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Attention: 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street SW
Washington, D.C. 20460-0001

8EHQ-97-13938

49980000145

Dear 8(e) Coordinator:

8EHQ-97-13938

In our May 23, 1997 letter, we informed the Agency of the preliminary results of a recently completed rat pilot dermal developmental study with the above referenced test material.

Enclosed, please find a copy of the final report.

Sincerely,

Enclosure(1): Final Report "A Dermal Dose Range-Finding Prenatal Developmental Toxicity Study of Flusilazole in Rats"

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COMPANY SANITIZED



Study Title

**A Dermal Dose Range-Finding Prenatal
Developmental Toxicity Study of Flusilazole in Rats**

FINAL REPORT

Data Requirements

None

Author

James L. Schardein, M.S., A.T.S.

Study Completed On

January 13, 1998

Performing Laboratory

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

for

**A Dermal Dose Range-Finding Prenatal
Developmental Toxicity Study of Flusilazole in Rats**

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A Dermal Dose Range-Finding Prenatal
Developmental Toxicity Study of Flusilazole in Rats

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

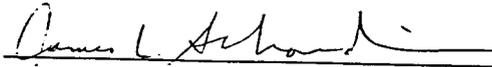
This study was conducted in compliance with United States EPA FIFRA (40 CFR 160)
and United States EPA TSCA (40 CFR 792) Good Laboratory Practice Standards.

Submitter:

Sponsor:

Date

Study Director:


James L. Schardein, M.S., A.T.S.
Study Director
WIL Research Laboratories, Inc.

1/13/98

Study Monitor:

Sponsoring Company
Representative:

Registration Manager

A Dermal Dose Range-Finding Prenatal
Developmental Toxicity Study of Flusilazole in Rats

GENERAL INFORMATION

9th Collective
Nomenclature:

1*H*-1,2,4-triazole, 1-[[*bis*(4-fluorophenyl)-methylsilyl]methyl]-
for active ingredient

Synonyms/Codes:

- Flusilazole
- Flusilazole
- Flusilazole-

- 1-[[*bis*(4-fluorophenyl)methylsilyl]methyl]-1*H*-1,2,4-triazole
- *bis*(4-fluorophenyl) (methyl)1*H*-1,2,4-triazol-1-ylmethylsilane

Structure:

CAS Registry Number:

None for formulation

85509-19-9 for flusilazole active ingredient

Composition:

Formulations:

Flusilazole is an emulsifiable concentrate formulation containing (nominal concentrations):

(Flusilazole), active ingredient
inert ingredients

A Dermal Dose Range-Finding Prenatal
Developmental Toxicity Study of Flusilazole /in Rats

GENERAL INFORMATION

Analysis to Confirm
Composition:

Known Impurities: None considered to be of toxicological significance at this time.

Physical
Characteristics:

Amber-brown liquid

Stability:

The test substance appeared to be stable under the conditions of the study: no evidence of instability was observed.

Sponsor:

Study Initiated/
Completed:

March 31, 1997/January 13, 1998

In-Life Initiated/
Completed:

April 4, 1997/April 24, 1997

All raw data and the final report will be stored in the archives of WIL Research Laboratories, Inc., Ashland, Ohio,

A Dermal Dose Range-Finding Prenatal
Developmental Toxicity Study of Flusilazole in Rats

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**A Dermal Dose Range-Finding Prenatal
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A Dermal Dose Range-Finding Prenatal
Developmental Toxicity Study of Flusilazole in Rats

I. SUMMARY

The objective of the study was to investigate the potential maternal toxicity and developmental toxicity of flusilazole in the CrI:CD[®](SD)BR rat and to determine dose levels for evaluation in a definitive developmental toxicity study in rats. The test substance, flusilazole, in the vehicle, optima, was administered to three groups of eight bred CrI:CD[®](SD)BR rats once daily from gestation days 6 through 19. The test substance was applied to the clipped intact dorsal skin (10% area) of each rat. The application sites were not abraded or occluded. Dosage concentrations were 5, 50 and 400 mg/ml administered at a dose volume of 0.5 ml/rat. Due to the excessive maternal toxicity noted in the 400 mg/ml group (Group 4), dosing was discontinued and the remaining animals were euthanized on gestation day 13 or 14. A concurrent control group composed of eight bred females received the vehicle, optima, on a comparable regimen at 0.5 ml/rat. All animals were fitted with Elizabethan collars six hours each day (during the exposure periods) to minimize oral ingestion of the control or test substance. Clinical observations, body weights and food consumption were recorded. Dermal observations were recorded daily prior to dose administration. On gestation day 20, a laparohysterectomy was performed on all surviving animals. The uteri and ovaries were examined and the numbers of fetuses, early and late resorptions, total implantations and corpora lutea were recorded. Mean gravid uterine weights and net body weight changes were calculated for each group. The fetuses were weighed, sexed and examined for external malformations and variations. In addition, two additional dose groups (Groups 5 and 6) each dosed at 400 mg/ml and containing eight bred female rats were selected for the satellite pharmacokinetic phase. Blood samples were drawn from these animals at selected intervals on gestation day 6 (Group 5) or on gestation days 7, 11, 15 and 19 (Group 6) for a measurement of flusilazole levels in the maternal plasma.

In the 400 mg/ml group, three females died between gestation days 11 and 14 and the remaining five females in this group were euthanized *in extremis* on gestation days 13 or 14. Six females in the 400 mg/ml group had thickened skin or scabbing at the application

site at necropsy. All other maternal animals survived to the scheduled necropsy on gestation day 20. At necropsy, 3 and 4 females in the 5 and 50 mg/ml groups, respectively, had enlarged placentae. Clinical observations related to treatment with the test substance included brown staining or matting around the mouth, urogenital or ventral abdominal areas, yellow staining around the urogenital and ventral abdominal areas and red material around the eyes and nose at concentrations of 50 and/or 400 mg/ml. Dermal irritation, characterized by very slight to severe erythema, was noted in all treated groups in a dose-related manner. Desquamation and fissuring were noted in a dose-related manner in the 50 and 400 mg/ml groups. In addition, atonia was observed in the 400 mg/ml group. Mean body weight losses and reductions in food consumption were noted in the 400 mg/ml group during gestation days 6-9 and 9-12. Mean body weight gain and food consumption in the 50 mg/ml group were reduced during gestation days 12-20.

Increased postimplantation losses in the 5 and 50 mg/ml groups were due to an increase in early and late resorptions and were attributed to the test substance. A corresponding decrease in the percentages of viable fetuses in the 5 and 50 mg/ml groups was noted. The only external malformation observed was localized fetal edema in one 50 mg/ml group fetus. No external fetal developmental variations were noted in this study.

Steady-state plasma levels of flusilazole (2-3 ppm) were achieved by 2 hr following a single dermal application of undiluted (400 mg flusilazole per mL of formulation) and were sustained throughout the 6 hr exposure period. The plasma concentration-time data suggest that flusilazole does not bioaccumulate since the maximum plasma concentration range (2-3 ppm) was observed in both the single (Group 5) and repeated dose experiments (Group 6). Within the confines of the study design, the plasma data also suggest that the dermal dose which is absorbed over the 6 hr exposure period is rapidly cleared from the systemic circulation prior to the next 6 hr exposure interval. Based on this observation, the terminal elimination half-life ($t_{1/2}$) for flusilazole was estimated to be equal to or less than 6 hr.

In conclusion, dermal irritation (characterized by very slight to severe erythema, desquamation, fissuring and/or atonia) was noted in a dose-related manner in all of the

treated groups. Maternal toxicity was expressed by mortalities at a concentration of 400 mg/ml and by inhibition of body weight gain and food consumption at dose levels of 50 and 400 mg/ml. No maternal toxicity was observed at a concentration of 5 mg/ml. Developmental toxicity was exhibited by increased postimplantation losses (early and late resorptions) in the 5 and 50 mg/ml groups.

A Dermal Dose Range-Finding Prenatal
Developmental Toxicity Study of Flusilazole in Rats

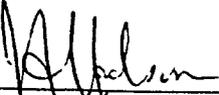
II. KEY STUDY PERSONNEL AND REPORT SUBMISSION

Report Prepared By:

Stephanie B. Gall, B.S.

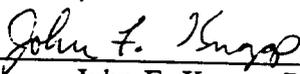
Report Writer I

Reviewed By:



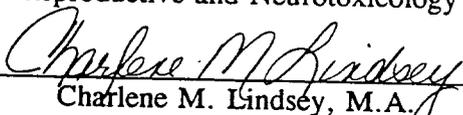
Joseph F. Holson, Ph.D.
President, Director

1/13/98
Date



John F. Knapp, B.S.
Manager II, Developmental,
Reproductive and Neurotoxicology

1/13/98
Date



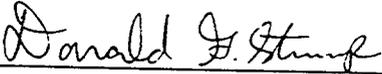
Charlene M. Lindsey, M.A.
Manager of Technical Report Writing

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Date



Mark D. Nemec, B.S., D.A.B.T.
Director of Developmental
and Reproductive Toxicology

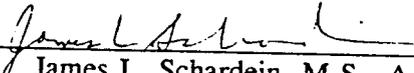
1/13/98
Date



Donald G. Stump, Ph.D.
Assistant Director of Developmental,
Reproductive and Neurotoxicology

1/13/98
Date

Approved and Submitted By:



James L. Schardein, M.S., A.T.S.
Senior Vice President, Director of Research

1/13/98
Date

II. KEY STUDY PERSONNEL AND REPORT SUBMISSION (continued)

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

A Dermal Dose Range-Finding Prenatal
Developmental Toxicity Study of Flusilazole in Rats

III. SPONSOR SIGNATURE PAGE

A Dermal Dose Range-Finding Prenatal
Developmental Toxicity Study of Flusilazole in Rats

IV. QUALITY ASSURANCE UNIT STATEMENT

<u>Date(s) of Inspection(s)</u>	<u>Phase Inspected</u>	<u>Date(s) Findings Reported to Study Director</u>	<u>Date(s) Findings Reported to Management</u>
4/22/97	Fetal External Examination	4/22/97	5/28/97
5/13-15, 20/97	Study Records Vol. I-1	5/20/97	6/27/97
5/15, 20/97	Study Records Vol. N-1	5/20/97	6/27/97
5/20, 21/97	Study Records Vol. C-1	5/21/97	6/27/97
6/19, 30, 7/1/97	Draft Report	7/1/97	8/29/97

The study was conducted and inspected in accordance with the United States EPA Good Laboratory Practice Standards (40 CFR Parts 160 and 792), the Standard Operating Procedures of WIL Research Laboratories, Inc., and the sponsor's protocol and protocol amendment(s), with the following exception. The data located in Appendices A and D, Table 13 and Figures 2 and 3 were the responsibility of the sponsor. Quality Assurance findings, derived from the inspections during the conduct of the study and from the inspections of the raw data and draft report, are documented and have been reported to the study director. A status report is submitted to management monthly.

The raw data, the retention sample(s), if applicable, and the final report will be stored in the Archives at WIL Research Laboratories, Inc., or another location specified by the sponsor.

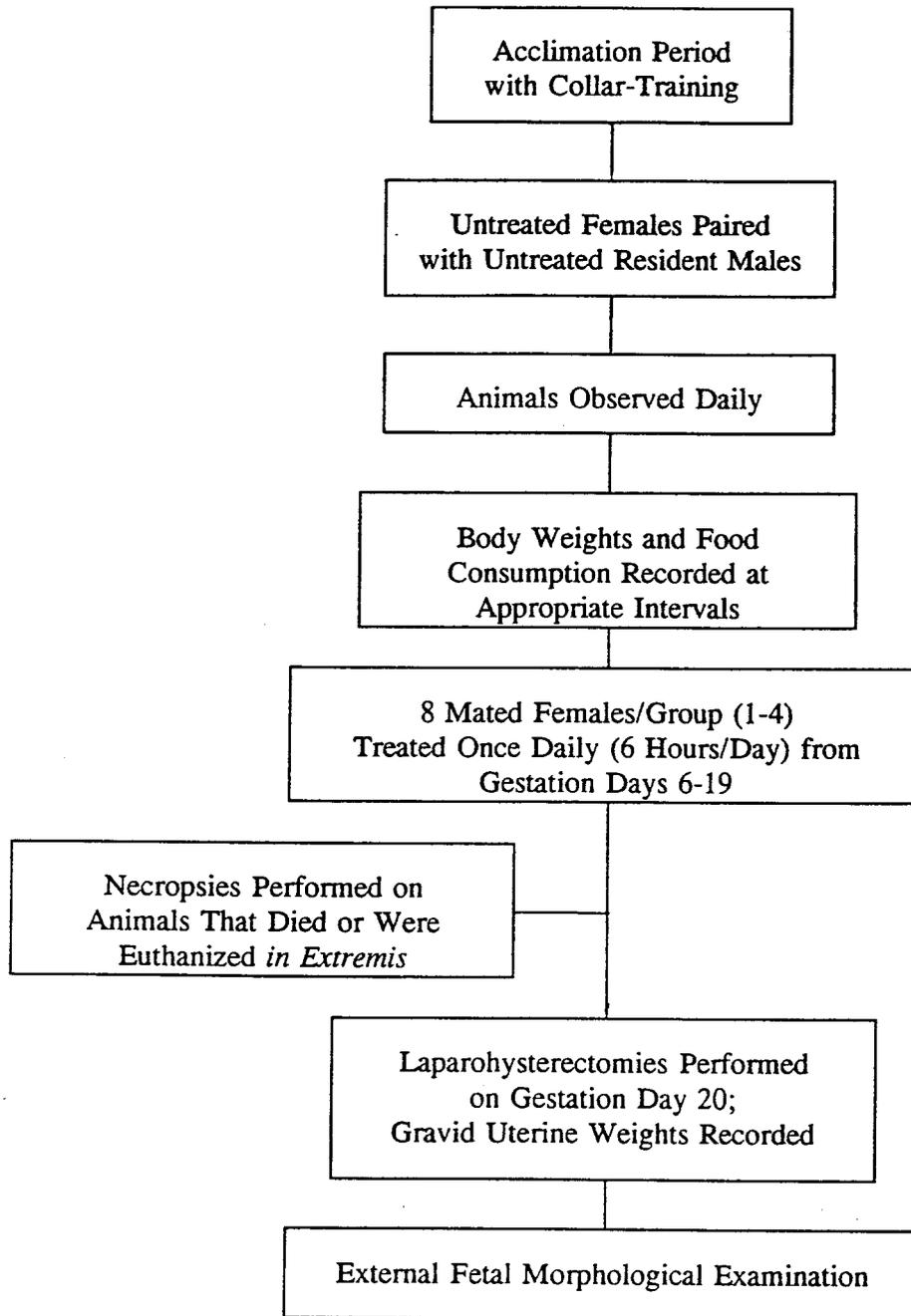
Deborah L. Little
 Deborah L. Little
 Manager of Quality Assurance

1/13/98
 Date

V. OBJECTIVE

The objective of the study was to investigate the potential maternal toxicity and developmental toxicity of flusilazole in the CrI:CD®(SD)BR rat and to determine dose levels for evaluation in a definitive developmental toxicity study in rats. The selected route of administration was dermal (topical application) since this is a possible route of clinical administration for the human. The animal model was selected on the basis of availability of historical control data and susceptibility of the species to known developmental toxicants.

VI. STUDY DESIGN



VII. EXPERIMENTAL DESIGN - MATERIALS AND METHODS

A. INTRODUCTION

The experimental phase of the study was initiated with the assignment of mated rats to treatment groups on April 4, 1997, and concluded with the last laparohysterectomy on April 24, 1997. The dosing period was from April 7 to April 23, 1997. Due to spacing constraints, the study title is presented on the report tables as "Dermal R-F Dev. Tox. Study of _____ in Rats."

B. TEST AND CONTROL SUBSTANCES

1. TEST SUBSTANCE IDENTIFICATION

The test substance, flusilazole _____ was received from _____ on April 4, 1997, as follows:

<u>Identification</u>	<u>No. of Containers Received</u>	<u>Description</u>
Flusilazole	1 Jar Gross Weight: 1063.3 g	Brown viscous liquid

Purity and stability data were the responsibility of the sponsor. A Certificate of Analysis was provided by the sponsor and is presented in Appendix A. The test substance was stored at room temperature. An approximate one-gram reserve sample of the test substance was taken on April 7, 1997, and stored in the Archives at WIL Research Laboratories, Inc.

2. CONTROL SUBSTANCE IDENTIFICATION

The vehicle control substance utilized in preparation of the test mixtures and for administration to the control group was Optima, an HPLC grade water, received from Fisher Scientific Company, Pittsburgh, Pennsylvania, on March 14, 1997.

3. PREPARATION

An appropriate amount of the vehicle control substance, Optima (HPLC grade 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 sampling and dosing procedures.

The test substance formulations were prepared as follows. An appropriate amount of the test substance, flusilazole, was dispensed for each group into a properly-labeled storage container containing a stir bar. The dosing preparations for the 400 mg/ml group were used undiluted as supplied by the sponsor. A sufficient volume of the vehicle control substance, Optima (HPLC grade water), was added to the 5 and 50 mg/ml preparations to bring the volume in the container to 100 ml. The preparations were stirred on a magnetic stir plate throughout the sampling and dosing procedures.

The preparations for all dose groups were made as needed (April 7, 14 and/or 21, 1997) and were stored at room temperature. The test substance formulations were visually inspected for homogeneity by the deputy director on April 7, 1997, and were found to be acceptable for use.

4. ADMINISTRATION

Approximately 24 hours before the initial application of the test substance, the back (approximately 10% of the body surface) of each rat was clipped with Oster® small animal clippers. Clipping was repeated, if necessary, during the treatment period.

The test substance, flusilazole, was applied to the intact dorsal skin of each test animal for six hours per day from gestation days 6 through 19. The concurrent control group was dosed with the vehicle control substance, Optima (HPLC grade water), following procedures identical to those described for the treated groups. The application sites were not abraded or occluded. All animals were dosed at approximately the same time each day. The following diagram represents study group assignment:

<u>Group Number</u>	<u>Test Substance</u>	<u>Dosage Concentration (mg/ml)</u>	<u>Dosage Volume (ml/rat)</u>	<u>Number of Females</u>
1	Vehicle Control	0	0.5	8
2	Flusilazole	5	0.5	8
3	Flusilazole	50	0.5	8
4	Flusilazole	400 ^a	0.5	8

^a = Undiluted test article

During the exposure period, oral ingestion of the control and test substances was prevented by placing an Elizabethan collar on each animal. The animals were acclimated to the collars prior to breeding according to the protocol. Following the 6-hour exposure period, the collars were removed and the application sites were wiped off using diluted detergent (1% Ivory hand soap) in optima and a wet towel, then towel-dried. The interior surfaces of the cages were wiped with moistened towels to remove any residual test substance.

5. SAMPLING AND ANALYSES

At the request of the sponsor, homogeneity and stability of the dosing formulations were not determined prior to the initiation of dosing. Two aliquots (10 ml) from the control group formulation, two aliquots each from the top, middle and bottom strata of the treated group formulations (Groups 2-3), and 1 ml each from the top, middle and bottom strata of the Group 4 formulation (as supplied by the sponsor) prepared for the initial week of administration were withdrawn on April 7, 1997 and frozen for possible future analysis. In addition, one 10 ml aliquot for the control group and each remaining treated group formulation (middle stratum) was taken during each subsequent weekly preparation (April 14 and 21, 1997) from the storage containers and stored frozen for possible future analysis of concentration.

C. ANIMAL RECEIPT AND ACCLIMATION

Sixty sexually mature, virgin female rats, CrI:CD®(SD)BR, were received in good health from Charles River Laboratories, Inc., Portage, Michigan, on March 20, 1997. The animals were approximately 70 days old. Upon receipt, each animal was observed by a qualified technician. The animals were initially weighed on March 21, 1997. All animals were uniquely identified by a Monel metal eartag displaying the animal number and housed for 12 days for acclimation purposes. During the acclimation period, the animals were observed twice daily for mortality and moribundity.

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, the females were 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. Animals were maintained in accordance with the "Guide for the Care and Use of Laboratory Animals¹." 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. 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 present in animal feed or water were not expected to interfere with the objectives of this study. Drinking water delivered by an automatic watering system and the feed 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 $72^{\circ} \pm 4^{\circ}\text{F}$ and a relative humidity between 30%-70%. Room temperature and relative humidity were recorded daily, with the following exception. Temperature and relative humidity were inadvertently not recorded on April 8, 1997. However, on April 9, 1997 the temperature and relative humidity were within the specified range; therefore, the deviation was not expected to affect the outcome of the study. Temperatures ranged from 70.1°F to 73.6°F and relative humidity ranged from 25.4% to 41.7% during the study period. The occasional deviations from the set temperature and relative humidity levels were expected to have no impact on the outcome of the study. 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 at the initiation of breeding) 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 in the vagina 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 _____ consisted of three treated groups and one control group. The individual body weights were entered into the WIL Toxicology Data Management System (WTDMS™). A printout containing the animal numbers, corresponding body weights and individual group assignments was generated based on body weight stratification in a block design. The animals then were arranged according to the printout. Body weight values ranged from 220 g to 260 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 day 0 through 20 of gestation (prior to test substance administration during the dosing period).

The females that died or were euthanized *in extremis* during the study were necropsied that day. The number and location of implantation sites and corpora lutea and the number of viable fetuses were recorded. Maternal tissues were retained in 10% neutral buffered formalin for possible future histopathological examination only as deemed necessary by the gross findings.

2. DERMAL IRRITATION

Application sites were examined for erythema, edema and other dermal findings once daily, prior to treatment when applicable, from gestation days 6 through 20. Erythema and edema were evaluated on a four step grading system of very slight, slight, moderate and severe (Appendix B). Other dermal findings, if present, were noted.

3. BODY WEIGHTS AND GRAVID UTERINE WEIGHTS

Individual maternal body weights were recorded on gestation days 0 and 6-20 (daily). 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 intervals 6-9, 9-12, 12-20, 6-20 and 0-20.

Gravid uterine weight was collected and net body weight (the day 20 body weight exclusive of the weight of the uterus and contents) and net body weight

change (the day 0-20 body weight change exclusive of the weight of the uterus and contents) were calculated and presented for each gravid female at the scheduled laparohysterectomy.

4. FOOD CONSUMPTION

Individual food consumption was recorded on gestation days 0 and 6-20 (daily). Food intake was reported as g/animal/day and g/kg/day for the corresponding body weight change intervals.

I. GESTATION DAY 20 LAPAROHYSTERECTOMY

All surviving maternal animals were euthanized by carbon dioxide inhalation on gestation day 20. The thoracic, abdominal and pelvic cavities were opened by a ventral midline incision and the contents 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 excised. The number of corpora lutea on each ovary was recorded. The trimmed uterus was weighed and opened, and the number and location of all fetuses, early and late resorptions and the total number of implantation sites were recorded. The individual uterine distribution of implantation sites was documented using the following procedure. All implantation sites, including resorptions, were numbered in consecutive order beginning with the left distal to the left proximal uterine horn, noting the position of the cervix, and continuing from the right proximal to the right distal uterine horn.

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 Salewski². Maternal tissues were retained only as deemed necessary by the gross findings.

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

1. Group Mean Litter Basis:

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

2. Proportional Litter Basis:

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

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

J. FETAL MORPHOLOGICAL EXAMINATION

A detailed external examination of each fetus was conducted to include, but was not limited to, the eyes, palate and external orifices. Findings were recorded as either developmental variations (alterations in anatomic structure that are considered to have no significant biological effect on animal health or body conformity, representing slight deviations from normal) or malformations (those structural anomalies that alter general body conformity, disrupt or interfere with body function or may be incompatible with life). The weight and sex were recorded for each fetus and the fetuses were euthanized and discarded. Crown-rump measurements were recorded for late resorptions, if present, and the tissues were discarded.

K. 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. Means were presented with the standard deviation (S.D.) and the number of animals (N) used to calculate the mean. The following statistical tests were performed by a Digital® MicroVAX® 3400 computer (with appropriate programming) in this laboratory and are referenced in the report tables:

<u>STATISTICAL TEST</u>	<u>PARAMETER</u>
- One-way ANOVA with Dunnett's test ³	Corpora Lutea, Total Implantations, Fetal Body Weights, Maternal Body Weights and Weight Changes, Maternal Net Body Weight Changes and Gravid Uterine Weights, Food Consumption
- Kruskal-Wallis test with Mann-Whitney U test ³	Litter Proportions of Intrauterine Data (Considering the Litter, Rather than the Fetus, as the Experimental Unit)

L. PHARMACOKINETIC PHASE

A pharmacokinetic phase was conducted in conjunction with the range-finding phase of the study. In the pharmacokinetic phase, eight rats per group (Groups 5 and 6) were administered 400 mg/ml of flusilazole on gestation day 6 (Group 5) or on gestation days 6-19 (Group 6). Blood samples were collected from two animals each at 1, 2, 4 and 6 hours following dosing on gestation day 6 (Group 5) and two animals each after the daily exposure on gestation days 7, 11, 15 and 19 (Group 6), with the following exception. At the request of the sponsor, all of the remaining animals in Group 6 were euthanized *in extremis* on April 16, 1997 (gestation days 12 or 14) precluding blood collection and plasma analysis on gestation day 19. Plasma was separated and submitted to the sponsor for analysis of the levels of flusilazole

The raw data and methodology of the biological (in-life) component of the pharmacokinetic phase are presented in Appendix C.

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 substance and the original final report will be retained at WIL Research Laboratories, Inc., in compliance with regulatory requirements.

VIII. RESULTS

A. CLINICAL OBSERVATIONS AND SURVIVAL

Summary Data: Tables 1, 2

Individual Data: Table 14

In the 400 mg/ml group, three females (nos. 65253, 65274 and 65303) died on gestation days 13, 14 and 11, respectively. Due to the excessive maternal toxicity observed at this concentration, the remaining five females in this group were euthanized *in extremis* on April 16, 1997 (corresponding to gestation days 13 or 14) at the request of the sponsor. Clinical observations in the 400 mg/ml group included red material around the eyes and nose, yellow staining around the urogenital and ventral abdominal areas and brown matting or staining around the mouth, ventral abdominal and urogenital areas.

All animals in the control, 5 and 50 mg/ml groups survived to the scheduled necropsy on gestation day 20. The only treatment-related clinical observations noted in the 50 mg/ml group were brown staining around the mouth and yellow staining around the urogenital area. Other clinical findings in the treated groups, such as hair loss, occurred in single animals or in a manner that was not suggestive of a relationship to treatment.

B. DERMAL IRRITATION

Summary Data: Table 3

Individual Data: Table 15

Erythema was observed in a dose-related manner in all of the flusilazole treated groups. In the 400 mg/ml group, all eight females had slight to severe erythema from gestation day 10 through death or euthanization (gestation day 14). Very slight to moderate erythema was noted at the application site of all eight females in the 50 mg/ml group by gestation day 12 and continuing through death or euthanization. In the 5 mg/ml group, three females were observed with very slight or slight erythema between gestation days 16 and 20. Desquamation was noted in 8 and 5 females in the 50 and 400 mg/ml groups, respectively, beginning on gestation day 11 and continuing through death, euthanization or study termination. Fissuring

was observed in one (gestation days 16-20) and seven (gestation days 10 through death or euthanization) females in these same respective dose groups. In the 400 mg/ml group, atonia was noted for five females on gestation days 12 or 13. No other signs of dermal irritation were observed at these levels. No signs of dermal irritation were noted in the control group.

C. BODY WEIGHTS AND GRAVID UTERINE WEIGHTS

Summary Data: Tables 4, 5, 6, Figure 1

Individual Data: Tables 16, 17, 18

In the 400 mg/ml group, a statistically significant ($p < 0.01$) mean body weight loss was noted during gestation days 6-9. During this interval, all 7 gravid females lost between 5 and 33 grams of body weight. A mean body weight loss continued in this group during gestation days 9-12; the difference from the control group was statistically significant ($p < 0.01$). Statistically significant ($p < 0.01$) decreases in mean body weights were noted for animals in the 400 mg/ml group for gestation days 9-13. Further assessment of body weight data in this group was precluded by mortalities and group termination.

In the 50 mg/ml group, mean body weight gains were similar to the control group values during gestation days 6-9 and 9-12. During the remainder of the treatment period (gestation days 12-20), mean body weight gain in this group was moderately reduced. When the entire treatment period (gestation days 6-20) was evaluated, mean body weight gain in the 50 mg/ml group was reduced compared to the control group value. Mean body weights in this group were reduced from gestation days 18-20. Mean net body weight, net body weight gain and gravid uterine weight in the 50 mg/ml group were slightly reduced compared to the control group values. None of the differences from the control group were statistically significant.

Mean body weights, body weight gains, net body weight, net body weight gain and gravid uterine weight in the 5 mg/ml group were unaffected by treatment with the test substance. Values in this group were comparable to the control group values; none of the differences were statistically significant.

D. FOOD CONSUMPTION

Summary Data: Tables 7, 8

Individual Data: Tables 19, 20

Food consumption, evaluated as g/animal/day and g/kg/day, was reduced in the 400 mg/ml group during gestation days 6-9 and 9-12; the differences from the control group were often statistically significant ($p < 0.01$). Further assessment of food consumption in this group was precluded by mortalities and group termination.

Food consumption (g/animal/day and g/kg/day) in the 50 mg/ml group was comparable to the control group during gestation days 6-9 and 9-12. During the remainder of the treatment period (gestation days 12-20), food consumption was slightly reduced in this group; the differences from the control group were statistically significant ($p < 0.05$). When the overall treatment period (gestation days 6-20) was evaluated, food consumption in the 50 mg/ml group was slightly reduced; the difference from the control group was not statistically significant.

Food consumption was unaffected by test substance administration at a dose level of 5 mg/ml. No statistically significant differences from the control group were observed.

E. NECROPSY DATA

Individual Data: Table 21

In the 400 mg/ml group, all eight females died or were euthanized *in extremis* between gestation days 11 and 14. At necropsy, five females had thickened skin at the application site and one female had scabbing. Two females (nos. 65270 and 65274) had reddened and/or enlarged adrenal glands; female no. 65270 also had a swollen liver with a white area and red fluid contents in the vagina. Female no. 65776 had white areas on the liver and a dilated renal pelvis. Uterine findings for the 400 mg/ml group females consisted of the following. Four females had all normally developing implantations, three females had normally developing implantations with one or two early resorptions and one female was nongravid.

At the scheduled necropsy on gestation day 20, three and four females in the 5 and 50 mg/ml groups, respectively, had enlarged placentae (generally at multiple

sites). One female (no. 65254) in the 50 mg/ml group had a dilated renal pelvis. In the 5 mg/ml group, female no. 65286 had green purulent material in the vagina. All other females were internally normal.

F. GESTATION DAY 20 LAPAROHYSTERECTOMY DATA

Summary Data: Tables 9, 10

Individual Data: Tables 22, 23, 24

Historical Control Data: Appendices E, F

No gravid females in the 400 mg/ml group survived to the scheduled necropsy on gestation day 20. In the 50 mg/ml group, a statistically significant ($p < 0.01$) increase in postimplantation loss (63.5% per litter) was observed when compared to the concurrent control group value (2.6% per litter) and the maximum value in the WIL historical control data (13.5% per litter). The increased incidence of postimplantation loss in this group was primarily due to an increase in the number of late resorptions (35.2% per litter) and early resorptions (26.9% per litter). When these values were compared to the concurrent control group values (0 and 2.6% per litter, respectively), the differences were statistically significant ($p < 0.01$). The values for late and early resorptions in the 50 mg/ml group were also outside the range of the WIL historical control data (0-3.2 and 1.8-13.5% per litter, respectively); a corresponding decrease in the number of viable fetuses (36.6% per litter) in this group was noted when compared to the control group value (97.4% per litter)

A slight increase in postimplantation loss (15.2% per litter) was noted in the 5 mg/ml group when compared to the concurrent control group value (2.6% per litter). As in the higher dose groups, the increase in postimplantation loss in this group was attributed to an increase in the number of early and late resorptions (11.9 and 3.3% per litter, respectively). When compared to the concurrent control group values (2.6 and 0% per litter, respectively), the differences were not statistically significant. In the 5 mg/ml group, a corresponding decrease in the number of viable fetuses (84.8% per litter) was noted when compared to the control group value (97.4% per litter). Other parameters evaluated included fetal body weights, fetal sex ratios and the

numbers of corpora lutea and implantation sites; no treatment-related differences from the control group were apparent.

G. FETAL MORPHOLOGICAL DATA

Summary Data: Tables 11, 12

Individual Data: Table 25

Historical Control Data: Appendices E, F

The numbers of fetuses (litters) available for morphological evaluation were 89(6), 84(7), 32(6) and 0(0) in the control, 5, 50 and 400 mg/ml groups, respectively. The only external malformation observed was localized fetal edema in one 50 mg/ml group fetus (no. 65280-01). It should be noted that one dead fetus (no. 65296-05) in the 50 mg/ml group also had localized fetal edema. No external developmental variations were observed in fetuses at any concentration.

H. PHARMACOKINETIC DATA

Summary Data: Table 13, Figures 2, 3

Individual Data: Appendix D

Following exposure to a single dermal application of undiluted on GD 6 (Group 5; serial sacrifice of n=2 at 1, 2, 4, and 6 hr) these trends were noted:

- detectable levels of flusilazole were observed in plasma at 1 hr (0.281 ppm);
- the absolute maximum plasma level achieved (C_{max}) occurred at 6 hr (2.51 ppm);
- approximately 2-3 ppm concentration of flusilazole was sustained through a majority of the exposure interval (2-6 hr), suggesting that steady-state penetration had been achieved by 2 hr, and that the dose applied to the skin had not been depleted prior to wash-off at 6 hr.

Following a daily 6 hour exposure of a single dermal application of undiluted starting on GD 6 with serial sacrifice of rats on GD 7, GD 11, GD 15, and GD 19 (Group 6; n=2 per day, except GD 19, n=1) these trends were noted:

- the levels of flusilazole in plasma were comparable (~3 ppm) on GD 7, 11, and 15; this repeating plasma concentration pattern suggests that steady-state was achieved, as the levels observed here for Group 6 were similar to the maximum sustained plasma levels of flusilazole measured following a single application of the on GD 6 (Group 5);
- GD 19 (n=1) was dissimilar to all other gestation days, and therefore, was considered not representative of actual flusilazole plasma concentration;
- the data suggest that flusilazole does not bioaccumulate since plasma levels are similar over the course of repeated dermal application (GD 7, 11, and 15); the

dermally absorbed dose was cleared from the systemic circulation prior to next dermal dose event;

- since the absorbed dose was cleared prior to the next dose interval, the terminal elimination half-life ($t_{1/2}$) of flusilazole can be estimated to be equal to or less than 6 hr from the relationship, τ (time between dose periods; 18 hr) $< 3 \cdot t_{1/2}$.

IX. DISCUSSION AND CONCLUSIONS

In the 400 mg/ml group, three females died between gestation days 11 and 13. Due to the excessive maternal toxicity observed, the remaining five females in this group were euthanized *in extremis* on April 16, 1997 (corresponding to gestation days 13 or 14). All other females survived to the scheduled necropsy on gestation day 20. Treatment-related clinical observations noted in the 50 and/or 400 mg/ml groups were brown staining or matting around the mouth, urogenital and ventral abdominal areas, yellow staining around the urogenital and ventral abdominal areas and red material around the eyes and nose. No treatment-related clinical observations were noted at a dose level of 5 mg/ml.

Very slight to severe erythema occurred at the application site in all of the treated groups. The majority of these findings were noted between gestation days 8 and 20. Desquamation and fissuring was noted in a dose-related manner in the 50 and 400 mg/ml groups. In addition, five females in the 400 mg/ml group had atonia on gestation days 12 or 13. No signs of dermal irritation were observed in the control group.

Statistically significant mean body weight losses were observed in the 400 mg/ml group during gestation days 6-9 and 9-12. Further assessment of body weight data in the 400 mg/ml group was precluded by mortalities and group termination. Mean body weight gain in the 50 mg/ml group was comparable to the control group value during gestation days 6-9 and 9-12 and was reduced during gestation days 12-20. Mean body weights were reduced in the 50 mg/ml group from gestation days 18-20. Mean net body weight, net body weight gain and gravid uterine weight in the 50 mg/ml group were slightly reduced when compared to the control group values. Mean body weights, body weight gains, net body weight, net body weight gain and gravid uterine weight in the 5 mg/ml group were unaffected by test substance administration.

Food consumption, evaluated as g/animal/day and g/kg/day, was reduced in the 400 mg/ml group during gestation days 6-9 and 9-12; the differences from the control group were often statistically significant. Further assessment of food consumption in the 400 mg/ml group was precluded by mortalities and group termination. During gestation days 6-9 and 9-12, food consumption in the 50 mg/ml group was comparable to the control group values. In the 50 mg/ml group, food consumption was reduced (statistically

significant) from gestation days 12-20. Food consumption in the 5 mg/ml group was unaffected by treatment with the test substance.

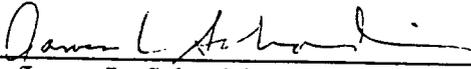
At the necropsy of the animals that died or were euthanized *in extremis*, six females in the 400 mg/ml group had thickened skin or scabbing at the application site. At the scheduled necropsy on gestation day 20, 3 and 4 females in the 5 and 50 mg/ml groups, respectively, had enlarged placentae. All other females were internally normal.

Increased postimplantation losses in the 5 and 50 mg/ml groups were noted when compared to the concurrent control group values and the maximum value in the WIL historical control data. The increases were attributed to increases in early and late resorptions. The majority of the differences were statistically significant. Corresponding decreases in the percentages of viable fetuses were observed in the 5 and 50 mg/ml groups when compared to the control group value and/or the WIL historical control data. Fetal body weights, fetal sex ratios and the numbers of corpora lutea and implantation sites in the 5 and 50 mg/ml groups were unaffected by test substance administration.

Fetuses (litters) available for morphological evaluation numbered 89(6), 84(7), 32(6) and 0(0) in the control, 5, 50 and 400 mg/ml groups, respectively. The only external malformation observed was localized fetal edema in one 50 mg/ml group fetus and was considered spontaneous in origin. No external developmental variations were noted in fetuses at any dose level.

Analysis of plasma from the satellite pharmacokinetic groups suggests that steady-state plasma levels of flusilazole of approximately 2-3 ppm were achieved following a single dermal application of undiluted and a continuous 6 hr exposure. The plasma data also suggest that flusilazole does not bioaccumulate since the maximum plasma concentration range reoccurred in both the single dose study (Group 5) and repeated dose study (Group 6 - excluding GD 19). Lastly, since the concentration of flusilazole in plasma does not increase upon repeated dermal exposure, the plasma data suggest that the dose which is absorbed over the 6 hr exposure period is cleared from the systemic circulation prior to the next exposure interval. Based on this observation, the terminal elimination half-life ($t_{1/2}$) of flusilazole was estimated to be equal to or less than 6 hr.

In conclusion, dermal irritation (characterized by very slight to severe erythema, desquamation, fissuring and/or atonia) was noted in a dose-related manner in all of the treated groups. Maternal toxicity was expressed by mortalities at a concentration of 400 mg/ml and by inhibition of body weight gain and food consumption at dose levels of 50 and 400 mg/ml. No maternal toxicity was observed at a concentration of 5 mg/ml. Developmental toxicity was exhibited by increased postimplantation losses (early and late resorptions) in the 5 and 50 mg/ml groups.



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Study Director

1/13/98
Date

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A Dermal Dose Range-Finding Prenatal
Developmental Toxicity Study of Flusilazole in Rats

TABLES 1-25

TABLE 1
 DERMAL R-F DEV. TOX. STUDY OF _____ IN RATS
 SUMMARY OF MATERNAL SURVIVAL AND PREGNANCY STATUS

DOSE GROUP :	1		2		3		4	
	NO.	%	NO.	%	NO.	%	NO.	%
FEMALES ON STUDY	8		8		8		8	
FEMALES THAT ABORTED OR DELIVERED	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
FEMALES THAT ABORTED	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
GRAVID	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
NONGRAVID	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
FEMALES EXAMINED AT SCHEDULED NECROPSY	8	100.0	8	100.0	8	100.0	8	100.0
NONGRAVID	2	25.0	1	12.5	2	25.0	2	25.0
GRAVID	6	75.0	7	87.5	6	75.0	6	75.0
WITH RESORPTIONS ONLY	0	0.0	0	0.0	0	0.0	0	0.0
WITH VIABLE FETUSES	6	100.0	7	100.0	6	100.0	6	100.0
TOTAL FEMALES GRAVID	6	75.0	7	87.5	6	75.0	6	75.0
1- 0 MG/ML								
2- 5 MG/ML								
3- 50 MG/ML								
4- 400 MG/ML								

TABLE 2 (DAILY EXAMINATIONS)
 DERMAL R-F DEV. TOX. STUDY OF IN RATS
 SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

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

TABLE RANGE: GROUP:	04-01-97 TO 04-24-97			
	1	2	3	4
NORMAL	168/ 8	143/ 8	109/ 8	64/ 8
-NO SIGNIFICANT CLINICAL OBSERVATIONS				
DISPOSITION				
-FOUND DEAD	0/ 0	0/ 0	0/ 0	3/ 3
-SENT TO LAB IN EXTREMIS	0/ 0	0/ 0	0/ 0	5/ 5
-SENT TO LAB FOR SCHEDULED LAPAROMYSTERECTOMY GESTATION DAY 20	8/ 8	8/ 8	8/ 8	0/ 0
BODY/INTEGUMENT				
-DRIED BROWN MATTING VENTRAL ABDOMINAL AREA	0/ 0	0/ 0	1/ 1	3/ 2
-DRIED BROWN STAINING UROGENITAL AREA	0/ 0	0/ 0	4/ 1	13/ 7
-WET YELLOW STAINING UROGENITAL AREA	0/ 0	0/ 0	8/ 3	23/ 8
-JAWS APPEAR SWOLLEN	0/ 0	6/ 1	0/ 0	0/ 0
-DRIED BROWN VENTRAL NECK AREA	0/ 0	0/ 0	0/ 0	2/ 2
-HAIR LOSS RIGHT FORELIMB	0/ 0	8/ 3	7/ 1	1/ 1
-HAIR LOSS LEFT FORELIMB	0/ 0	7/ 3	5/ 1	1/ 1
-WET RED VAGINAL DISCHARGE	0/ 0	0/ 0	7/ 2	1/ 1
-WET YELLOW STAINING VENTRAL ABDOMINAL AREA	0/ 0	0/ 0	0/ 0	9/ 5
-DRIED YELLOW STAINING UROGENITAL AREA	0/ 0	0/ 0	37/ 7	1/ 1
1- 0 MG/ML	2- 5 MG/ML	3- 50 MG/ML	4- 400 MG/ML	

TABLE 2 (DAILY EXAMINATIONS)
 DERMAL R-F DEV. TOX. STUDY OF IN RATS
 SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

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

TABLE RANGE: 04-01-97 TO 04-24-97

GROUP:	1	2	3	4
BODY/INTEGUMENT				
-LETHARGIC	0/0	0/0	0/0	1/1
-HUNCHED APPEARANCE	0/0	0/0	0/0	1/1
-BODY COOL TO TOUCH	0/0	0/0	0/0	1/1
-DRIED BROWN MATERIAL RIGHT FORELIMB	0/0	0/0	0/0	1/1
-DRIED BROWN MATERIAL LEFT FORELIMB	0/0	0/0	0/0	1/1
-DRIED RED STAINING UROGENITAL AREA	0/0	0/0	0/0	1/1
-DRIED RED STAINING VENTRAL ABDOMINAL AREA	0/0	0/0	3/2	0/0
-DRIED RED STAINING RIGHT HINDLIMB	0/0	0/0	2/1	0/0
-DRIED RED STAINING LEFT HINDLIMB	0/0	0/0	2/1	0/0
-DRIED RED STAINING ENTIRE LENGTH OF TAIL	0/0	0/0	2/1	0/0
-WET RED MATERIAL ON CAGE PAPER	0/0	0/0	1/1	0/0
CARDIO-PULMONARY				
-SHALLOW RESPIRATION	0/0	0/0	0/0	1/1
EYES/EARS/NOSE				
-RIGHT EAR APPEARS PURPLE IN COLOR AND SWOLLEN	0/0	12/1	13/1	0/0
-RIGHT EAR APPEARS RED AND SWOLLEN	0/0	6/2	0/0	0/0
-DRIED RED MATERIAL AROUND LEFT EYE	0/0	0/0	0/0	16/4
1- 0 MG/ML	2- 5 MG/ML	3- 50 MG/ML	4- 400 MG/ML	

TABLE 2 (DAILY EXAMINATIONS)
 DERMAL R-F DEV. TOX. STUDY OF IN RATS
 SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

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

TABLE RANGE:		04-01-97 TO 04-24-97			
GROUP:		1	2	3	4
EYES/EARS/NOSE					
-DRIED RED MATERIAL AROUND NOSE		0/0	0/0	3/2	25/7
-DRIED RED MATERIAL AROUND RIGHT EYE		0/0	0/0	0/0	15/4
ORAL/DENTAL					
-DRIED BROWN STAINING AROUND MOUTH		0/0	0/0	3/2	8/6
1- 0 MG/ML	2- 5 MG/ML	3- 50 MG/ML	4- 400 MG/ML		

TABLE 3
 DERMAL R-F DEV. TOX. STUDY OF
 DERMAL OBSERVATIONS: TOTAL INCIDENCE / NO. OF ANIMALS
 IN RATS
 PAGE 1

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

TABLE RANGE: 04-01-97 TO 04-24-97

DERMAL OBS	1	2	3	4
-SCORED, NOT REMARKABLE	120/8	111/8	39/8	22/8
-NO ERYTHEMA	0/0	0/0	1/1	0/0
-ERYTHEMA - VERY SLIGHT	0/0	8/3	41/8	0/0
-ERYTHEMA - SLIGHT	0/0	1/1	31/8	3/3
-ERYTHEMA - MODERATE	0/0	0/0	8/1	8/8
-ERYTHEMA - SEVERE	0/0	0/0	0/0	9/6
-NO EDEMA	0/0	9/3	0/0	19/7
-FISSURING	0/0	0/0	81/8	39/8
-DESQUAMATION	0/0	0/0	5/1	22/7
-ATONIA	0/0	0/0	41/8	11/5
1- 0 MG/ML	2- 5 MG/ML	3- 50 MG/ML	4- 400 MG/ML	5/5

TABLE 4
 DERMAL R-F DEV. TOX. STUDY OF
 MEAN BODY WEIGHTS (GRAMS) DURING GESTATION
 IN RATS
 PAGE 1

DAY	MEAN S.D./N	GROUP :			
		1	2	3	4
DAY 0	239. 10.7/ 6	239. 10.7/ 6	242. 11.6/ 7	239. 11.1/ 6	242. 11.1/ 7
DAY 6	270. 12.4/ 6	270. 12.4/ 6	273. 7.7/ 7	272. 14.0/ 6	277. 10.7/ 7
DAY 7	274. 10.0/ 6	274. 10.0/ 6	274. 9.6/ 7	274. 13.9/ 6	271. 9.5/ 7
DAY 8	278. 11.2/ 6	278. 11.2/ 6	278. 6.9/ 7	278. 14.5/ 6	268. 6.8/ 7
DAY 9	282. 10.0/ 6	282. 10.0/ 6	282. 4.5/ 7	282. 14.3/ 6	261.** 12.9/ 7
DAY 10	285. 12.5/ 6	285. 12.5/ 6	288. 5.8/ 7	286. 15.2/ 6	252.** 21.0/ 7
DAY 11	292. 11.6/ 6	292. 11.6/ 6	291. 6.1/ 7	289. 14.3/ 6	256.** 14.9/ 6
DAY 12	298. 13.6/ 6	298. 13.6/ 6	297. 8.0/ 7	294. 11.0/ 6	248.** 28.7/ 6
DAY 13	302. 13.7/ 6	302. 13.7/ 6	303. 7.0/ 7	298. 11.9/ 6	250.** 13.4/ 5
DAY 14	308. 11.9/ 6	308. 11.9/ 6	309. 9.8/ 7	302. 11.0/ 6	255. 0.0/ 1

1- 0 MG/ML 2- 5 MG/ML 3- 50 MG/ML 4- 400 MG/ML
 ** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
 NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 4
 DERMAL R-F DEV. TOX. STUDY OF : IN RATS
 MEAN BODY WEIGHTS (GRAMS) DURING GESTATION

DAY	MEAN S.D./N	GROUP :			
		1	2	3	4
DAY 15	313. 14.7/ 6	316. 9.8/ 7	309. 12.5/ 6	0. 0.0/ 0	
DAY 16	322. 13.8/ 6	328. 11.1/ 7	319. 15.6/ 6	0. 0.0/ 0	
DAY 17	336. 17.3/ 6	337. 11.9/ 7	326. 14.3/ 6	0. 0.0/ 0	
DAY 18	351. 19.4/ 6	351. 14.3/ 7	334. 17.5/ 6	0. 0.0/ 0	
DAY 19	365. 27.9/ 6	366. 21.4/ 7	343. 16.9/ 6	0. 0.0/ 0	
DAY 20	381. 26.5/ 6	382. 23.4/ 7	351. 17.6/ 6	0. 0.0/ 0	

1- 0 MG/ML 2- 5 MG/ML 3- 50 MG/ML 4- 400 MG/ML
 NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING A TWO-TAILED DUNNETT'S TEST
 NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

FIGURE 1
DERMAL R-F DEV. TOX. STUDY OF
MEAN BODY WEIGHTS (GRAMS) DURING GESTATION
IN RATS

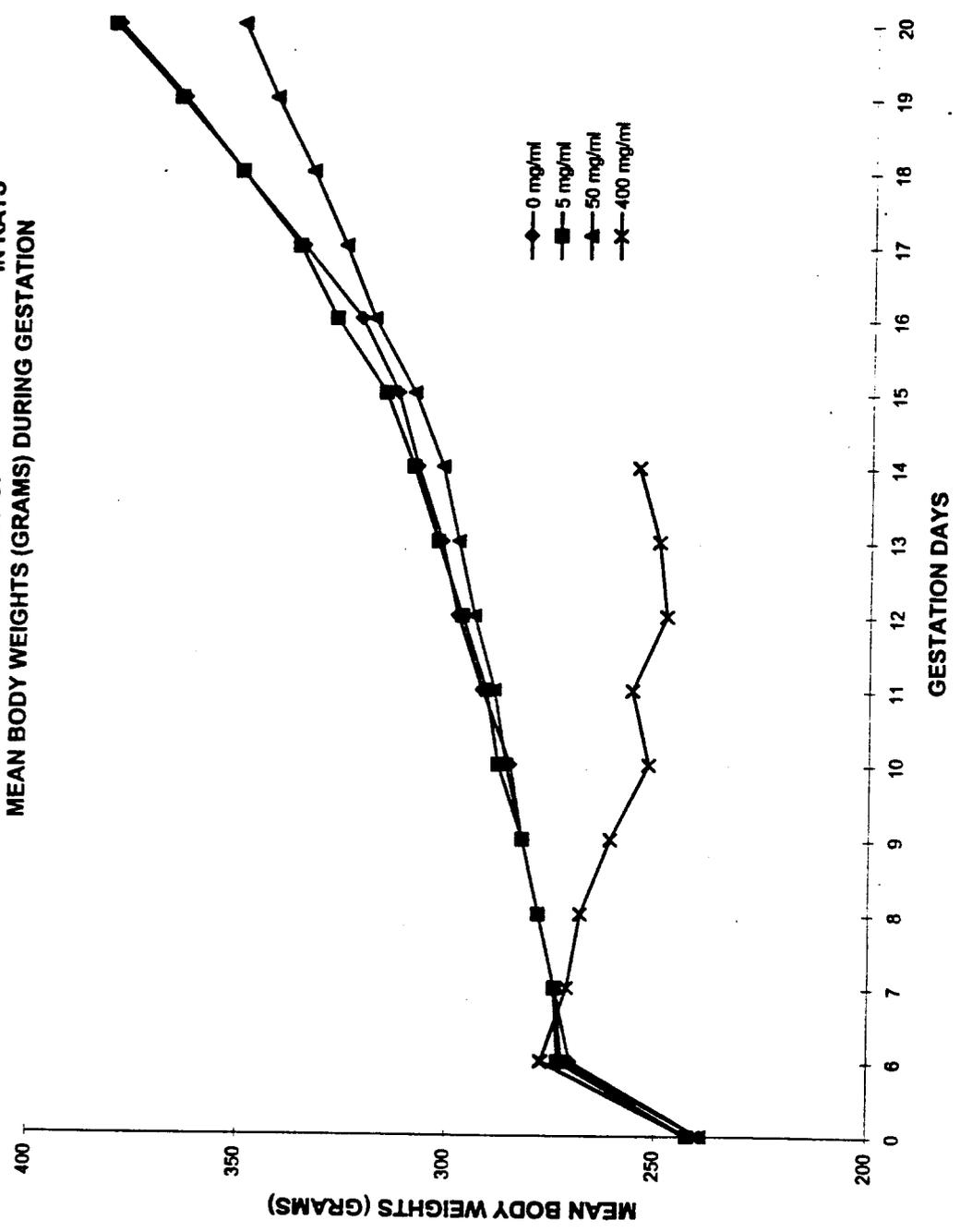


TABLE 5
 DERMAL R-F DEV. TOX. STUDY OF . . . IN RATS
 MEAN BODY WEIGHT CHANGES (GRAMS) DURING GESTATION

GROUP :		1	2	3	4
DAY 0- 6 MEAN	30.	30.	31.	34.	35.
S.D./N	9.2/ 6	6.7/ 7	4.5/ 6	9.4/ 7	
DAY 6- 7 MEAN	4.	1.	2.	-6.**	
S.D./N	4.4/ 6	6.2/ 7	3.3/ 6	4.5/ 7	
DAY 7- 8 MEAN	4.	4.	4.	-3.*	
S.D./N	3.2/ 6	5.0/ 7	3.4/ 6	3.4/ 7	
DAY 8- 9 MEAN	5.	4.	3.	-7.*	
S.D./N	2.3/ 6	5.6/ 7	2.6/ 6	10.9/ 7	
DAY 9- 10 MEAN	2.	6.	4.	-9.**	
S.D./N	5.4/ 6	3.8/ 7	2.5/ 6	9.4/ 7	
DAY 10- 11 MEAN	7.	3.	3.	-3.	
S.D./N	7.0/ 6	5.3/ 7	1.9/ 6	12.2/ 6	
DAY 11- 12 MEAN	6.	6.	5.	-8.*	
S.D./N	5.3/ 6	4.5/ 7	5.0/ 6	17.3/ 6	
DAY 12- 13 MEAN	4.	7.	4.	-9.	
S.D./N	5.8/ 6	2.6/ 7	2.6/ 6	22.7/ 5	
DAY 13- 14 MEAN	6.	6.	4.	1.	
S.D./N	2.9/ 6	3.9/ 7	3.5/ 6	0.0/ 1	
DAY 14- 15 MEAN	5.	7.	7.	0.	
S.D./N	3.9/ 6	5.6/ 7	4.4/ 6	0.0/ 0	

1- 0 MG/ML 2- 5 MG/ML 3- 50 MG/ML 4- 400 MG/ML
 * = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST
 ** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
 MEAN DIFFERENCES CALCULATED FROM INDIVIDUAL DIFFERENCES
 NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 5
 DERMAL R-F DEV. TOX. STUDY OF : IN RATS
 MEAN BODY WEIGHT CHANGES (GRAMS) DURING GESTATION

GROUP :	1	2	3	4
DAY 15- 16 MEAN	10.	12.	11.	0.
S.D./N	3.3/ 6	5.0/ 7	4.2/ 6	0.0/ 0
DAY 16- 17 MEAN	13.	10.	7.	0.
S.D./N	5.1/ 6	3.9/ 7	6.6/ 6	0.0/ 0
DAY 17- 18 MEAN	16.	14.	8.*	0.
S.D./N	4.5/ 6	4.5/ 7	4.8/ 6	0.0/ 0
DAY 18- 19 MEAN	14.	15.	9.	0.
S.D./N	10.3/ 6	9.8/ 7	2.9/ 6	0.0/ 0
DAY 19- 20 MEAN	16.	16.	8.	0.
S.D./N	3.6/ 6	5.1/ 7	6.6/ 6	0.0/ 0
DAY 6- 9 MEAN	13.	9.	9.	-16.**
S.D./N	6.0/ 6	6.3/ 7	5.4/ 6	11.3/ 7
DAY 9- 12 MEAN	16.	15.	13.	-18.**
S.D./N	5.8/ 6	4.7/ 7	4.8/ 6	27.9/ 6
DAY 12- 20 MEAN	83.	85.	57.	0.
S.D./N	18.3/ 6	19.1/ 7	15.2/ 6	0.0/ 0
DAY 6- 20 MEAN	111.	109.	79.	0.
S.D./N	24.3/ 6	23.4/ 7	19.5/ 6	0.0/ 0
DAY 0- 20 MEAN	142.	141.	112.	0.
S.D./N	27.3/ 6	23.3/ 7	20.1/ 6	0.0/ 0

1- 0 MG/ML 2- 5 MG/ML 3- 50 MG/ML 4- 400 MG/ML
 * = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST
 ** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
 MEAN DIFFERENCES CALCULATED FROM INDIVIDUAL DIFFERENCES
 NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 6
 DERMAL R-F DEV. TOX. STUDY OF
 IN RATS
 MEAN GRAVID UTERINE WEIGHTS AND NET BODY WEIGHT CHANGES (GRAMS)

	GROUP:			
	1	2	3	4
INITIAL BODY WT.	239. 10.7 6	242. 11.6 7	239. 11.1 6	NA
TERMINAL BODY WT.	381. 26.5 6	382. 23.4 7	351. 17.6 6	NA
GRAVID UTERINE WT.	82.8 18.57 6	82.7 26.90 7	66.0 9.83 6	NA
NET BODY WT.	298.0 13.04 6	299.4 15.84 7	284.8 14.16 6	NA
NET BODY WT. CHANGE	58.9 10.44 6	57.9 14.91 7	46.1 12.22 6	NA

1- 0 MG/ML 2- 5 MG/ML 3- 50 MG/ML 4- 400 MG/ML
 NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING A TWO-TAILED DUNNETT'S TEST
 NA = NO DAMS SURVIVED TO THE SCHEDULED NECROPSY

TABLE 7
 DERMAL R-F DEV. TOX. STUDY OF
 MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY) IN RATS

DAY	GROUP :			
	1	2	3	4
DAY 0- 6 MEAN	19.	21.	21.	21.
S.D./N	2.3/ 6	1.4/ 7	2.1/ 6	2.0/ 7
DAY 6- 7 MEAN	21.	19.	21.	20.
S.D./N	3.2/ 6	4.1/ 7	1.8/ 6	2.6/ 7
DAY 7- 8 MEAN	23.	21.	21.	17.**
S.D./N	1.2/ 6	2.6/ 7	3.0/ 6	1.9/ 7
DAY 8- 9 MEAN	24.	23.	21.	15.**
S.D./N	1.9/ 6	2.5/ 7	2.3/ 6	5.0/ 7
DAY 9- 10 MEAN	22.	23.	23.	13.**
S.D./N	2.4/ 6	1.3/ 7	1.8/ 6	6.3/ 7
DAY 10- 11 MEAN	23.	22.	24.	16.
S.D./N	3.1/ 6	2.2/ 7	3.9/ 6	9.4/ 6
DAY 11- 12 MEAN	25.	25.	25.	16.*
S.D./N	1.8/ 6	2.0/ 7	2.4/ 6	10.2/ 6
DAY 12- 13 MEAN	23.	25.	24.	12.*
S.D./N	2.3/ 6	1.6/ 7	2.1/ 6	13.4/ 2
DAY 13- 14 MEAN	24.	25.	24.	0.
S.D./N	0.8/ 6	2.6/ 6	1.6/ 6	0.0/ 0
DAY 14- 15 MEAN	25.	25.	22.	0.
S.D./N	2.2/ 6	2.9/ 7	2.9/ 6	0.0/ 0

1- 0 MG/ML 2- 5 MG/ML 3- 50 MG/ML 4- 400 MG/ML
 * = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST
 ** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
 NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 7
 DERMAL R-F DEV. TOX. STUDY OF
 MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY) IN RATS

GROUP :	1	2	3	4
DAY 15- 16 MEAN	26.	25.	23.	0.
S.D./N	2.1/ 6	2.9/ 7	3.1/ 6	0.0/ 0
DAY 16- 17 MEAN	27.	27.	22.*	0.
S.D./N	1.2/ 6	1.7/ 7	5.0/ 6	0.0/ 0
DAY 17- 18 MEAN	27.	26.	21.**	0.
S.D./N	1.4/ 6	1.9/ 7	3.5/ 6	0.0/ 0
DAY 18- 19 MEAN	26.	26.	21.*	0.
S.D./N	3.5/ 6	1.4/ 7	3.8/ 6	0.0/ 0
DAY 19- 20 MEAN	26.	25.	21.	0.
S.D./N	2.7/ 6	3.1/ 7	2.4/ 6	0.0/ 0
DAY 6- 9 MEAN	23.	21.	21.	17.**
S.D./N	1.5/ 6	2.6/ 7	1.8/ 6	1.9/ 7
DAY 9- 12 MEAN	23.	23.	24.	16.**
S.D./N	1.7/ 6	1.3/ 7	2.3/ 6	7.2/ 6
DAY 12- 20 MEAN	25.	26.	22.*	0.
S.D./N	1.5/ 6	1.3/ 7	2.2/ 6	0.0/ 0
DAY 6- 20 MEAN	25.	24.	22.	0.
S.D./N	1.0/ 6	1.1/ 7	2.1/ 6	0.0/ 0
DAY 0- 20 MEAN	23.	23.	22.	0.
S.D./N	1.6/ 6	1.1/ 7	1.9/ 6	0.0/ 0

1- 0 MG/ML 2- 5 MG/ML 3- 50 MG/ML 4- 400 MG/ML
 * = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST
 ** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
 NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE B
 DERMAL R-F DEV. TOX. STUDY OF
 IN RATS
 MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/KG/DAY)

GROUP :		1	2	3	4
DAY 0- 6	MEAN	76.	83.	80.	81.
	S.D./N	7.0/ 6	6.4/ 7	5.4/ 6	6.6/ 7
DAY 6- 7	MEAN	78.	70.	76.	73.
	S.D./N	13.2/ 6	14.9/ 7	5.8/ 6	7.7/ 7
DAY 7- 8	MEAN	83.	77.	75.	61.**
	S.D./N	4.4/ 6	9.5/ 7	8.6/ 6	6.8/ 7
DAY 8- 9	MEAN	85.	82.	75.	56.**
	S.D./N	6.5/ 6	9.5/ 7	6.3/ 6	18.5/ 7
DAY 9- 10	MEAN	78.	80.	80.	49.**
	S.D./N	7.8/ 6	5.0/ 7	4.7/ 6	24.1/ 7
DAY 10- 11	MEAN	79.	77.	83.	62.
	S.D./N	10.0/ 6	7.5/ 7	12.6/ 6	35.3/ 6
DAY 11- 12	MEAN	84.	86.	85.	61.
	S.D./N	2.6/ 6	6.4/ 7	8.1/ 6	38.1/ 6
DAY 12- 13	MEAN	78.	85.	80.	45.*
	S.D./N	5.1/ 6	4.2/ 7	5.9/ 6	51.6/ 2
DAY 13- 14	MEAN	78.	80.	81.	0.
	S.D./N	3.9/ 6	7.6/ 6	7.5/ 6	0.0/ 0
DAY 14- 15	MEAN	81.	80.	73.	0.
	S.D./N	6.6/ 6	9.4/ 7	7.6/ 6	0.0/ 0

1- 0 MG/ML 2- 5 MG/ML 3- 50 MG/ML 4- 400 MG/ML
 * = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST
 ** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
 NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE R
 DERMAL R-F DEV. TOX. STUDY OF
 IN RATS
 MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/KG/DAY)

GROUP :	1	2	3	4
DAY 15- 16 MEAN	81.	78.	72.	0.
S.D./N	5.9/ 6	8.8/ 7	11.3/ 6	0.0/ 0
DAY 16- 17 MEAN	83.	80.	67.*	0.
S.D./N	4.9/ 6	6.0/ 7	13.6/ 6	0.0/ 0
DAY 17- 18 MEAN	78.	76.	64.**	0.
S.D./N	3.2/ 6	3.7/ 7	8.6/ 6	0.0/ 0
DAY 18- 19 MEAN	71.	74.	60.*	0.
S.D./N	7.1/ 6	5.2/ 7	9.0/ 6	0.0/ 0
DAY 19- 20 MEAN	68.	66.	61.	0.
S.D./N	5.1/ 6	9.8/ 7	5.9/ 6	0.0/ 0
DAY 6- 9 MEAN	82.	76.	75.	64.**
S.D./N	6.4/ 6	9.4/ 7	4.2/ 6	6.0/ 7
DAY 9- 12 MEAN	80.	81.	83.	60.
S.D./N	5.3/ 6	4.1/ 7	7.1/ 6	26.4/ 6
DAY 12- 20 MEAN	77.	77.	70.*	0.
S.D./N	2.7/ 6	3.8/ 7	4.9/ 6	0.0/ 0
DAY 6- 20 MEAN	79.	78.	74.	0.
S.D./N	2.1/ 6	2.7/ 7	5.2/ 6	0.0/ 0
DAY 0- 20 MEAN	74.	75.	72.	0.
S.D./N	3.6/ 6	3.5/ 7	4.1/ 6	0.0/ 0

1- 0 MG/ML 2- 5 MG/ML 3- 50 MG/ML 4- 400 MG/ML
 * = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST
 ** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
 NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

TABLE 9
 DERMAL R-F DEV. TOX. STUDY OF
 SUMMARY OF MEAN FETAL DATA AT THE SCHEDULED NECROPSY IN RATS

GROUP	SEX		VARIABLE FETUSES	DEAD FETUSES	RESORPTIONS			POST IMPLANTATION LOSS	CORPORA LUTEA	PRE IMPLANTATION LOSS	FETAL WEIGHTS IN GRAMS	NO. OF GRAVID FEMALES
	M	F			EARLY	LATE	IMPLANTATION SITES					
1	TOTAL 46	43	69	0	2	0	2	91	100	9	NA	6
	MEAN 7.7	7.2	14.8	0.0	0.3	0.0	0.3	15.2	16.7	1.5	3.7	
	S.D. 1.97	2.56	3.13	0.00	0.52	0.00	0.52	2.79	2.50	1.05	0.15	
2	TOTAL 42	42	84	0	9	2	11	95	119	24	NA	7
	MEAN 6.0	6.0	12.0	0.0	1.3	0.3	1.6	13.6	17.0	3.4	4.0	
	S.D. 2.45	3.06	4.51	0.00	1.25	0.49	1.27	3.60	1.73	4.16	0.20	
3	TOTAL 24	8	32	1	23	30	54	86	98	12	NA	6
	MEAN 4.0	1.3	5.3	0.2	3.8	5.0	9.0	14.3	16.3	2.0	3.7	
	S.D. 2.37	0.82	2.66	0.41	0.75	2.00	2.10	1.37	1.51	1.10	0.40	

4 THERE WERE NO GRAVID DAMS SURVIVING TO THE SCHEDULED NECROPSY IN THIS GROUP

NA = NOT APPLICABLE

MEAN NUMBER OF IMPLANTATION SITES, MEAN NUMBER OF CORPORA LUTEA AND MEAN FETAL BODY WEIGHTS COMPARED USING DUNNETT'S TEST

1- 0 MG/ML 2- 5 MG/ML 3- 50 MG/ML 4- 400 MG/ML

TABLE 10
 DERMAL R-F DEV. TOX. STUDY OF IN RATS
 SUMMARY OF MEAN FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)

GROUP NUMBER:	1	2	3	4
CORPORA LUTEA				
MEAN	16.7	17.0	16.3	NA
S.D.	2.50	1.73	1.51	
N	6	7	6	
IMPLANTATION SITES				
MEAN	15.2	13.6	14.3	NA
S.D.	2.79	3.60	1.37	
N	6	7	6	
VIABLE FETUSES (%)				
MEAN	97.4	84.8	36.6**	NA
S.D.	3.98	17.20	16.54	
N	6	7	6	
DEAD FETUSES (%)				
MEAN	0.0	0.0	1.4	NA
S.D.	0.00	0.00	3.39	
N	6	7	6	
EARLY RESORPTIONS (%)				
MEAN	2.6	11.9	26.9**	NA
S.D.	3.98	12.74	5.31	
N	6	7	6	
LATE RESORPTIONS (%)				
MEAN	0.0	3.3	35.2**	NA
S.D.	0.00	6.40	14.14	
N	6	7	6	
1- 0 MG/ML	2- 5 MG/ML	3- 50 MG/ML	4- 400 MG/ML	

PROPORTIONAL (%) DATA COMPARED USING THE KRUSKAL-WALLIS TEST
 CORPORA LUTEA AND IMPLANTATION SITES COMPARED USING DUNNETT'S TEST
 ** = SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP AT THE 0.01 LEVEL
 NA = NO DAMS SURVIVED TO THE SCHEDULED NECROPSY

TABLE 10
 DERMAL R-F DEV. TOX. STUDY OF
 SUMMARY OF MEAN FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER) IN RATS

GROUP NUMBER:	1	2	3	4
TOTAL RESORPTIONS (%)				
MEAN	2.6	15.2	62.1**	NA
S.D.	3.98	17.20	15.71	
N	6	7	6	
PRE-IMPLANTATION LOSS (%)				
MEAN	9.3	19.2	12.1	NA
S.D.	6.68	23.16	6.52	
N	6	7	6	
POST-IMPLANTATION LOSS (%)				
MEAN	2.6	15.2	63.5**	NA
S.D.	3.98	17.20	16.54	
N	6	7	6	
MALES (%)				
MEAN	52.3	55.1	72.3	NA
S.D.	11.32	22.57	20.00	
N	6	7	6	
FEMALES (%)				
MEAN	47.7	44.9	27.7	NA
S.D.	11.32	22.57	20.00	
N	6	7	6	
MALE FETAL WEIGHTS (g)				
MEAN	3.7	4.1	3.7	NA
S.D.	0.12	0.23	0.52	
N	6	7	6	
1- 0 MG/ML	2- 5 MG/ML	3- 50 MG/ML	4- 400 MG/ML	

PROPORTIONAL (%) DATA COMPARED USING THE KRUSKAL-WALLIS TEST

FETAL WEIGHTS COMPARED USING DUNNETT'S TEST

** = SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP AT THE 0.01 LEVEL
 NA = NO DAMS SURVIVED TO THE SCHEDULED NECROPSY

TABLE 10
 DERMAL R-F DEV. TOX. STUDY OF
 SUMMARY OF MEAN FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER) IN RATS

GROUP NUMBER:	1	2	3	4
FEMALE FETAL WEIGHTS (g)				
MEAN	3.6	3.9	3.7	NA
S.D.	0.19	0.19	0.63	
N	6	6	5	
COMBINED FETAL WEIGHTS (g)				
MEAN	3.7	4.0	3.7	NA
S.D.	0.15	0.20	0.40	
N	6	7	6	
1- 0 MG/ML	2- 5 MG/ML	3- 50 MG/ML	4- 400 MG/ML	

FETAL WEIGHTS COMPARED USING DUNNETT'S TEST
 NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP
 NA = NO DAMS SURVIVED TO THE SCHEDULED NECROPSY

TABLE 11
 DERMAL R-F DEV. TOX. STUDY OF
 NUMBER OF FETUSES AND LITTERS WITH MALFORMATIONS - SUMMARY

	FETUSES				LITTERS				DAY 20
	1	2	3	4	1	2	3	4	
DOSE GROUP:									
NUMBER EXAMINED EXTERNALLY LOCALIZED FETAL EDEMA	89	84	32	0	6	7	6	0	
TOTAL NUMBER WITH MALFORMATIONS EXTERNAL :	0	0	1	0	0	0	1	0	
1- 0 MG/ML	0	0	1	0	0	0	1	0	
2- 5 MG/ML	3-	50 MG/ML	4-	400 MG/ML					

TABLE 12
 DERMAL R-F DEV. TOX. STUDY OF
 NUMBER OF FETUSES AND LITTERS WITH VARIATIONS - SUMMARY

DOSE GROUP:	FETUSES				LITTERS				DAY 20
	1	2	3	4	1	2	3	4	
NUMBER EXAMINED EXTERNALLY	89	84	32	0					
NUMBER WITH FINDINGS	0	0	0	0	6	7	6	0	
1- 0 MG/ML	2-	5 MG/ML	3-	50 MG/ML	4-	400 MG/ML			

Table 13

Concentration of flusilazole in rat plasma (ppm)

Sample ^a	Mean	±	SD
1 hr	0.281	±	0.045
2 hr	2.24	±	1.55
4 hr	1.64	±	0.79
6 hr	2.51	±	0.75
GD 7	2.68	±	1.51
GD 11	4.17	±	1.90
GD 15	2.73	±	2.26
GD 19	35.2	±	9.9

^a all samples n = 2, except GD 19 which was n = 1;
1, 2, 4, and 6 hr - Group 5;
GD7, 11, 15 and 19 - Group 6

OBSERVATION	ANIMAL GROUP	GESTATIONAL DAY															
		0	1	2	3	4	5	6	7	8	9	10	11	12			
HAIR LOSS LEFT FORELIMB	65266												1	1	1	2	2
	65304																1
	65280															1	1
	65290															2	1
MET RED VAGINAL DISCHARGE	65254																3
	65308																1
	65253																2
MET YELLOW STAINING VENTRAL ABDOMINAL AREA	65270																3
	65274																3
	65290																3
	65294																2
	65307																3
DRIED YELLOW STAINING UROGENITAL AREA	65259																3
	65263																3
	65269																3
	65280																3
	65296																3
	65298																3
	65308																3
	65276																4
LETHARGIC	65290																4
MUNCHED APPEARANCE	65290																4

GRADE CODE: P = PRESENT 1 = SLIGHT 2 = MODERATE 3 = SEVERE
 1- 0 MG/ML 2- 5 MG/ML 3- 50 MG/ML 4- 400 MG/ML

TABLE 14 (DAILY EXAMINATIONS)
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL CLINICAL OBSERVATIONS IN RATS PAGE 6

OBSERVATION	ANIMAL GROUP	GESTATIONAL DAY																
		0	1	2	3	4	5	6	7	8	9	0	1	1	1	1	1	1
BODY COOL TO TOUCH	65290	4																P
DRIED BROWN MATERIAL RIGHT FORELIMB	65270	4																2
DRIED BROWN MATERIAL LEFT FORELIMB	65270	4																2
DRIED RED STAINING UROGENITAL AREA	65254	3																2 1
	65269	3																1
DRIED RED STAINING VENTRAL ABDOMINAL AREA	65254	3																2 2
DRIED RED STAINING RIGHT HINDLIMB	65254	3																2 1
DRIED RED STAINING LEFT HINDLIMB	65254	3																2 1
DRIED RED STAINING ENTIRE LENGTH OF TAIL	65254	3																2 2
WET RED MATERIAL ON CAGE PAPER	65254	3																P
SHALLOW RESPIRATION	65290	4																P
RIGHT EAR APPEARS PURPLE IN COLOR AND SWOLLEN	65261	2																P P P P P P P P P P P P
	65280	3																P P P P P P P P P P P P
RIGHT EAR APPEARS RED AND SWOLLEN	65261	2																P
	65304	2																P P P P P P
DRIED RED MATERIAL AROUND LEFT EYE	65253	4																1

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

1- 0 MG/ML 2- 5 MG/ML 3- 50 MG/ML 4- 400 MG/ML

TABLE 15
DERMAL R-F DEV. TOX. STUDY OF
INDIVIDUAL DERMAL OBSERVATIONS
IN RATS

GROUP :		50 MG/ML		ANIMAL NO. / SEX			
65254/F	65259/F	65263/F	65269/F	65280/F	65296/F	65298/F	65308/F
GESTATION DAY	SNR	SNR	SNR	SNR	SNR	SNR	SNR
6	SNR	SNR	SNR	SNR	SNR	SNR	SNR
7	SNR	SNR	SNR	SNR	SNR	SNR	SNR
8	SNR	SNR	SNR	SNR	SNR	SNR	SNR
9	SNR	SNR	SNR	SNR	SNR	SNR	SNR
10	SNR	SNR	SNR	SNR	SNR	SNR	SNR
11	2/0	SNR	SNR	1/0	SNR	2/0	SNR
12	2/0	1/0	SNR	2/0/d	1/0	2/0	1/0
13	2/0	1/0	2/0	2/0/d	1/0	2/0/d	2/0
14	1/0	2/0	2/0	2/0/d	2/0	3/0/d	2/0/d
15	1/0	2/0/d	2/0/d	2/0	2/0	3/0/d	2/0/d
16	1/0	1/0/d	1/0/d	1/0	2/0	3/0/df	1/0
17	1/0/d	1/0/d	1/0/d	1/0/d	1/0	3/0/df	1/0/d
18	2/0	1/0	1/0/d	2/0/d	0/0/d	3/0/df	1/0
19	2/0/d	1/0	1/0/d	1/0/d	1/0/d	3/0/df	2/0
20	1/0/d	1/0	1/0/d	1/0/d	1/0/d	3/0/df	1/0

ERYTHEMA+/EDEMA+/OTHER FINDINGS

+ = REFER TO DRAIZE SCALE FOR DERMAL SCORING CRITERIA

SEX CODE: M = MALE

F = FEMALE

f = FISSURING

d = DESQUAMATION

SNR = SCORED, NOT REMARKABLE

TABLE 15
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL DERMAL OBSERVATIONS
 IN RATS
 PAGE 4

GROUP :	400 MG/ML	ANIMAL NO. / SEX									
		65253/F	65270/F	65274/F	65276/F	65290/F	65294/F	65303/F	65307/F		
GESTATION DAY		ERYTHEMA+/EDEMA+/OTHER FINDINGS									
6	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR
7	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR
8	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR
9	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR
10	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR
11	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR
12	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR
13	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR
14	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR
15	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR	SNR

+ = REFER TO DRAIZE SCALE FOR DERMAL SCORING CRITERIA
 SEX CODE: M = MALE F = FEMALE
 f = FISSURING d = DESQUAMATION
 a = ATONIA
 SNR = SCORED, NOT REMARKABLE

TABLE 16
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL BODY WEIGHTS (GRAMS) DURING GESTATION

PREGNANCY STATUS	DAMS FROM GROUP 1: 0 MG/ML												
	DAY 0	6	7	8	9	10	11	12	13				
65255 G	236.	252.	260.	259.	265.	264.	271.	275.	277.				
65256 G	248.	288.	290.	292.	295.	298.	301.	312.	307.				
65257 NG	240.	268.	272.	273.	281.	283.	288.	284.	294.				
65258 G	234.	268.	269.	276.	281.	288.	297.	305.	309.				
65268 G	225.	263.	274.	280.	287.	283.	302.	301.	314.				
65287 G	255.	278.	278.	285.	286.	296.	294.	307.	310.				
65289 G	237.	268.	271.	274.	280.	279.	287.	290.	296.				
65300 NG	252.	262.	262.	260.	256.	261.	266.	260.	262.				
MEAN	239.	270.	274.	278.	282.	285.	292.	298.	302.				
S.D.	10.7	12.4	10.0	11.2	10.0	12.5	11.6	13.6	13.7				
N	6	6	6	6	6	6	6	6	6				

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

TABLE 16
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL BODY WEIGHTS (GRAMS) DURING GESTATION
 IN RATS

PREGNANCY STATUS	DAYS FROM GROUP 1: 0 MG/ML										
	DAY 14	15	16	17	18	19	20				
65255 G	287.	287.	300.	312.	327.	324.	341.	341. SCHEDULED NECROPSY DAY 20			
65256 G	315.	317.	321.	333.	341.	362.	373.	373. SCHEDULED NECROPSY DAY 20			
65257 MG	294.	294.	279.	282.	283.	282.	276.	276. SCHEDULED NECROPSY DAY 20			
65258 G	315.	324.	333.	345.	361.	381.	395.	395. SCHEDULED NECROPSY DAY 20			
65268 G	317.	322.	335.	352.	374.	390.	403.	403. SCHEDULED NECROPSY DAY 20			
65287 G	313.	323.	332.	353.	369.	393.	410.	410. SCHEDULED NECROPSY DAY 20			
65289 G	300.	304.	313.	319.	335.	342.	363.	363. SCHEDULED NECROPSY DAY 20			
65300 MG	260.	264.	264.	262.	264.	264.	265.	265. SCHEDULED NECROPSY DAY 20			
MEAN	308.	313.	322.	336.	351.	365.	381.				
S.D.	11.9	14.7	13.8	17.3	19.4	27.9	26.5				
N	6	6	6	6	6	6	6				

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

TABLE 16
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL BODY WEIGHTS (GRAMS) DURING GESTATION IN RATS
 PAGE 3

PREGNANCY STATUS	DAYS FROM GROUP 2: 5 MG/ML												
	DAY 0	6	7	8	9	10	11	12	13				
65261 G	249.	281.	271.	278.	285.	293.	296.	308.	314.				
65266 MG	235.	260.	246.	255.	264.	262.	276.	252.	263.				
65267 G	220.	264.	259.	265.	277.	281.	282.	290.	296.				
65277 G	256.	281.	285.	287.	281.	295.	289.	299.	308.				
65286 G	247.	280.	285.	280.	285.	290.	293.	296.	303.				
65302 G	244.	271.	275.	275.	278.	284.	284.	288.	295.				
65304 G	239.	264.	266.	276.	277.	281.	291.	290.	300.				
65309 G	236.	270.	277.	282.	288.	291.	299.	306.	308.				
MEAN	242.	273.	274.	278.	282.	288.	291.	297.	303.				
S.D.	11.6	7.7	9.6	6.9	4.5	5.8	6.1	8.0	7.0				
N	7	7	7	7	7	7	7	7	7				

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

TABLE 16
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL BODY WEIGHTS (GRAMS) DURING GESTATION
 IN RATS

PREGNANCY STATUS	50 MG/ML						
	DAY 14	15	16	17	18	19	20
DAMS FROM GROUP 3:							
65254 G	304.	317.	326.	331.	346.	355.	358. SCHEDULED NECROPSY DAY 20
65259 MG	280.	285.	289.	286.	283.	284.	292. SCHEDULED NECROPSY DAY 20
65263 G	320.	327.	344.	352.	362.	369.	375. SCHEDULED NECROPSY DAY 20
65269 G	289.	299.	312.	325.	333.	344.	359. SCHEDULED NECROPSY DAY 20
65280 G	292.	292.	297.	312.	319.	333.	344. SCHEDULED NECROPSY DAY 20
65296 G	301.	308.	316.	319.	323.	331.	346. SCHEDULED NECROPSY DAY 20
65298 MG	250.	251.	247.	250.	250.	246.	253. SCHEDULED NECROPSY DAY 20
65308 G	304.	309.	320.	317.	318.	324.	323. SCHEDULED NECROPSY DAY 20
MEAN	302.	309.	319.	326.	334.	343.	351.
S.D.	11.0	12.5	15.6	14.3	17.5	16.9	17.6
N	6	6	6	6	6	6	6

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

TABLE 16
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL BODY WEIGHTS (GRAMS) DURING GESTATION IN RATS

PREGNANCY STATUS	DAMS FROM GROUP 4: 400 MG/ML												
	DAY 0	6	7	8	9	10	11	12	13				
65253 G	225.	266.	261.	260.	260.	250.	229.	193.	NA				
65270 G	260.	291.	287.	277.	277.	270.	262.	243.	262.				
65274 G	236.	272.	263.	263.	267.	267.	271.	271.	227.				
65276 G	240.	268.	267.	266.	259.	248.	261.	253.	251.				
65290 NG	231.	227.	246.	237.	236.	234.	223.	212.	212.				
65294 G	239.	290.	276.	274.	260.	260.	250.	263.	254.				
65303 G	247.	269.	267.	264.	236.	208.	NA	NA	NA				
65307 G	249.	283.	279.	275.	270.	261.	264.	265.	255.				
MEAN	242.	277.	271.	268.	261.	252.	256.	248.	250.				
S.D.	11.1	10.7	9.5	6.8	12.9	21.0	14.9	28.7	13.4				
N	7	7	7	7	7	7	6	6	5				

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

TABLE 16
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL BODY WEIGHTS (GRAMS) DURING GESTATION
 IN RATS

PREGNANCY STATUS	DAY 14	DAY 15	DAY 16	DAY 17	DAY 18	DAY 19	DAY 20	DAMS FROM GROUP 4: 400 MG/ML	
								GRAVID	NONGRAVID
65253	NA	GRAVID, DIED DAY 13	NA						
65270	NA	GRAVID, EUTHANIZED DAY 13	NA						
65274	NA	GRAVID, DIED DAY 14	NA						
65276	NA	GRAVID, EUTHANIZED DAY 13	NA						
65290	NA	NONGRAVID, EUTHANIZED DAY 13	NA						
65294	255.	NA	NA	NA	NA	NA	NA	GRAVID, EUTHANIZED DAY 14	NA
65303	NA	GRAVID, DIED DAY 11	NA						
65307	NA	GRAVID, EUTHANIZED DAY 13	NA						
MEAN	255.	0.	0.	0.	0.	0.	0.		0.
S.D.	0.0	0.0	0.0	0.0	0.0	0.0	0.0		0.0
N	1	0	0	0	0	0	0		0

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

TABLE 17
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL BODY WEIGHT CHANGES (GRAMS) DURING GESTATION
 IN RATS
 PAGE 1

PREGNANCY STATUS	DAYS FROM GROUP 1: 0 MG/ML													
	DAY 0-6	6-7	7-8	8-9	9-10	10-11	11-12	12-13	13-14					
65255 G	16.	8.	-1.	6.	-1.	7.	4.	2.	10.					
65256 G	40.	2.	2.	3.	3.	3.	11.	-5.	8.					
65257 NG	28.	4.	1.	8.	2.	5.	-4.	10.	0.					
65258 G	34.	1.	7.	5.	7.	9.	8.	4.	6.					
65268 G	38.	11.	6.	7.	-4.	19.	-1.	13.	3.					
65287 G	23.	0.	7.	1.	10.	-2.	13.	3.	3.					
65289 G	31.	3.	3.	6.	-1.	8.	3.	6.	4.					
65300 NG	10.	0.	-2.	-4.	5.	5.	-6.	2.	-2.					
MEAN	30.	4.	4.	5.	2.	7.	6.	4.	6.					
S.D.	9.2	4.4	3.2	2.3	5.4	7.0	5.3	5.8	2.9					
N	6	6	6	6	6	6	6	6	6					

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

TABLE 17
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL BODY WEIGHT CHANGES (GRAMS) DURING GESTATION
 IN RATS

PREGNANCY STATUS	DAMS FROM GROUP 1: 0 MG/ML										
	DAY14-15	15-16	16-17	17-18	18-19	19-20	6-9	9-12	12-20		
65255 G	0.	13.	12.	15.	-3.	17.	13.	10.	66.		
65256 G	2.	4.	12.	8.	21.	11.	7.	17.	61.		
65257 NG	0.	-15.	3.	1.	-1.	-6.	13.	3.	-8.		
65258 G	9.	9.	12.	16.	20.	14.	13.	24.	90.		
65268 G	5.	13.	17.	22.	16.	13.	24.	14.	102.		
65287 G	10.	9.	21.	16.	24.	17.	8.	21.	103.		
65289 G	4.	9.	6.	16.	7.	21.	12.	10.	73.		
65300 NG	4.	0.	-2.	2.	0.	1.	-6.	4.	5.		
MEAN	5.	10.	13.	16.	14.	16.	13.	16.	83.		
S.D.	3.9	3.3	5.1	4.5	10.3	3.6	6.0	5.8	18.3		
N	6	6	6	6	6	6	6	6	6		

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

TABLE 17
 DERMAL R-F DEV. TOX. STUDY OF IN RATS
 INDIVIDUAL BODY WEIGHT CHANGES (GRAMS) DURING GESTATION

PREGNANCY STATUS		DAY 6-20	0-20
DAMS FROM GROUP 1: 0 MG/ML			
65255	G	89.	105. SCHEDULED NECROPSY DAY 20
65256	G	85.	125. SCHEDULED NECROPSY DAY 20
65257	NG	8.	36. SCHEDULED NECROPSY DAY 20
65258	G	127.	161. SCHEDULED NECROPSY DAY 20
65268	G	140.	178. SCHEDULED NECROPSY DAY 20
65287	G	132.	155. SCHEDULED NECROPSY DAY 20
65289	G	95.	126. SCHEDULED NECROPSY DAY 20
65300	NG	3.	13. SCHEDULED NECROPSY DAY 20
MEAN 111. 142.			
S.D. 24.3 27.3			
N 6 6			

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

TABLE 17
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL BODY WEIGHT CHANGES (GRAMS) DURING GESTATION
 IN RATS

PREGNANCY STATUS	DAYS FROM GROUP 2: 5 MG/ML												
	DAY 0-6	6-7	7-8	8-9	9-10	10-11	11-12	12-13	13-14				
65261 G	32.	-10.	7.	7.	8.	3.	12.	6.	11.				
65266 NG	25.	-14.	9.	9.	-2.	14.	-24.	11.	-7.				
65267 G	44.	-5.	6.	12.	4.	1.	8.	6.	1.				
65277 G	25.	4.	2.	-6.	14.	-6.	10.	9.	3.				
65286 G	33.	5.	-5.	5.	5.	3.	3.	7.	4.				
65302 G	27.	4.	0.	3.	6.	0.	4.	7.	7.				
65304 G	25.	2.	10.	1.	4.	10.	-1.	10.	4.				
65309 G	34.	7.	5.	6.	3.	8.	7.	2.	11.				
MEAN	31.	1.	4.	4.	6.	3.	6.	7.	6.				
S.D.	6.7	6.2	5.0	5.6	3.8	5.3	4.5	2.6	3.9				
N	7	7	7	7	7	7	7	7	7				

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

TABLE 17
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL BODY WEIGHT CHANGES (GRAMS) DURING GESTATION
 IN RATS

PREGNANCY STATUS	5 MG/ML										
	DAY14-15	15-16	16-17	17-18	18-19	19-20	6-9	9-12	12-20		
DAMS FROM GROUP 2:											
65261 G	3.	15.	5.	19.	15.	27.	4.	23.	101.		
65266 NG	10.	-2.	3.	-6.	4.	3.	4.	-12.	16.		
65267 G	17.	7.	8.	18.	2.	15.	13.	13.	74.		
65277 G	10.	9.	15.	9.	26.	12.	0.	18.	93.		
65286 G	5.	4.	5.	7.	3.	13.	5.	11.	48.		
65302 G	1.	16.	13.	14.	24.	14.	7.	10.	96.		
65304 G	2.	16.	10.	14.	14.	15.	13.	13.	85.		
65309 G	8.	15.	12.	16.	23.	14.	18.	18.	101.		
MEAN	7.	12.	10.	14.	15.	16.	9.	15.	85.		
S.D.	5.6	5.0	3.9	4.5	9.8	5.1	6.3	4.7	19.1		
N	7	7	7	7	7	7	7	7	7		

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

TABLE 17
 DERMAL R-F DEV. TOX. STUDY OF IN RATS
 INDIVIDUAL BODY WEIGHT CHANGES (GRAMS) DURING GESTATION
 PAGE 6

PREGNANCY STATUS	DAY 6-20	0-20
DAMS FROM GROUP 2: 5 MG/ML		
65261	G	128.
65266	NG	8.
65267	G	100.
65277	G	111.
65286	G	64.
65302	G	113.
65304	G	111.
65309	G	137.
		160. SCHEDULED NECROPSY DAY 20
		33. SCHEDULED NECROPSY DAY 20
		144. SCHEDULED NECROPSY DAY 20
		136. SCHEDULED NECROPSY DAY 20
		97. SCHEDULED NECROPSY DAY 20
		140. SCHEDULED NECROPSY DAY 20
		136. SCHEDULED NECROPSY DAY 20
		171. SCHEDULED NECROPSY DAY 20
MEAN		109.
S.D.		23.4
N		7

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

TABLE 17
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL BODY WEIGHT CHANGES (GRAMS) DURING GESTATION
 IN RATS
 PAGE 7

PREGNANCY STATUS	DAYS FROM GROUP 3: 50 MG/ML													
	DAY 0-6	6-7	7-8	8-9	9-10	10-11	11-12	12-13	13-14					
65254 G	39.	-2.	0.	5.	5.	2.	11.	7.	-3.					
65259 NG	31.	-3.	5.	7.	4.	-3.	-4.	-13.	7.					
65263 G	38.	6.	8.	2.	7.	1.	-4.	2.	6.					
65269 G	30.	6.	7.	0.	5.	4.	7.	1.	5.					
65280 G	29.	2.	6.	4.	6.	1.	5.	2.	7.					
65296 G	36.	0.	1.	7.	3.	5.	5.	4.	4.					
65298 NG	41.	-5.	7.	-7.	1.	1.	-3.	-12.	-10.					
65308 G	30.	0.	2.	1.	0.	5.	7.	7.	4.					
MEAN	34.	2.	4.	3.	4.	3.	5.	4.	4.					
S.D.	4.5	3.3	3.4	2.6	2.5	1.9	5.0	2.6	3.5					
N	6	6	6	6	6	6	6	6	6					

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

TABLE 17
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL BODY WEIGHT CHANGES (GRAMS) DURING GESTATION
 IN RATS

PREGNANCY STATUS	DAYS FROM GROUP 3: 50 MG/ML										
	14-15	15-16	16-17	17-18	18-19	19-20	6-9	9-12	12-20		
65254 G	13.	9.	5.	15.	9.	3.	3.	18.	58.		
65259 MG	5.	4.	-3.	-3.	1.	8.	9.	-3.	6.		
65263 G	7.	17.	8.	10.	7.	6.	16.	4.	63.		
65269 G	10.	13.	13.	8.	11.	15.	13.	16.	76.		
65280 G	0.	5.	15.	7.	14.	11.	12.	12.	61.		
65296 G	7.	8.	3.	4.	8.	15.	8.	13.	53.		
65298 MG	1.	-4.	3.	0.	-4.	7.	-5.	-1.	-19.		
65308 G	5.	11.	-3.	1.	6.	-1.	3.	12.	30.		
MEAN	7.	11.	7.	8.	9.	8.	9.	13.	57.		
S.D.	4.4	4.2	6.6	4.8	2.9	6.6	5.4	4.8	15.2		
N	6	6	6	6	6	6	6	6	6		

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

TABLE 17
 DERMAL R-F DEV. TOX. STUDY OF IN RATS
 INDIVIDUAL BODY WEIGHT CHANGES (GRAMS) DURING GESTATION
 PAGE 9

PREGNANCY		DAY 6-20	0-20
STATUS			
DAMS FROM GROUP 3:		50 MG/ML	
65254	G	79.	118. SCHEDULED NECROPSY DAY 20
65259	MG	12.	43. SCHEDULED NECROPSY DAY 20
65263	G	83.	121. SCHEDULED NECROPSY DAY 20
65269	G	105.	135. SCHEDULED NECROPSY DAY 20
65280	G	85.	114. SCHEDULED NECROPSY DAY 20
65296	G	74.	110. SCHEDULED NECROPSY DAY 20
65298	MG	-25.	16. SCHEDULED NECROPSY DAY 20
65308	G	45.	75. SCHEDULED NECROPSY DAY 20
MEAN		79.	112.
S.D.		19.5	20.1
N		6	6

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

TABLE 17
 DERMAL R-F DEV. TOX. STUDY OF IN RATS
 INDIVIDUAL BODY WEIGHT CHANGES (GRAMS) DURING GESTATION

PREGNANCY		DAY 0-6	6-7	7-8	8-9	9-10	10-11	11-12	12-13	13-14
STATUS		DAY 0-6	6-7	7-8	8-9	9-10	10-11	11-12	12-13	13-14
DAMS FROM GROUP 4:		400 MG/ML								
65253	G	41.	-5.	-1.	0.	-10.	-21.	-36.	NA	NA
65270	G	31.	-4.	-10.	0.	-7.	-8.	-19.	19.	NA
65274	G	36.	-9.	0.	4.	0.	4.	0.	-44.	NA
65276	G	28.	-1.	-1.	-7.	-11.	13.	-8.	-2.	NA
65290	NG	-4.	19.	-9.	-1.	-2.	-11.	-11.	0.	NA
65294	G	51.	-14.	-2.	-14.	0.	-10.	13.	-9.	1.
65303	G	22.	-2.	-3.	-28.	-28.	NA	NA	NA	NA
65307	G	34.	-4.	-4.	-5.	-9.	3.	1.	-10.	NA
MEAN		35.	-6.	-3.	-7.	-9.	-3.	-8.	-9.	1.
S.D.		9.4	4.5	3.4	10.9	9.4	12.2	17.3	22.7	0.0
N		7	7	7	7	7	6	6	5	1

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

TABLE 17
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL BODY WEIGHT CHANGES (GRAMS) DURING GESTATION
 IN RATS

PREGNANCY STATUS	DAYS FROM GROUP 4: 400 MG/ML											
	DAY14-15	15-16	16-17	17-18	18-19	19-20	6-9	9-12	12-20			
65253 G	NA	NA	NA	NA	NA	NA	-6.	-67.	NA			
65270 G	NA	NA	NA	NA	NA	NA	-14.	-34.	NA			
65274 G	NA	NA	NA	NA	NA	NA	-5.	4.	NA			
65276 G	NA	NA	NA	NA	NA	NA	-9.	-6.	NA			
65290 MG	NA	NA	NA	NA	NA	NA	9.	-24.	NA			
65294 G	NA	NA	NA	NA	NA	NA	-30.	3.	NA			
65303 G	NA	NA	NA	NA	NA	NA	-33.	NA	NA			
65307 G	NA	NA	NA	NA	NA	NA	-13.	-5.	NA			
MEAN	0.	0.	0.	0.	0.	0.	-16.	-18.	0.			
S.D.	0.0	0.0	0.0	0.0	0.0	0.0	11.3	27.9	0.0			
N	0	0	0	0	0	0	7	6	0			

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

TABLE 17
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL BODY WEIGHT CHANGES (GRAMS) DURING GESTATION
 IN RATS
 PAGE 12

PREGNANCY		DAY 6-20	0-20
STATUS		DAY 6-20	0-20
DAMS FROM GROUP 4: 400 MG/ML			
65253	G	NA	NA GRAVID, DIED DAY 13
65270	G	NA	NA GRAVID, EUTHANIZED DAY 13
65274	G	NA	NA GRAVID, DIED DAY 14
65276	G	NA	NA GRAVID, EUTHANIZED DAY 13
65290	NG	NA	NA NONGRAVID, EUTHANIZED DAY 13
65294	G	NA	NA GRAVID, EUTHANIZED DAY 14
65303	G	NA	NA GRAVID, DIED DAY 11
65307	G	NA	NA GRAVID, EUTHANIZED DAY 13
MEAN		0.	0.
S.D.		0.0	0.0
N		0	0

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

TABLE 1A
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL GRAVID UTERINE WT. AND NET BODY WT. CHANGE (GRAMS) IN RATS
 PAGE 1

DAM #	PREGNANCY STATUS	INITIAL BODY WT.	TERMINAL BODY WT.	GRAVID UTERINE WT.	NET BODY WT.	NET BODY WT. CHANGE	GROUP 1: 0 MG/ML	
							GRAVID UTERINE WT.	NET BODY WT. CHANGE
65255	G	236.	341.	66.9	276.1	40.1		
65256	G	248.	373.	66.4	306.6	58.6		
65257	NG	240.	276.	NA	NA	NA		
65258	G	234.	395.	94.2	300.8	66.8		
65268	G	225.	403.	107.8	295.2	70.2		
65287	G	255.	410.	95.5	314.5	59.5		
65289	G	237.	363.	68.0	295.0	58.0		
65300	NG	252.	265.	NA	NA	NA		
MEAN		239.	381.	82.8	298.0	58.9		
S.D.		10.7	26.5	18.57	13.04	10.44		
N		6	6	6	6	6		

G = GRAVID, NG = NONGRAVID, NOT INCLUDED IN CALCULATION OF THE MEAN
 NA = NOT APPLICABLE

TABLE 18
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL GRAVID UTERINE WT. AND NET BODY WT. CHANGE (GRAMS)
 IN RATS

DAM #	PREGNANCY STATUS	GROUP 2: 5 MG/ML		TERMINAL GRAVID UTERINE WT.	GRAVID UTERINE WT.	NET BODY WT.	NET BODY WT. CHANGE
		INITIAL BODY WT.	TERMINAL BODY WT.				
65261	G	249.	409.	90.7	318.3	69.3	69.3
65266	NG	235.	268.	NA	NA	NA	NA
65267	G	220.	364.	76.6	287.4	67.4	67.4
65277	G	256.	392.	90.9	301.1	45.1	45.1
65286	G	247.	344.	25.1	318.9	71.9	71.9
65302	G	244.	384.	103.8	280.2	36.2	36.2
65304	G	239.	375.	90.3	284.7	45.7	45.7
65309	G	236.	407.	101.5	305.5	69.5	69.5
MEAN		242.	382.	82.7	299.4	57.9	57.9
S.D.		11.6	23.4	26.90	15.84	14.91	14.91
N		7	7	7	7	7	7

G = GRAVID, NG = NONGRAVID, NOT INCLUDED IN CALCULATION OF THE MEAN
 NA = NOT APPLICABLE

TABLE 18
 DERMAL R-F DEV. TOX. STUDY OF . . . IN RATS
 INDIVIDUAL GRAVID UTERINE WT. AND NET BODY WT. CHANGE (GRAMS)

DAM #	PREGNANCY STATUS	GROUP 3: 50 MG/ML					
		INITIAL BODY WT.	TERMINAL BODY WT.	GRAVID UTERINE WT.	NET BODY WT.	NET BODY WT. CHANGE	NET BODY WT. CHANGE
65254	G	240.	358.	67.6	290.4	50.4	50.4
65259	MG	249.	292.	NA	NA	NA	NA
65263	G	254.	375.	65.8	309.2	55.2	55.2
65269	G	224.	359.	81.4	277.6	53.6	53.6
65280	G	230.	344.	69.8	274.2	44.2	44.2
65296	G	236.	346.	59.0	287.0	51.0	51.0
65298	MG	237.	253.	NA	NA	NA	NA
65308	G	248.	323.	52.6	270.4	22.4	22.4
MEAN		239.	351.	66.0	284.8	46.1	46.1
S.D.		11.1	17.6	9.83	14.16	12.22	12.22
N		6	6	6	6	6	6

G = GRAVID, MG = NONGRAVID, NOT INCLUDED IN CALCULATION OF THE MEAN
 NA = NOT APPLICABLE

TABLE 18
 DERMAL R-F DEV. TOX. STUDY OF : IN RATS
 INDIVIDUAL GRAVID UTERINE WT. AND NET BODY WT. CHANGE (GRAMS) PAGE 4

PREGNANCY STATUS	INITIAL BODY WT.	TERMINAL BODY WT.	GRAVID UTERINE WT.	NET BODY WT.	NET BODY WT. CHANGE
DAM # GROUP 4: 400 MG/ML					

THERE WERE NO GRAVID DAMS SURVIVING TO THE SCHEDULED NECROPSY IN THIS GROUP

TABLE 19
 DERMAL R-F DEV. TOX. STUDY OF
 INDIVIDUAL FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY) IN RATS
 PAGE 1

PREGNANCY STATUS	DAY													
	0-6	6-7	7-8	8-9	9-10	10-11	11-12	12-13	13-14					
DAMS FROM GROUP 1: 0 MG/ML														
65255 G	16.	22.	21.	23.	20.	20.	22.	19.	24.					
65256 G	22.	21.	22.	25.	21.	20.	26.	23.	24.					
65257 MG	18.	22.	21.	21.	24.	22.	22.	23.	23.					
65258 G	21.	23.	24.	24.	26.	27.	26.	25.	25.					
65268 G	17.	22.	24.	27.	20.	26.	26.	25.	24.					
65287 G	20.	15.	23.	22.	24.	21.	25.	24.	23.					
65289 G	20.	24.	22.	22.	22.	23.	23.	24.	23.					
65300 MG	18.	23.	0.A	18.	21.	22.	21.	18.	23.					
MEAN	19.	21.	23.	24.	22.	23.	25.	23.	24.					
S.D.	2.3	3.2	1.2	1.9	2.4	3.1	1.8	2.3	0.8					
N	6	6	6	6	6	6	6	6	6					

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

TABLE 19
 DERMAL R-F DEV. TOX. STUDY OF : IN RATS
 INDIVIDUAL FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY)

PREGNANCY STATUS	DAYS FROM GROUP 1: 0 MG/ML											
	DAY 14-15	15-16	16-17	17-18	18-19	19-20	6-9	9-12	12-20			
65255 G	24.	25.	28.	25.	20.	22.	22.	21.	23.			
65256 G	24.	23.	26.	25.	28.	26.	23.	22.	25.			
65257 NG	23.	15.	18.	20.	20.	13.	21.	23.	19.			
65258 G	26.	29.	28.	28.	29.	29.	24.	26.	27.			
65268 G	23.	25.	27.	28.	26.	24.	24.	24.	25.			
65287 G	29.	27.	29.	27.	28.	28.	20.	23.	27.			
65289 G	24.	25.	26.	27.	23.	24.	23.	23.	25.			
65300 NG	20.	21.	16.	21.	25.	19.	21.	21.	20.			
MEAN	25.	26.	27.	27.	26.	26.	23.	23.	25.			
S.D.	2.2	2.1	1.2	1.4	3.5	2.7	1.5	1.7	1.5			
N	6	6	6	6	6	6	6	6	6			

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

TABLE 19
 DERMAL R-F DEV. TOX. STUDY OF IN RATS
 INDIVIDUAL FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY) PAGE 3

PREGNANCY STATUS	DAY 6-20	DAY 0-20
DAMS FROM GROUP 1: 0 MG/ML		
65255	G	23. 20. SCHEDULED NECROPSY DAY 20
65256	G	24. 23. SCHEDULED NECROPSY DAY 20
65257	NG	21. 20. SCHEDULED NECROPSY DAY 20
65258	G	26. 25. SCHEDULED NECROPSY DAY 20
65268	G	25. 23. SCHEDULED NECROPSY DAY 20
65287	G	25. 23. SCHEDULED NECROPSY DAY 20
65289	G	24. 23. SCHEDULED NECROPSY DAY 20
65300	NG	21. 20. SCHEDULED NECROPSY DAY 20
MEAN		25. 23.
S.D.		1.0 1.6
N		6 6

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