 15.0 | 15.0 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 69471 | 20.0 | 16.0 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 20.0 | 0.0 |
| 69478 | 21.0 | 18.0 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 14.3 | 0.0 |
| 69465 | 16.0 | 15.0 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 6.3 | 0.0 |
| 69477 | 16.0 | 15.0 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 6.3 | 0.0 |
| MEAN | 17.6 | 15.8 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 9.4 | 0.0 |
| S.D. | 2.70 | 1.30 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 7.81 | 0.00 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

TABLE 21
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)



DAMS FROM GROUP 3: 30 MG/KG/DAY

| DAM # | CORPORA LUTEA | IMPLANTATION SITES | FETUSES LIVE | FETUSES DEAD | RESORPTIONS EARLY | RESORPTIONS LATE | RESORPTIONS TOTAL | PRE-IMPLANTATION LOSS | POST-IMPLANTATION LOSS |
|---|---|---|---|---|---|---|---|---|---|
| | # | # | % | % | % | % | % | % | % |
| 69487 | 9.0 | 8.0 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 11.1 | 0.0 |
| 69473 | 14.0 | 14.0 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 69482 | 20.0 | 19.0 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 5.0 | 0.0 |
| 69466 | 20.0 | 15.0 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 25.0 | 0.0 |
| 69479 | 17.0 | 17.0 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| MEAN | 16.0 | 14.6 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 8.2 | 0.0 |
| S.D. | 4.64 | 4.16 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 10.43 | 0.00 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

TABLE 21
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)



DAMS FROM GROUP 4: 100 MG/KG/DAY

| DAM # | CORPORA LUTEA | IMPLANTATION SITES | FETUSES LIVE | FETUSES DEAD | RESORPTIONS EARLY | RESORPTIONS LATE | RESORPTIONS TOTAL | PRE-IMPLANTATION LOSS | POST-IMPLANTATION LOSS |
|---|---|---|---|---|---|---|---|---|---|
| | # | # | % | % | % | % | % | % | % |
| 69492 | 16.0 | 1.0 | 0.0 | 0.0 | 100.0 | 0.0 | 100.0 | 93.8 | 100.0 |
| 69483 | 8.0 | 3.0 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 62.5 | 0.0 |
| MEAN | 12.0 | 2.0 | 50.0 | 0.0 | 50.0 | 0.0 | 50.0 | 78.2 | 50.0 |
| S.D. | 5.66 | 1.41 | 70.71 | 0.00 | 70.71 | 0.00 | 70.71 | 22.13 | 70.71 |
| N | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |

TABLE 21
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)



DAMS FROM GROUP 5: 300 MG/KG/DAY

| DAM # | CORPORA LUTEA | IMPLANTATION SITES | FETUSES LIVE | FETUSES DEAD | RESORPTIONS EARLY | RESORPTIONS LATE | RESORPTIONS TOTAL | PRE-IMPLANTATION LOSS | POST-IMPLANTATION LOSS |
|---|---|---|---|---|---|---|---|---|---|
| | # | # | % | % | % | % | % | % | % |

THERE WERE NO GRAVID DAMS IN THIS GROUP

A Study to Evaluate Early Embryonic Development in Rats

# APPENDIX A

Preliminary Seven-Day Toxicity Study
(WIL Research Laboratories, Inc.)

A Study to Evaluate Early Embryonic Development in Rats

## APPENDIX A

Preliminary Seven-Day Toxicity Study
(WIL Research Laboratories, Inc.)

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8. Individual Clinical Observations (1-Hour Post-Dosing)

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A Study to Evaluate Early Embryonic Development in Rats

## APPENDIX A

Preliminary Seven-Day Toxicity Study
(WIL Research Laboratories, Inc.)

## I. GENERAL PROCEDURES

Prior to the initiation of the dose range-finding developmental toxicity study, a seven-day toxicity screen was conducted using non-mated females. The experimental design consisted of a control group and four treated groups, each composed of three rats. The following diagram presents the study group assignment:

| Group Number | Group Name | Dosage Level (mg/kg/day) | Dosage Concentration (mg/ml) | Dosage Volume (ml/kg) | Number of Females |
|---|---|---|---|---|---|
| 1 | Vehicle Control | 0 | 0 | 10 | 3 |
| 2 | Low Dose | 10 | 10 | 1 | 3 |
| 3 | Intermediate Dose-1 | 30 | 10 | 3 | 3 |
| 4 | Intermediate Dose-2 | 100 | 30 | 3.3 | 3 |
| 5 | High Dose | 300 | 30 | 10 | 3 |

The test article was administered orally as a single daily dose for seven consecutive days, beginning on study day 0 (April 28, 1997). Body weights were recorded individually on study days 0 (prior to treatment), 3, 5 and 7 (prior to euthanization). The animals were observed twice daily for moribundity and mortality. Detailed clinical observations and one hour post-dosing observations were recorded daily. All animals were euthanized and subjected to a gross necropsy on study day 7 (May 5, 1997). The kidneys and liver from all animals were weighed.

The females for WIL-160079A were randomly selected from the shipment of rats received on April 17, 1997. Dosing formulations for WIL-160079A were prepared on April 28, 1997. All methods, procedures and conditions relevant to this portion of the investigation, unless mentioned above, were identical to those described for the study to evaluate early embryonic development.

## II. RESULTS

All animals in the control, 10, 30, 100 and 300 mg/kg/day groups survived to the scheduled euthanization. Rocking, lurching or swaying while walking was noted in one animal in the 300 mg/kg/day group at the daily examinations between the second and fourth days of treatment and in two animals in this group one hour following dosing on the second day of treatment. Splayed hindlimbs and dark red eyes were each noted in two animals in the 300 mg/kg/day group on the first or second day of dosing. Other clinical signs in the treated groups were noted in single animals and were not attributed to treatment.

Mean body weights and body weight gains were unaffected by treatment at all dose levels. Values in the treated groups were generally similar to the control group values; differences were slight and were not statistically significant.

At the scheduled necropsy, no treatment-related internal findings were noted. Kidney and liver weights in the treated groups were similar to the control group values; differences were slight and were not statistically significant.

Based on the results of this study, dose levels of 10, 30, 100 and 300 mg/kg/day were selected for the study to evaluate early embryonic development in rats.

APPENDIX A - TABLE 1
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
INDIVIDUAL SURVIVAL AND DISPOSITION



| ANIMAL | SEX | GROUP | TYPE OF DEATH | AGE IN WEEKS A | DATE OF DEATH | DAYS ON STUDY |
|---|---|---|---|---|---|---|
| 66936 | F | 0 MG/KG/DAY | SCHEDULED EUTHANIZATION | 13 | 05-MAY-97 | 7 |
| 66960 | F | 0 MG/KG/DAY | SCHEDULED EUTHANIZATION | 13 | 05-MAY-97 | 7 |
| 66989 | F | 0 MG/KG/DAY | SCHEDULED EUTHANIZATION | 13 | 05-MAY-97 | 7 |
| 66939 | F | 10 MG/KG/DAY | SCHEDULED EUTHANIZATION | 13 | 05-MAY-97 | 7 |
| 66973 | F | 10 MG/KG/DAY | SCHEDULED EUTHANIZATION | 13 | 05-MAY-97 | 7 |
| 66991 | F | 10 MG/KG/DAY | SCHEDULED EUTHANIZATION | 13 | 05-MAY-97 | 7 |
| 66948 | F | 30 MG/KG/DAY | SCHEDULED EUTHANIZATION | 13 | 05-MAY-97 | 7 |
| 66978 | F | 30 MG/KG/DAY | SCHEDULED EUTHANIZATION | 13 | 05-MAY-97 | 7 |
| 66996 | F | 30 MG/KG/DAY | SCHEDULED EUTHANIZATION | 13 | 05-MAY-97 | 7 |
| 66954 | F | 100 MG/KG/DAY | SCHEDULED EUTHANIZATION | 13 | 05-MAY-97 | 7 |
| 66981 | F | 100 MG/KG/DAY | SCHEDULED EUTHANIZATION | 13 | 05-MAY-97 | 7 |
| 66998 | F | 100 MG/KG/DAY | SCHEDULED EUTHANIZATION | 13 | 05-MAY-97 | 7 |
| 66958 | F | 300 MG/KG/DAY | SCHEDULED EUTHANIZATION | 13 | 05-MAY-97 | 7 |
| 66983 | F | 300 MG/KG/DAY | SCHEDULED EUTHANIZATION | 13 | 05-MAY-97 | 7 |
| 67002 | F | 300 MG/KG/DAY | SCHEDULED EUTHANIZATION | 13 | 05-MAY-97 | 7 |

A = CALCULATED TO THE NEAREST WHOLE WEEK USING THE MEAN AGE IN WEEKS AT INITIATION OF DOSING (12)

APPENDIX A - TABLE 2 (DAILY EXAMINATIONS)
A STUDY TO EVALUATE EARLY EMBRYONIC DEVELOPMENT IN RATS
SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS



----- F E M A L E -----

| TABLE RANGE: | 04-28-97 TO 05-05-97 | | | | |
|---|---|---|---|---|---|
| GROUP: | 1 | 2 | 3 | 4 | 5 |
| NORMAL | | | | | |
| -NO SIGNIFICANT CLINICAL OBSERVATIONS | 24/ 3 | 24/ 3 | 23/ 3 | 22/ 3 | 20/ 3 |
| DISPOSITION | | | | | |
| -SCHEDULED EUTHANIZATION | 3/ 3 | 3/ 3 | 3/ 3 | 3/ 3 | 3/ 3 |
| BEHAVIOR/CNS | | | | | |
| -ANIMAL ROCKS,LURCHES AND SWAYS AS IT WALKS | 0/ 0 | 0/ 0 | 0/ 0 | 0/ 0 | 3/ 1 |
| EYES/EARS/NOSE | | | | | |
| -RIGHT EYE EXOPHTHALMIC | 0/ 0 | 0/ 0 | 1/ 1 | 1/ 1 | 1/ 1 |
| -LEFT EYE EXOPHTHALMIC | 0/ 0 | 0/ 0 | 1/ 1 | 1/ 1 | 1/ 1 |
| -DRIED RED MATERIAL AROUND NOSE | 0/ 0 | 0/ 0 | 0/ 0 | 1/ 1 | 0/ 0 |

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 30 MG/KG/DAY 4- 100 MG/KG/DAY 5- 300 MG/KG/DAY