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1-16-98

[] SANITIZED

RE: Follow-up Submission regarding Document Control Number []
[]

Gentlemen:

This is a follow-up to a previous TSCA 8 (e) substantial risk notification that was submitted by [] and entered/filed under EPA-TSCA's Document Control Number []. Enclosed is a copy of the final report entitled, "A Dose Range-Finding Developmental Toxicity Study Of Furfural In Rats".

CAS No.: 98-01-1

If you have any questions, please feel free to contact me at [].

Sincerely,

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Enclosure:

8EHQ-97-13916

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FINAL REPORT

**Volume 1 of 2
(Text and Summary Tables 1-15A)**

SANITIZED

STUDY TITLE

**A DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY STUDY OF FURFURAL IN RATS**

EPA GUIDELINE NUMBER

Not Applicable

STUDY DIRECTOR

Mark D. Nemec, B.S., D.A.B.T.

STUDY INITIATED ON

December 16, 1996

STUDY COMPLETED ON

August 1, 1997

PERFORMING LABORATORY

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

LABORATORY STUDY NUMBER

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SPONSOR

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[]

A Dose Range-Finding Developmental
Toxicity Study of Furfural in Rats

COMPLIANCE STATEMENT

This study, designated [] was conducted in compliance with the United States Environmental Protection Agency (EPA) Good Laboratory Practice Standards (40 CFR Parts 160 and 792), October 16, 1989 and September 18, 1989; the Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice [C(81) 30 (Final) Annex 2], 1981; the Japanese Ministry of Agriculture, Forestry and Fisheries (MAFF) Good Laboratory Practice Standards (59 NohSan No. 3850), August 10, 1984; the Standard Operating Procedures of WIL Research Laboratories, Inc.; and the protocol as approved by the sponsor.

Mark D. Nemec
Mark D. Nemec, B.S., D.A.B.T.
Study Director

8/1/97
Date

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A Dose Range-Finding Developmental
Toxicity Study of Furfural in Rats

TABLE OF CONTENTS

Note: Some table titles have been shortened due to software spacing constraints.

VOLUME 1		<u>Page</u>
I.	Summary	10
II.	Objective	12
III.	Study Design	13
IV.	Experimental Procedures	14
A.	Introduction	14
B.	Test and Control Articles	14
1.	Test Article Identification	14
2.	Vehicle Control Article Identification	15
3.	Preparation	15
4.	Administration	16
5.	Sampling and Analyses	16
C.	Animal Receipt and Acclimation	17
D.	Animal Housing	17
E.	Diet, Drinking Water and Maintenance	18
F.	Environmental Conditions	18
G.	Assignment of Animals to Treatment Groups and Breeding Procedures	18
H.	Maternal Observations During Gestation	19
1.	Clinical Observations and Survival	19
2.	Body Weights and Gravid Uterine Weights	20
3.	Food Consumption	20
I.	Gestation Day 20 Laparohysterectomy	21
J.	Fetal Morphological Examination	22
K.	Statistical Analyses	22
L.	Data Retention	23

[]

VOLUME 1 (continued)		<u>Page</u>
V.	Results	24
A.	Clinical Observations and Survival	24
B.	Body Weights and Gravid Uterine Weights	24
C.	Food Consumption	25
D.	Necropsy Data	26
E.	Gestation Day 20 Laparohysterectomy Data	26
F.	Fetal Morphological Data	27
VI.	Discussion and Conclusions	28
VII.	Key Study Personnel and Report Submission	30
VIII.	Quality Assurance Unit Statement	31
IX.	References	32

A Dose Range-Finding Developmental
Toxicity Study of Furfural in Rats

INDEX OF TABLES

Due to the high levels of maternal toxicity at the original two highest dose levels (500 and 1000 mg/kg/day; []), the breeding phase for the study was reinitiated to further characterize the potential maternal and developmental toxicity of the test article at dose levels between 100 and 500 mg/kg/day []. Report tables for the additional dose levels ("A" tables) are presented immediately following the appropriate table for the initial dose groups.

Note: Some table titles have been shortened due to software spacing constraints.

VOLUME 1 (continued)	<u>Page</u>
1. Summary of Maternal Survival and Pregnancy Status	34
1A. Summary of Maternal Survival and Pregnancy Status	35
2. Summary of Clinical Findings: Total Occurrence/No. of Animals (Daily Examinations)	36
2A. Summary of Clinical Findings: Total Occurrence/No. of Animals (Daily Examinations)	38
3. Summary of Clinical Findings: Total Occurrence/No. of Animals (At Time of Dosing)	39
4. Summary of Clinical Findings: Total Occurrence/No. of Animals (1-Hour Post-Dosing)	40
4A. Summary of Clinical Findings: Total Occurrence/No. of Animals (1-Hour Post-Dosing)	41
5A. Summary of Clinical Findings: Total Occurrence/No. of Animals (2-Hour Post-Dosing)	43
6A. Summary of Clinical Findings: Total Occurrence/No. of Animals (4-Hour Post-Dosing)	45
7. Mean Body Weights (Grams) During Gestation	47
7A. Mean Body Weights (Grams) During Gestation	49

[]

VOLUME 1 (continued)		<u>Page</u>
8.	Mean Body Weight Changes (Grams) During Gestation	51
8A.	Mean Body Weight Changes (Grams) During Gestation	53
9.	Mean Gravid Uterine Weights and Net Body Weight Changes (Grams)	55
9A.	Mean Gravid Uterine Weights and Net Body Weight Changes (Grams)	56
10.	Mean Food Consumption During Gestation (Grams/Animal/Day)	57
10A.	Mean Food Consumption During Gestation (Grams/Animal/Day)	59
11.	Mean Food Consumption During Gestation (Grams/Kg/Day)	61
11A.	Mean Food Consumption During Gestation (Grams/Kg/Day)	63
12.	Summary of Mean Fetal Data at the Scheduled Necropsy	65
12A.	Summary of Mean Fetal Data at the Scheduled Necropsy	66
13.	Summary of Mean Fetal Data at the Scheduled Necropsy (% Per Litter)	67
13A.	Summary of Mean Fetal Data at the Scheduled Necropsy (% Per Litter)	70
14.	Number of Fetuses and Litters with Malformations - Summary	73
14A.	Number of Fetuses and Litters with Malformations - Summary	74
15.	Number of Fetuses and Litters with Variations - Summary	75
15A.	Number of Fetuses and Litters with Variations - Summary	76
VOLUME 2		
16.	Individual Clinical Observations (Daily Examinations)	78
16A.	Individual Clinical Observations (Daily Examinations)	83
17.	Individual Clinical Observations (At Time of Dosing)	87

[]

VOLUME 2 (continued)		<u>Page</u>
18.	Individual Clinical Observations (1-Hour Post-Dosing)	88
18A.	Individual Clinical Observations (1-Hour Post-Dosing)	89
19A.	Individual Clinical Observations (2-Hour Post-Dosing)	94
20A.	Individual Clinical Observations (4-Hour Post Dosing)	98
21.	Individual Body Weights (Grams) During Gestation	101
21A.	Individual Body Weights (Grams) During Gestation	113
22.	Individual Body Weight Changes (Grams) During Gestation	121
22A.	Individual Body Weight Changes (Grams) During Gestation	133
23.	Individual Gravid Uterine Weights and Net Body Weight Changes (Grams)	141
23A.	Individual Gravid Uterine Weights and Net Body Weight Changes (Grams)	147
24.	Individual Food Consumption During Gestation (Grams/Animal/Day)	151
24A.	Individual Food Consumption During Gestation (Grams/Animal/Day)	163
25.	Individual Food Consumption During Gestation (Grams/Kg/Day)	171
25A.	Individual Food Consumption During Gestation (Grams/Kg/Day)	183
26.	Individual Dam Gross Necropsy Examinations	191
26A.	Individual Dam Gross Necropsy Examinations	199
27.	Individual Fetal Data at the Scheduled Necropsy	205
27A.	Individual Fetal Data at the Scheduled Necropsy	211
28.	Individual Fetal Data at the Scheduled Necropsy (% Per Litter)	215
28A.	Individual Fetal Data at the Scheduled Necropsy (% Per Litter)	221
29.	Individual Fetal Weights (Grams)	225

[]

	<u>Page</u>
VOLUME 2 (continued)	
29A. Individual Fetal Weights (Grams)	229
30. Individual Fetal External Examinations	231
30A. Individual Fetal External Examinations	247

[]

A Dose Range-Finding Developmental
Toxicity Study of Furfural in Rats

INDEX OF APPENDICES

	<u>Page</u>
VOLUME 2 (continued)	
A. Analytical Chemistry Report (WIL Research Laboratories, Inc.)	253
B. WIL Historical Control Data [CrI:CD [®] (SD)BR Rats] - Summary	268
C. WIL Historical Control Data [CrI:CD [®] (SD)BR Rats] - Individual	278
D. Study Protocol	398

A Dose Range-Finding Developmental
Toxicity Study of Furfural in Rats

I. SUMMARY

The potential maternal toxicity and developmental toxicity of furfural were evaluated. The test article, furfural, in the vehicle, reverse osmosis treated water (deionized and sparged with nitrogen), was initially administered to five groups of eight bred Crl:CD®(SD)BR rats once daily from gestation days 6 through 15. Initially, dosage levels were 10, 50, 100, 500 and 1000 mg/kg/day administered at a dose volume of 5 ml/kg. Due to the excessive mortalities observed at the 500 and 1000 mg/kg/day groups, the breeding phase for the study was reinitiated to further characterize the potential maternal and developmental toxicity of the test article at dose levels between 100 and 500 mg/kg/day (150, 250 and 350 mg/kg/day). Two concurrent control groups (one for each breeding phase) each composed of eight bred females received the vehicle, reverse osmosis treated water (deionized and sparged with nitrogen), on a comparable regimen at 5 ml/kg. The route of administration was oral by gastric intubation. Clinical observations, body weights and food consumption were recorded. 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 the 150, 250, 350, 500 and 1000 mg/kg/day groups, one, six, six, four and three females, respectively, died within one hour following dosing on gestation days 6 or 7. Due to the excessive mortalities, the remaining two, two, four and five females in the 250, 350, 500 and 1000 mg/kg/day groups, respectively, were not dosed and were euthanized on gestation days 5 or 6. All other maternal animals survived to the scheduled necropsy on gestation day 20. At necropsy, dark red lungs (all lobes) were noted for 2, 4 and 1 females in the 350, 500 and 1000 mg/kg/day groups, respectively. Clinical findings related to treatment with the test article in the 150, 250 and/or 350 mg/kg/day groups were rales, lethargy, prostration, hyperactivity, whole body tremors, labored respiration, exophthalmia, vocalization, shallow respiration, eyes appearing

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dark in color and body/extremities cool to the touch. In the 150 mg/kg/day group, a reduced mean body weight gain and reductions in food consumption were observed during gestation days 6-9. Mean body weight, net body weight, net body weight gain and gravid uterine weight in the 150 mg/kg/day group were unaffected by test article administration. Body weight data and food consumption in the 10, 50 and 100 mg/kg/day groups were unaffected by treatment with the test article.

Intrauterine growth and survival were unaffected by test article administration at any dose level available for evaluation (150 mg/kg/day and below). The only external malformation observed during this study was an omphalocele in one 10 mg/kg/day group fetus. No developmental variations were noted in fetuses in this study.

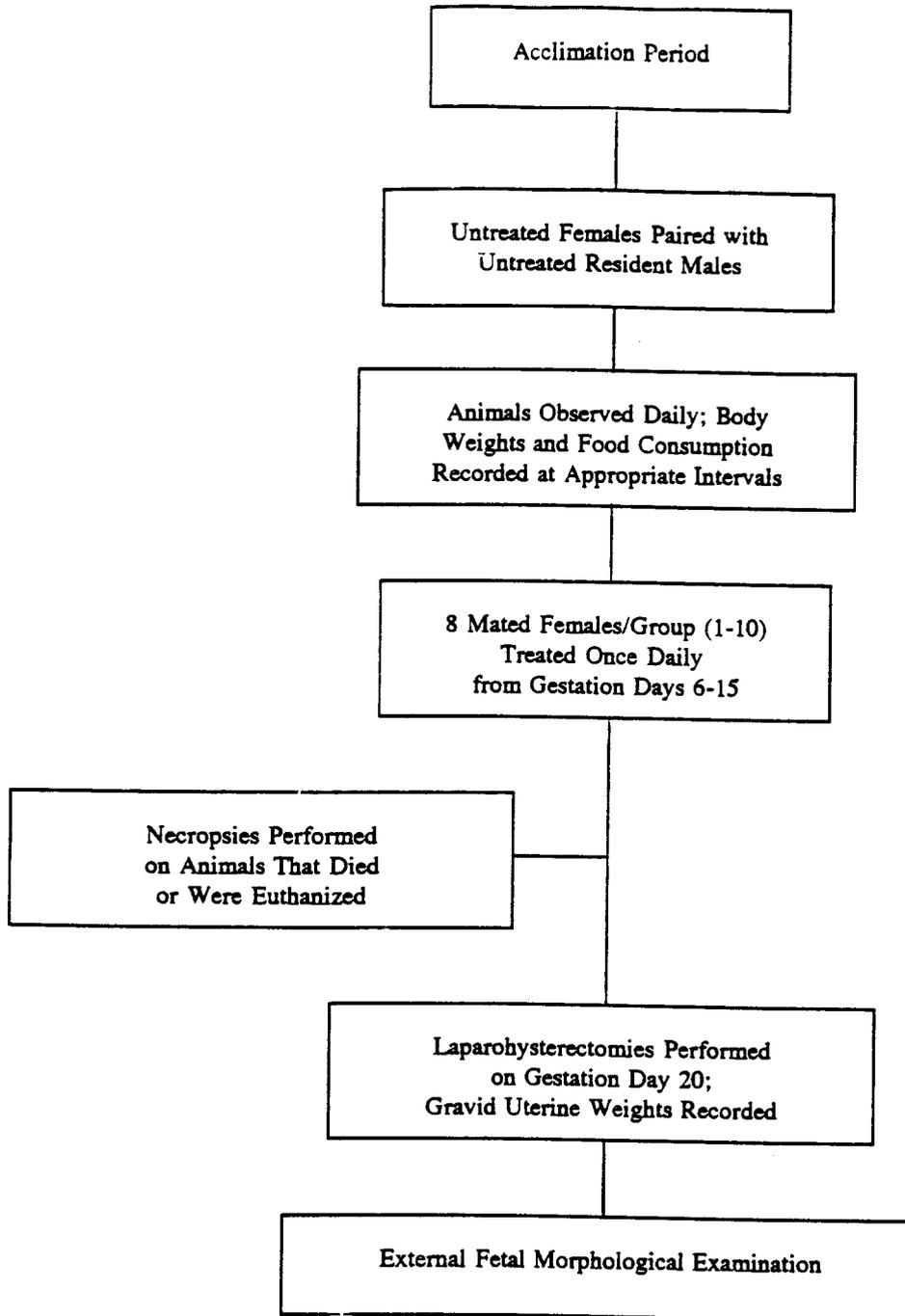
Based on the results of this study, dose levels of 50, 100 and 150 mg/kg/day were selected for the definitive developmental toxicity study of furfural in rats.

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II. OBJECTIVE

The objective of the study was to investigate the potential maternal toxicity and developmental toxicity of furfural 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 oral. The animal model was selected on the basis of availability of historical control data and susceptibility of the species to known developmental toxicants.

III. STUDY DESIGN



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IV. EXPERIMENTAL PROCEDURES

A. INTRODUCTION

The experimental phase of the study was initiated with the assignment of bred female rats to treatment groups on January 14, 1997. The experimental design initially consisted of five furfural treated groups receiving dose levels of 10, 50, 100, 500 and 1000 mg/kg/day and one concurrent control group. Due to the high levels of maternal toxicity at dose levels of 500 and 1000 mg/kg/day, the breeding phase of the study was reinitiated on February 25, 1997 to further characterize the potential maternal and developmental toxicity of the test article at dose levels between 100 and 500 mg/kg/day. For the initial study, the dosing period was from January 20 to January 31, 1997, and the last laparohysterectomy was on February 5, 1997. For the continued study, the dosing period was from March 3 to March 14, 1997, and the last laparohysterectomy was on March 19, 1997. The initial study was designated [] and the continued study was designated [] for computer entry. Report tables for the additional dose levels are presented immediately following the appropriate table for the initial dose groups. Due to spacing constraints, the study title is presented on the report tables as "A Dose R-F Developmental Toxicity Study of Furfural in Rats".

B. TEST AND CONTROL ARTICLES

1. TEST ARTICLE IDENTIFICATION

The test article, furfural, was received from [] on December 20, 1996, as follows:

<u>Identification</u>	<u>No. of Containers Received</u>	<u>Description</u>
Furfural CAS No. 98-01-1 []	2 Bottles Gross weight: #1-1712.0 g* #2-1709.9 g	Clear, yellowish to dark amber liquid

* = Bottle used in []

[]

Purity data for the test article provided by the sponsor indicated a purity of 99.4%. Purity analyses conducted at WIL Research Laboratories, Inc. indicated that the test article purity was 99.8% and 100%. For the purposes of dose calculations, the test article was considered to be 100% furfural. The test article was stored in a sealed container at room temperature and protected from light in a fire cabinet. An approximate one-gram reserve sample of the test article was taken on January 8, 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 and for administration to the control group was reverse osmosis treated water, deionized and sparged with nitrogen.

3. PREPARATION

An appropriate amount of the vehicle, reverse osmosis treated water (deionized and sparged with nitrogen), was dispensed into a properly labeled storage container for administration to the control groups. A stir bar was added and the vehicle was stirred continuously throughout the sampling and dosing procedures. A sufficient amount of the vehicle was dispensed daily for administration to the control group.

An appropriate amount of the test article, furfural, was weighed for each treated group into a labeled, precalibrated storage container. A sufficient amount of the vehicle was added to bring the volume of each preparation to the calibration mark. A stir bar was added and the preparations were stirred continuously throughout the sampling, dispensing and dosing procedures. A sufficient volume of each test formulation was dispensed daily for administration to the treated groups.

Dosing formulations were prepared weekly (January 20 and 27, 1997, for [] and February 28, March 7 and 14, 1997, for []) The test article formulations were stored at room temperature protected from light. The dosing preparations were visually inspected for homogeneity by

the study director on January 20, 1997, and were found to be acceptable for use.

4. ADMINISTRATION

The test mixtures were administered orally by gavage as a single daily dose from gestation days 6 through 15 using a syringe fitted with a 16-gauge stainless steel gavage cannula (Popper and Sons, Inc., New Hyde Park, New York). A dosage volume of 5 ml/kg was used for each dosage level. The control animals received the vehicle, reverse osmosis treated water (deionized and sparged with nitrogen), on a comparable regimen at 5 ml/kg. Individual dosages were based on the most recently recorded body weights to provide the closest mg/kg/day dose. The following diagram presents the study group assignment:

<u>Group Number</u>	<u>Test Article</u>	<u>Dosage Level (mg/kg/day)</u>	<u>Dosage Concentration (mg/ml)</u>	<u>Dosage Volume (ml/kg)</u>	<u>Number of Females</u>
1	Vehicle Control	0	0	5	8
2	Furfural	10	2	5	8
3	Furfural	50	10	5	8
4	Furfural	100	20	5	8
5	Furfural	500	100	5	8
6	Furfural	1000	200	5	8
7 ^a	Vehicle Control	0	0	5	8
8 ^b	Furfural	150	30	5	8
9 ^c	Furfural	250	50	5	8
10 ^d	Furfural	350	70	5	8

^a = Appears as Group 1 on [report tables
^b = Appears as Group 2 on [report tables
^c = Appears as Group 3 on [report tables
^d = Appears as Group 4 on [report tables

5. SAMPLING AND ANALYSES

The test article was analyzed on January 20, 1997 by the Analytical Chemistry Department at WIL Research Laboratories, Inc., to verify identity and purity. On January 8, 1997 (prior to the initiation of dosing), duplicate 10-ml aliquots were collected from the top, middle and bottom strata of the control group formulations and each of the treated

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group formulations. One set of these samples was analyzed for homogeneity. The second set of samples was combined and stored for 8-day stability verification. For the January 20 (Groups 1-6), January 27 (Groups 1-4), and February 28, 1997 (Groups 7, 8 and 10) weekly dosing preparations, duplicate 10-ml aliquots were collected from the middle stratum of each dosing formulation and analyzed for concentration. Samples were inadvertently not collected from Group 9 (February 28, 1997 preparation) and Groups 7-10 (March 7 and 14, 1997 preparations). The methodology and results of these analyses are presented in Appendix A. The dosing formulations were homogeneous, stable for 8 days and contained the amounts of the test article specified in the protocol.

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 December 30, 1996, for [] The animals were approximately 70 days old. The animals for [] were selected from a shipment of rats received in good health from the same supplier on February 13, 1997, and were approximately 70 days old. Upon receipt, each female was observed by a qualified technician. The animals were initially weighed on December 31, 1996 [] or February 14, 1997 [] All animals were uniquely identified by a Monel metal eartag displaying the animal number and housed for 15 days [] or 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

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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 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 $72^{\circ} \pm 4^{\circ}\text{F}$ and a relative humidity between 30% and 70%. Room temperature and relative humidity were recorded daily. Temperatures ranged from 70.9°F to 72.9°F and relative humidity ranged from 24.7% to 50.1% during the study period. The occasional and slight deviations from the set humidity levels were not noted as having an adverse effect 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

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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 then separated.

The experimental design for [] consisted of eight treated groups (Groups 2-6, [] and Groups 8-10, [] and two vehicle control groups (Group 1, [] and Group 7, []). The bred females were consecutively assigned in a block design to groups containing eight 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 eight females were placed into Groups 1-6 [] beginning on January 14, 1997) or Groups 7-10 [] beginning on February 25, 1997). Body weight values ranged from 215 g to 279 g for [] and from 227 g to 274 g for [] 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 article administration during the dosing period). Animals in [] were observed for signs of

[]

toxicity approximately one hour following dosing, with the following exception. A one hour post-dose comment was not performed on January 30, 1997. However, the animals were observed at the evening room check and no overt signs of toxicity were noted; therefore, the deviation was considered to have no effect on the outcome of the study. Observations noted at the time of dosing were also recorded, if present. Animals in [] were observed for signs of toxicity approximately one hour following dosing. In addition, observations noted at two and four hours following dosing, if present, were also recorded.

Animals not surviving to the scheduled euthanization were necropsied, and the cause of death or moribundity was recorded, if possible. In addition, the number and location of implantation sites and corpora lutea were recorded.

2. BODY WEIGHTS AND GRAVID UTERINE WEIGHTS

Individual maternal body weights were recorded on gestation days 0, 6-16 (daily) and 20. 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, 12-16, 6-16 and 0-20.

Gravid uterine weight was collected and net body weight (the day 20 body weight minus the weight of the uterus and contents) and net body weight change (the day 0-20 body weight change minus the weight of the uterus and contents) were calculated and presented for each gravid female at the scheduled laparohysterectomy.

3. FOOD CONSUMPTION

Individual food consumption was recorded on gestation days 0, 6-16 (daily) and 20. 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, 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.

Maternal tissues were preserved in 10% neutral buffered formalin for possible future histopathological examination only as indicated by the gross findings.

Uteri with no macroscopic evidence of nidation were opened and subsequently placed in 10% ammonium sulfide solution for detection of early implantation loss as described by Salewski².

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:

$$\text{Summation per Group (\%)} = \frac{\text{Postimplantation Loss/Litter (\%)}^2}{\text{No. of Litters/Group}}$$

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

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 on the report tables:

[]

STATISTICAL TEST

PARAMETER

- One-way ANOVA with
Dunnnett's test³

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-test³

Litter Proportions of
Intrauterine Data (Considering
the Litter, Rather than the
Fetus, as the Experimental
Unit)

L. 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 in the Archives at WIL Research Laboratories, Inc., in compliance with regulatory requirements.

V. RESULTS

A. CLINICAL OBSERVATIONS AND SURVIVAL

Summary Data: Tables 1, 1A, 2, 2A, 3, 4, 4A, 5A, 6A

Individual Data: Tables 16, 16A, 17, 18, 18A, 19A, 20A

One, six, six, four and three females in the 150, 250, 350, 500 and 1000 mg/kg/day groups, respectively, died within one hour following dosing on gestation day 6 or 7. Due to the excessive maternal mortalities, the remaining two, two, four and five females in the 250, 350, 500 and 1000 mg/kg/day groups, respectively, were not dosed and were euthanized on January 21, 1997 [] corresponding to gestation days 5 or 6) or March 5, 1997 [] corresponding to gestation day 6). The remaining seven animals in the 150 mg/kg/day group survived to study termination (gestation day 20). Treatment-related clinical observations noted one, two and/or four hours following dosing in the 150, 250 and/or 350 mg/kg/day groups included rales, lethargy, prostration, hyperactivity, whole body tremors, labored respiration, exophthalmia, vocalization, shallow respiration, eyes appearing dark in color and body/extremities cool to the touch. Exophthalmia and eyes appearing dark in color continued in the 150 mg/kg/day group through gestation day 15.

All animals in the control, 10, 50 and 100 mg/kg/day groups survived to the scheduled necropsy on gestation day 20. No clinical signs relating to test article administration were observed in the 10, 50 and 100 mg/kg/day groups. Clinical findings in these groups, such as hair loss, occurred similarly in the control groups, in single animals or in a manner that was not suggestive of a relationship to treatment.

B. BODY WEIGHTS AND GRAVID UTERINE WEIGHTS

Summary Data: Tables 7, 7A, 8, 8A, 9, 9A

Individual Data: Tables 21, 21A, 22, 22A, 23, 23A

An assessment of body weight data in the 250, 350, 500 and 1000 mg/kg/day groups was precluded by mortalities and group termination.

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In the 150 mg/kg/day group, a decreased mean body weight gain was noted during gestation days 6-9. During this interval, 4 of 6 gravid females lost between 2 and 17 grams of body weight. During the remainder of the treatment period (gestation days 9-12 and 12-16), mean body weight gains in the 150 mg/kg/day group were comparable to the control group values. Mean body weight gain in this group was reduced during the entire treatment period (gestation days 6-16). Mean body weight, net body weight, net body weight gain and gravid uterine weight in the 150 mg/kg/day group were comparable to the concurrent control group values.

Mean body weights, body weight gains, net body weights, net body weight gains and gravid uterine weights in the 10, 50 and 100 mg/kg/day groups were unaffected by test article administration.

C. FOOD CONSUMPTION

Summary Data: Tables 10, 10A, 11, 11A

Individual Data: Tables 24, 24A, 25, 25A

An assessment of food consumption in the 250, 350, 500 and 1000 mg/kg/day groups was precluded by mortalities and group termination.

In the 150 mg/kg/day group, a decrease in food consumption (g/animal/day and g/kg/day) was noted during gestation days 6-9. The difference from the concurrent control group was not statistically significant. All other values in this group were comparable to the concurrent control group values; none of the differences were statistically significant.

Food consumption was unaffected by test article administration at dose levels of 10, 50 and 100 mg/kg/day. The only statistically significant ($p < 0.05$) difference from the concurrent control group were decreases in food consumption (g/kg/day or g/animal/day) in the 10 mg/kg/day group during the post-treatment period (gestation days 16-20) and in the 100 mg/kg/day group during gestation days 15-16. The corresponding g/animal/day or g/kg/day values for these intervals were similar to the concurrent control group values. All other values in these groups were comparable to the concurrent control group values.

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D. NECROPSY DATA

Individual Data: Tables 26, 26A

In the 150, 250, 350, 500 and 1000 mg/kg/day groups, one, six, six, four and three females, respectively, died within one hour following dosing on gestation day 6 or 7. At necropsy, 2, 4 and 1 females in the 350, 500 and 1000 mg/kg/day groups had dark red lungs (all lobes). Female no. 63535 in the 350 mg/kg/day group had red fluid contents in the urinary bladder. Female no. 63571 in the same dose group had a cyst on one ovary. Two females (nos. 63562 and 63582) in the 250 mg/kg/day group had dark red contents in the stomach; female no. 63562 also had a distended urinary bladder. Due to the excessive mortalities, the remaining two, two, four and five females in the 250, 350, 500 and 1000 mg/kg/day groups, respectively, were not dosed and were euthanized on gestation day 5 or 6. All other females that died were internally normal.

At the scheduled necropsy on gestation day 20, no test article-related internal findings were observed at any dose level. Two females (nos. 63543 and 63575) in the control group [] and one female (no. 63569) in the 150 mg/kg/day group had dilated renal pelves. Female no. 60973 in the 50 mg/kg/day group had clear fluid contents in both uterine horns. All other females were internally normal.

E. GESTATION DAY 20 LAPAROHYSTERECTOMY DATA

Summary Data: Tables 12, 12A, 13, 13A

Individual Data: Tables 27, 27A, 28, 28A, 29, 29A

Historical Control Data: Appendices B, C

No gravid females in the 250, 350, 500 and 1000 mg/kg/day groups survived to the scheduled necropsy on gestation day 20.

Intrauterine growth and survival in the 10, 50, 100 and 150 mg/kg/day groups were unaffected by test article administration. Parameters evaluated included postimplantation loss, live litter size, fetal sex ratios, mean fetal body weights and the mean numbers of corpora lutea and implantation sites. All

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values in these treated groups were similar to the concurrent control group values; no statistically significant differences were observed.

F. FETAL MORPHOLOGICAL DATA

Summary Data: Tables 14, 14A, 15, 15A

Individual Data: Tables 30, 30A

Historical Control Data: Appendices B, C

The number of fetuses (litters) available for morphological examination were 100(8), 83(6), 113(8), 98(7), 109(8), 81(6), 0(0), 0(0), 0(0) and 0(0) in the control [] control [] 10, 50, 100, 150, 250, 350, 500 and 1000 mg/kg/day groups, respectively. The only external malformation observed was an omphalocele in one 10 mg/kg/day group fetus (no. 60923-14). No developmental variations were noted in fetuses in this study.

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VI. DISCUSSION AND CONCLUSIONS

In the 150, 250, 350, 500 and 1000 mg/kg/day groups, one, six, six, four and three females, respectively, died within one hour following dosing on gestation days 6 or 7. Due to the excessive mortalities, the remaining two, two, four and five females in the 250, 350, 500 and 1000 mg/kg/day groups, respectively, were not dosed and were euthanized on gestation days 5 or 6. All other females survived to the scheduled necropsy on gestation day 20. Treatment-related clinical observations in the 150, 250 and/or 350 mg/kg/day groups were lethargy, prostration, shallow respiration, vocalization, labored respiration, rales, hyperactivity, whole body tremors, exophthalmia, eyes appearing dark in color and body/extremities cool to the touch. These findings were noted at the daily examinations, at the time of dosing and/or at various post-dose intervals (1, 2 or 4 hours). No other treatment-related clinical findings were observed.

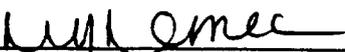
In the 150 mg/kg/day group, reduced mean body weight gain and decreases in food consumption were noted during gestation days 6-9. Mean body weight, net body weight, net body weight gain and gravid uterine weight in the 150 mg/kg/day group were comparable to the concurrent control group values. Body weight data and food consumption in the 10, 50 and 100 mg/kg/day groups were unaffected by test article administration. An assessment of body weight data and food consumption in the 250, 350, 500 and 1000 mg/kg/day groups was precluded by mortalities and group termination.

At the necropsies of the animals that died, dark red lungs (all lobes) were noted for 2, 4 and 1 females in the 350, 500 and 1000 mg/kg/day groups, respectively. At the scheduled necropsy on gestation day 20, no test article-related internal findings were observed.

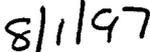
Intrauterine growth and survival were unaffected by test article administration at any dose level. Parameters evaluated included postimplantation loss, viable litter size, fetal sex ratio, and the mean numbers of corpora lutea and implantation sites. Fetuses (litters) available for morphological examination numbered 100(8), 83(6), 113(8), 98(7), 109(8), 81(6), 0(0), 0(0), 0(0) and 0(0) in the control [] control [] 10, 50 100, 150, 250, 350, 500 and 1000 mg/kg/day groups,

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respectively. The only external malformation observed was an omphalocele in one 10 mg/kg/day group fetus. No developmental variations were noted in fetuses in this study.

In conclusion, maternal toxicity was expressed at dose levels of 150, 250, 350, 500 and 1000 mg/kg/day by mortalities and changes in the clinical condition of the animals. No maternal toxicity was apparent at dose levels of 10, 50 and 100 mg/kg/day. No developmental toxicity was observed at the dose levels available for evaluation (150 mg/kg/day and below). Based on the results of this study, dose levels of 50, 100 and 150 were selected for the definitive developmental toxicity study of furfural in rats.



Mark D. Nemec, B.S., D.A.B.T.
Study Director



Date

VIII. 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>
1/13, 15/97	Cohabitation and Confirmation of Breeding	1/15/97	2/26/97
5/7, 8, 13, 21/97	Study Records (I-1)	5/21/97	6/27/97
5/9, 12, 21/97	Study Records (I-2)	5/21/97	6/27/97
5/14, 21/97	Study Records (N-1)	5/21/97	6/27/97
5/13, 14, 21/97	Study Records (N-2)	5/21/97	6/27/97
5/29, 30 & 6/6, 9/97	Study Records (A-1)	6/9/97	7/29/97
5/29, 30 & 6/6, 9/97	Draft Report (Analytical)	6/9/97	7/29/97
6/1-4, 6, 9/97	Draft Report (without Analytical)	6/9/97	7/29/97

This study was conducted and inspected in accordance with the current EPA, OECD and MAFF Good Laboratory Practice Regulations, the Standard Operating Procedures of WIL Research Laboratories, Inc., and the sponsor's protocol and protocol amendment(s). Quality Assurance inspections during the conduct of the study and findings from review 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.

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.

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

8/1/97
Date

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IX. REFERENCES

1. National Research Council (1996) Guide for the Care and Use of Laboratory Animals, Institute of Laboratory Animal Resources, Commission on Life Sciences. National Academy Press, Washington, D.C.
2. Salewski (Köln), V. E. (1964) Farbemethode zum makroskopischen Nachweis von Implantationstellen am Uterus der Ratte. Naunyn - Schm. Archiv. für Exper. Pathologie und Pharm. 247:367.
3. BMDP (1979) Biomedical Computer Programs. (Dixon, W.J. and Brown, M.B., eds.) University of California Press, Berkeley, CA, pp. 612, 780, 781.

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**A Dose Range-Finding Developmental
Toxicity Study of Furfural in Rats**

TABLES 1-15A

PROJECT NO. []

TABLE 1
A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
SUMMARY OF MATERNAL SURVIVAL AND PREGNANCY STATUS

PAGE 1

DOSE GROUP :	1		2		3		4		5		6	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
FEMALES ON STUDY	8	0.0	8	0.0	8	0.0	8	0.0	8	0.0	8	0.0
FEMALES THAT ABORTED OR DELIVERED	0	0.0	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	4	50.0	3	37.5
FEMALES THAT ABORTED NONGRAVID	0	0.0	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	1	25.0	0	0.0
FEMALES THAT WERE EUTHANIZED	0	0.0	0	0.0	0	0.0	0	0.0	4	50.0	5	62.5
NONGRAVID	0	0.0	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	4	100.0	5	100.0
FEMALES EXAMINED AT SCHEDULED NECROPSY	8	100.0	8	100.0	8	100.0	8	100.0	0	0.0	0	0.0
NONGRAVID	0	0.0	0	0.0	1	12.5	0	0.0	0	0.0	0	0.0
GRAVID	8	100.0	8	100.0	7	87.5	8	100.0	0	0.0	0	0.0
WITH RESORPTIONS ONLY	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
WITH VIABLE FETUSES	8	100.0	8	100.0	7	100.0	8	100.0	0	0.0	0	0.0
TOTAL FEMALES GRAVID	8	100.0	8	100.0	7	87.5	8	100.0	7	87.5	8	100.0
1- 0 MG/KG/DAY	2- 10 MG/KG/DAY	3- 50 MG/KG/DAY	4- 100 MG/KG/DAY	5- 500 MG/KG/DAY	6- 1000 MG/KG/DAY							

PROJECT NO. [] TABLE 1A
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL 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	1	12.5	6	75.0	6	75.0
FEMALES THAT ABORTED NONGRAVID	0	0.0	0	0.0	0	0.0	0	0.0
GRAVID	0	0.0	0	0.0	1	16.7	1	16.7
	0	0.0	1	100.0	5	83.3	5	83.3
FEMALES THAT WERE EUTHANIZED NONGRAVID	0	0.0	0	0.0	2	25.0	2	25.0
GRAVID	0	0.0	0	0.0	0	0.0	0	0.0
	0	0.0	0	0.0	2	100.0	2	100.0
FEMALES EXAMINED AT SCHEDULED NECROPSY NONGRAVID	8	100.0	7	87.5	0	0.0	0	0.0
GRAVID	2	25.0	1	14.3	0	0.0	0	0.0
	6	75.0	6	85.7	0	0.0	0	0.0
WITH RESORPTIONS ONLY	0	0.0	0	0.0	0	0.0	0	0.0
WITH VIABLE FETUSES	6	100.0	6	100.0	0	0.0	0	0.0
TOTAL FEMALES GRAVID	6	75.0	7	87.5	7	87.5	7	87.5

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 MG/KG/DAY

35

PROJECT NO. []
 TABLE 2 (DAILY EXAMINATIONS)
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

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

TABLE RANGE:	01-14-97 TO 02-05-97				
GROUP:	1	2	3	4	5
NORMAL					
-NO SIGNIFICANT CLINICAL OBSERVATIONS	129/ 8	168/ 8	139/ 8	166/ 8	54/ 8
DISPOSITION					
-FOUND DEAD	0/ 0	0/ 0	0/ 0	0/ 0	4/ 4
-SENT TO LAB AT STUDY DIRECTOR'S REQUEST	0/ 0	0/ 0	0/ 0	0/ 0	4/ 4
-SENT TO LAB FOR SCHEDULED LAPAROMYSTERECTOMY; GESTATION DAY 20	8/ 8	8/ 8	8/ 8	8/ 8	0/ 0
BODY/INTEGUMENT					
-HAIR LOSS RIGHT FORELIMB	2/ 1	0/ 0	22/ 2	0/ 0	0/ 0
-HAIR LOSS LEFT FORELIMB	2/ 1	0/ 0	29/ 2	0/ 0	0/ 0
-HAIR LOSS RIGHT LATERAL ABDOMINAL AREA	12/ 1	0/ 0	0/ 0	0/ 0	0/ 0
-HAIR LOSS RIGHT HINDLIMB	4/ 1	0/ 0	0/ 0	0/ 0	0/ 0
-HAIR LOSS LEFT HINDLIMB	5/ 1	0/ 0	0/ 0	0/ 0	0/ 0
-HAIR LOSS DORSAL POSTERIOR LEFT	1/ 1	0/ 0	0/ 0	0/ 0	0/ 0
-HAIR LOSS DORSAL POSTERIOR RIGHT	1/ 1	0/ 0	0/ 0	0/ 0	0/ 0
-HAIR LOSS VENTRAL THORACIC AREA	0/ 0	0/ 0	0/ 0	2/ 1	0/ 0
EYES/EARS/NOSE					
-DRIED RED MATERIAL AROUND LEFT EYE	19/ 1	0/ 0	0/ 0	0/ 0	0/ 0
ORAL/DENTAL					
-UPPER INCISORS MALALIGNED	20/ 1	0/ 0	0/ 0	0/ 0	0/ 0

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 50 MG/KG/DAY 4- 100 MG/KG/DAY 5- 500 MG/KG/DAY 6- 1000 MG/KG/DAY

30

PROJECT NO. []

TABLE 2 (DAILY EXAMINATIONS)
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

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

TABLE RANGE: 01-14-97 TO 02-05-97
 GROUP: 1 2 3 4 5 6

ORAL/DENTAL -TEETH LONG, TRIMMED	1- 0 MG/KG/DAY	2- 10 MG/KG/DAY	3- 50 MG/KG/DAY	4- 100 MG/KG/DAY	5- 500 MG/KG/DAY	6- 1000 MG/KG/DAY
			1/ 1	0/ 0	0/ 0	0/ 0

PROJECT NO. []

TABLE 2A (DAILY EXAMINATIONS)
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

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

TABLE RANGE:	1	2	3	4
GROUP:				
	02-25-97	TO 03-19-97		
NORMAL				
-NO SIGNIFICANT CLINICAL OBSERVATIONS	167/ 8	114/ 8	56/ 8	56/ 8
DISPOSITION				
-FOUND DEAD	0/ 0	1/ 1	6/ 6	6/ 6
-SENT TO LAB AT STUDY DIRECTOR'S REQUEST	0/ 0	0/ 0	2/ 2	2/ 2
-SENT TO LAB FOR SCHEDULED LAPAROMYSTERECTOMY; GESTATION DAY 20	8/ 8	7/ 7	0/ 0	0/ 0
BODY/INTEGUMENT				
-HAIR LOSS RIGHT FORELIMB	0/ 0	8/ 1	0/ 0	0/ 0
-HAIR LOSS LEFT FORELIMB	0/ 0	7/ 1	0/ 0	0/ 0
-HAIR LOSS ABDOMINAL AREA	0/ 0	5/ 1	0/ 0	0/ 0
EYES/EARS/NOSE				
-RIGHT EYE APPEARS EXOPHTHALMIC	0/ 0	8/ 4	0/ 0	0/ 0
-LEFT EYE APPEARS EXOPHTHALMIC	0/ 0	8/ 4	0/ 0	0/ 0
-RIGHT EYE APPEARS DARK IN COLOR	1/ 1	29/ 6	0/ 0	0/ 0
-LEFT EYE APPEARS DARK IN COLOR	1/ 1	29/ 6	0/ 0	0/ 0
-DRIED RED MATERIAL AROUND NOSE	0/ 0	2/ 1	0/ 0	0/ 0
1- 0 MG/KG/DAY	2- 150 MG/KG/DAY	3- 250 MG/KG/DAY	4- 350 MG/KG/DAY	

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PROJECT NO. []

TABLE 3 (AT TIME OF DOSING)
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

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

TABLE RANGE:	1	2	3	4	5	6
GROUP:						
		01-20-97 TO 01-31-97				

ORAL/DENTAL -SALIVATION PRIOR TO DOSE ADMINISTRATION	0/0	0/0	0/0	1/1	0/0	0/0
1- 0 MG/KG/DAY	2- 10 MG/KG/DAY	3- 50 MG/KG/DAY	4- 100 MG/KG/DAY	5- 500 MG/KG/DAY	6- 1000 MG/KG/DAY	

TABLE 4 (1-HOUR POST-DOSING)
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

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

TABLE RANGE:	1	2	3	4	5	6
GROUP:						
		01-20-97 TO 01-31-97				

1-HOUR POST-DOSE

THERE WERE NO SIGNIFICANT FINDINGS AT ONE HOUR FOLLOWING DOSING

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 50 MG/KG/DAY 4- 100 MG/KG/DAY 5- 500 MG/KG/DAY 6- 1000 MG/KG/DAY

PROJECT NO. []

TABLE 4A (1-HOUR POST-DOSING)
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

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

TABLE RANGE:	1	2	3	4
GROUP:				
BEHAVIOR/CNS				
-LETHARGIC	0/0	1/1	0/0	1/1
-PROSTRATE	0/0	1/1	3/3	2/2
-VOCALIZATION	0/0	2/1	2/2	2/2
-WHOLE BODY TREMORS	0/0	1/1	0/0	0/0
-HYPERACTIVE	0/0	0/0	1/1	0/0
BODY/INTEGUMENT				
-BODY COOL TO TOUCH	0/0	0/0	0/0	2/2
-EXTREMITIES COOL TO TOUCH	0/0	1/1	4/4	2/2
CARDIO-PULMONARY				
-SHALLOW RESPIRATION	0/0	3/2	3/3	1/1
-LABORED RESPIRATION	0/0	0/0	0/0	3/3
EYES/EARS/NOSE				
-RIGHT EYE APPEARS EXOPHTHALMIC	0/0	59/8	4/4	3/3
-LEFT EYE APPEARS EXOPHTHALMIC	0/0	57/8	4/4	3/3
-RIGHT EYE APPEARS DARK IN COLOR	0/0	13/7	1/1	3/3
-LEFT EYE APPEARS DARK IN COLOR	0/0	14/7	1/1	3/3
-LACRIMATION RIGHT EYE	0/0	1/1	0/0	2/2
-LACRIMATION LEFT EYE	0/0	1/1	0/0	2/2

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 MG/KG/DAY

PROJECT NO. []
 TABLE 4A (1-HOUR POST-DOSING)
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

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

TABLE RANGE:	1	2	3	4
GROUP:				
		03-03-97 TO 03-14-97		

EYES/EARS/NOSE	1	2	3	4
-DRIED RED MATERIAL AROUND NOSE	1/ 1	5/ 3	0/ 0	0/ 0
-RIGHT EYELID SLIGHTLY DROOPING	0/ 0	1/ 1	0/ 0	0/ 0
-LEFT EYELID SLIGHTLY DROOPING	0/ 0	1/ 1	0/ 0	0/ 0
-CONJUNCTIVA OF LEFT EYE APPEARS RED IN COLOR	0/ 0	1/ 1	0/ 0	0/ 0
ORAL/DENTAL				
-SALIVATION	0/ 0	2/ 2	0/ 0	0/ 0

1- 0 MG/KG/DAY	2- 150 MG/KG/DAY	3- 250 MG/KG/DAY	4- 350 MG/KG/DAY

PROJECT NO. []
 TABLE 5A (2-HOURS POST-DOSING)
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

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

	TABLE RANGE:			
	1	2	3	4
	03-03-97 TO 03-14-97			
	GROUP:			
BEHAVIOR/CNS				
-LETHARGIC	0/0	0/0	2/2	3/3
-PROSTRATE	0/0	2/1	3/3	1/1
-VOCALIZATION	0/0	1/1	1/1	1/1
-WHOLE BODY TREMORS	0/0	1/1	0/0	0/0
BODY/INTEGUMENT				
-BODY COOL TO TOUCH	0/0	0/0	0/0	2/2
-EXTREMITIES COOL TO TOUCH	0/0	1/1	4/4	3/3
CARDIO-PULMONARY				
-SHALLOW RESPIRATION	0/0	0/0	2/2	2/2
-LABORED RESPIRATION	0/0	1/1	2/2	1/1
-RALES	0/0	1/1	2/2	0/0
EYES/EARS/NOSE				
-RIGHT EYE APPEARS EXOPHTHALMIC	0/0	7/6	4/4	3/3
-LEFT EYE APPEARS EXOPHTHALMIC	0/0	6/5	4/4	3/3
-RIGHT EYE APPEARS DARK IN COLOR	0/0	1/1	0/0	3/3
-LEFT EYE APPEARS DARK IN COLOR	0/0	1/1	0/0	3/3
-LACRIMATION RIGHT EYE	0/0	0/0	1/1	2/2
-LACRIMATION LEFT EYE	0/0	0/0	1/1	2/2

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 MG/KG/DAY

PROJECT NO. []

TABLE 5A (2-HOURS POST-DOSING)
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

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

TABLE RANGE: 03-03-97 TO 03-14-97
 GROUP: 1 2 3 4

	1	2	3	4
EYES/EARS/NOSE				
-MET RED MATERIAL AROUND NOSE	0/0	1/1	1/1	0/0
-CLEAR NASAL DISCHARGE	0/0	1/1	1/1	0/0
ORAL/DENTAL				
-SALIVATION	0/0	2/2	0/0	0/0

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 MG/KG/DAY

TABLE 6A (4-HOURS POST-DOSING)
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

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

	TABLE RANGE: GROUP:			
	1	2	3	4
BEHAVIOR/CNS				
-LETHARGIC	0/0	1/1	1/1	0/0
-PROSTRATE	0/0	2/2	2/2	1/1
-VOCALIZATION	0/0	1/1	0/0	0/0
BODY/INTEGUMENT				
-BODY COOL TO TOUCH	0/0	0/0	2/2	0/0
-EXTREMITIES COOL TO TOUCH	0/0	2/2	3/3	0/0
CARDIO-PULMONARY				
-SHALLOW RESPIRATION	0/0	2/2	0/0	0/0
-LABORED RESPIRATION	0/0	1/1	3/3	1/1
-RALES	0/0	2/2	2/2	1/1
-GASPING	0/0	0/0	1/1	0/0
EYES/EARS/NOSE				
-RIGHT EYE APPEARS EXOPHTHALMIC	0/0	6/5	3/3	0/0
-LEFT EYE APPEARS EXOPHTHALMIC	0/0	6/5	3/3	0/0
-RIGHT EYE APPEARS DARK IN COLOR	0/0	1/1	1/1	1/1
-LEFT EYE APPEARS DARK IN COLOR	0/0	1/1	1/1	1/1
-LACRIMATION RIGHT EYE	0/0	0/0	1/1	0/0
-LACRIMATION LEFT EYE	0/0	0/0	1/1	0/0

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 MG/KG/DAY

PROJECT NO. []

PAGE 2

TABLE 6A (4-HOURS POST-DOSING)
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

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

TABLE RANGE: 03-03-97 TO 03-14-97
 GROUP: 1 2 3 4

	1	2	3	4
EYES/EARS/NOSE				
-DRIED RED MATERIAL AROUND NOSE	0/0	1/1	1/1	0/0
-WET RED MATERIAL AROUND NOSE	0/0	1/1	0/0	0/0
-CLEAR NASAL DISCHARGE	0/0	0/0	1/1	0/0
ORAL/DENTAL				
-SALIVATION	0/0	1/1	0/0	0/0

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 MG/KG/DAY

PROJECT NO. [] TABLE 7
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 MEAN BODY WEIGHTS (GRAMS) DURING GESTATION

GROUP :	1	2	3	4	5	6
DAY 0	MEAN S.D./N	243. 15.5/ 8	248. 10.4/ 7	253. 8.5/ 8	247. 10.3/ 7	249. 14.0/ 8
DAY 6	MEAN S.D./N	272. 12.9/ 8	284. 12.3/ 7	291. 16.5/ 8	275. 13.4/ 5	280. 14.6/ 6
DAY 7	MEAN S.D./N	273. 12.6/ 8	285. 9.0/ 7	289. 17.5/ 8	0. 0.0/ 0	0. 0.0/ 0
DAY 8	MEAN S.D./N	275. 12.0/ 8	288. 13.0/ 7	290. 17.8/ 8	0. 0.0/ 0	0. 0.0/ 0
DAY 9	MEAN S.D./N	281. 13.9/ 8	293. 13.6/ 7	295. 17.8/ 8	0. 0.0/ 0	0. 0.0/ 0
DAY 10	MEAN S.D./N	286. 14.2/ 8	299. 14.5/ 7	301. 20.4/ 8	0. 0.0/ 0	0. 0.0/ 0
DAY 11	MEAN S.D./N	290. 10.6/ 8	307. 14.5/ 7	307. 17.1/ 8	0. 0.0/ 0	0. 0.0/ 0
DAY 12	MEAN S.D./N	296. 13.1/ 8	310. 11.7/ 7	313. 19.0/ 8	0. 0.0/ 0	0. 0.0/ 0
DAY 13	MEAN S.D./N	299. 16.8/ 8	314. 11.0/ 7	317. 21.2/ 8	0. 0.0/ 0	0. 0.0/ 0
DAY 14	MEAN S.D./N	308. 14.2/ 8	321. 13.6/ 7	324. 23.1/ 8	0. 0.0/ 0	0. 0.0/ 0

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 50 MG/KG/DAY 4- 100 MG/KG/DAY 5- 500 MG/KG/DAY 6- 1000 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. []

TABLE 7
A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
MEAN BODY WEIGHTS (GRAMS) DURING GESTATION

GROUP :	1	2	3	4	5	6
DAY 15	MEAN 316. S.D./N 13.5/ 8	313. 15.6/ 8	328. 10.7/ 7	333. 18.1/ 8	0. 0.0/ 0	0. 0.0/ 0
DAY 16	MEAN 321. S.D./N 17.9/ 8	322. 15.7/ 8	338. 10.5/ 7	342. 18.7/ 8	0. 0.0/ 0	0. 0.0/ 0
DAY 20	MEAN 377. S.D./N 29.7/ 8	383. 18.4/ 8	401. 13.6/ 7	402. 25.5/ 8	0. 0.0/ 0	0. 0.0/ 0

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 50 MG/KG/DAY 4- 100 MG/KG/DAY 5- 500 MG/KG/DAY 6- 1000 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

GROUP :		1	2	3	4
DAY 0	MEAN S.D./N	250. 7.6/ 6	251. 14.3/ 7	248. 11.8/ 7	250. 7.3/ 7
DAY 6	MEAN S.D./N	283. 8.5/ 6	285. 12.9/ 7	270. 17.7/ 7	278. 9.9/ 7
DAY 7	MEAN S.D./N	282. 9.6/ 6	274. 16.5/ 7	0. 0.0/ 0	0. 0.0/ 0
DAY 8	MEAN S.D./N	288. 8.4/ 6	274. 21.8/ 6	0. 0.0/ 0	0. 0.0/ 0
DAY 9	MEAN S.D./N	292. 11.7/ 6	281. 19.6/ 6	0. 0.0/ 0	0. 0.0/ 0
DAY 10	MEAN S.D./N	293. 12.1/ 6	289. 19.5/ 6	0. 0.0/ 0	0. 0.0/ 0
DAY 11	MEAN S.D./N	302. 10.4/ 6	295. 18.0/ 6	0. 0.0/ 0	0. 0.0/ 0
DAY 12	MEAN S.D./N	306. 13.1/ 6	302. 19.2/ 6	0. 0.0/ 0	0. 0.0/ 0
DAY 13	MEAN S.D./N	315. 16.1/ 6	306. 20.4/ 6	0. 0.0/ 0	0. 0.0/ 0
DAY 14	MEAN S.D./N	318. 15.1/ 6	314. 21.5/ 6	0. 0.0/ 0	0. 0.0/ 0

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 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

		GROUP :			
		1	2	3	4
DAY 15	MEAN	325.	318.	0.	0.
	S.D./N	12.3/ 6	22.2/ 6	0.0/ 0	0.0/ 0
DAY 16	MEAN	332.	326.	0.	0.
	S.D./N	14.0/ 6	21.6/ 6	0.0/ 0	0.0/ 0
DAY 20	MEAN	397.	388.	0.	0.
	S.D./N	21.4/ 6	25.7/ 6	0.0/ 0	0.0/ 0

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 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. []

TABLE 8
A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
MEAN BODY WEIGHT CHANGES (GRAMS) DURING GESTATION

PAGE 1

GROUP :	1	2	3	4	5	6
DAY 0- 6 MEAN	28.	28.	37.	38.	29.	30.
S.D./N	8.1/ 8	9.0/ 8	6.0/ 7	11.1/ 8	3.8/ 5	6.6/ 6
DAY 6- 7 MEAN	2.	0.	1.	-2.	0.	0.
S.D./N	5.3/ 8	3.3/ 8	4.7/ 7	2.7/ 8	0.0/ 0	0.0/ 0
DAY 7- 8 MEAN	2.	2.	3.	1.	0.	0.
S.D./N	3.7/ 8	3.0/ 8	4.2/ 7	2.3/ 8	0.0/ 0	0.0/ 0
DAY 8- 9 MEAN	6.	6.	5.	5.	0.	0.
S.D./N	4.1/ 8	5.0/ 8	1.7/ 7	1.9/ 8	0.0/ 0	0.0/ 0
DAY 9- 10 MEAN	4.	5.	6.	6.	0.	0.
S.D./N	2.0/ 8	4.2/ 8	1.8/ 7	3.9/ 8	0.0/ 0	0.0/ 0
DAY 10- 11 MEAN	4.	7.	8.	7.	0.	0.
S.D./N	6.2/ 8	4.9/ 8	3.9/ 7	4.0/ 8	0.0/ 0	0.0/ 0
DAY 11- 12 MEAN	6.	4.	3.	6.	0.	0.
S.D./N	2.7/ 8	1.5/ 8	5.3/ 7	4.0/ 8	0.0/ 0	0.0/ 0
DAY 12- 13 MEAN	3.	5.	4.	3.	0.	0.
S.D./N	6.4/ 8	5.2/ 8	4.7/ 7	3.6/ 8	0.0/ 0	0.0/ 0
DAY 13- 14 MEAN	9.	7.	7.	7.	0.	0.
S.D./N	3.9/ 8	4.2/ 8	4.9/ 7	5.2/ 8	0.0/ 0	0.0/ 0
DAY 14- 15 MEAN	8.	7.	7.	10.	0.	0.
S.D./N	5.2/ 8	6.0/ 8	6.1/ 7	6.5/ 8	0.0/ 0	0.0/ 0

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 50 MG/KG/DAY 4- 100 MG/KG/DAY 5- 500 MG/KG/DAY 6- 1000 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

PROJECT NO. []

TABLE 8
A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
MEAN BODY WEIGHT CHANGES (GRAMS) DURING GESTATION

PAGE ?

GROUP :	1	2	3	4	5	6
DAY 15-16 MEAN	5.	9.	10.	9.	0.	0.
S.D./N	7.3/8	5.2/8	3.3/7	5.5/8	0.0/0	0.0/0
DAY 16-20 MEAN	57.	61.	63.	60.	0.	0.
S.D./N	14.1/8	7.1/8	5.6/7	15.0/8	0.0/0	0.0/0
DAY 6-9 MEAN	10.	8.	9.	4.	0.	0.
S.D./N	8.2/8	6.6/8	4.4/7	5.3/8	0.0/0	0.0/0
DAY 9-12 MEAN	14.	16.	17.	19.	0.	0.
S.D./N	5.2/8	5.2/8	3.5/7	2.1/8	0.0/0	0.0/0
DAY 12-16 MEAN	25.	28.	28.	29.	0.	0.
S.D./N	7.9/8	4.8/8	5.1/7	4.6/8	0.0/0	0.0/0
DAY 6-16 MEAN	49.	52.	53.	52.	0.	0.
S.D./N	7.2/8	6.8/8	7.5/7	5.2/8	0.0/0	0.0/0
DAY 0-20 MEAN	134.	140.	153.	149.	0.	0.
S.D./N	16.0/8	11.4/8	13.9/7	22.2/8	0.0/0	0.0/0

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 50 MG/KG/DAY 4- 100 MG/KG/DAY 5- 500 MG/KG/DAY 6- 1000 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

PROJECT NO. []

TABLE 8A
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 MEAN BODY WEIGHT CHANGES (GRAMS) DURING GESTATION

GROUP :		1	2	3	4
DAY 0- 6	MEAN	33.	34.	22.	27.
	S.D./N	7.2/ 6	7.5/ 7	11.9/ 7	4.4/ 7
DAY 6- 7	MEAN	-1.	-11.	0.	0.
	S.D./N	4.2/ 6	10.1/ 7	0.0/ 0	0.0/ 0
DAY 7- 8	MEAN	6.	-3.	0.	0.
	S.D./N	3.4/ 6	6.8/ 6	0.0/ 0	0.0/ 0
DAY 8- 9	MEAN	4.	7.	0.	0.
	S.D./N	5.9/ 6	4.5/ 6	0.0/ 0	0.0/ 0
DAY 9- 10	MEAN	2.	8.	0.	0.
	S.D./N	6.3/ 6	4.2/ 6	0.0/ 0	0.0/ 0
DAY 10- 11	MEAN	9.	6.	0.	0.
	S.D./N	6.0/ 6	3.9/ 6	0.0/ 0	0.0/ 0
DAY 11- 12	MEAN	4.	7.	0.	0.
	S.D./N	4.0/ 6	2.1/ 6	0.0/ 0	0.0/ 0
DAY 12- 13	MEAN	9.	4.	0.	0.
	S.D./N	4.7/ 6	5.6/ 6	0.0/ 0	0.0/ 0
DAY 13- 14	MEAN	3.	9.	0.	0.
	S.D./N	5.4/ 6	4.2/ 6	0.0/ 0	0.0/ 0
DAY 14- 15	MEAN	7.	4.	0.	0.
	S.D./N	5.2/ 6	3.6/ 6	0.0/ 0	0.0/ 0

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 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

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PROJECT NO. []

TABLE 8A
A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
MEAN BODY WEIGHT CHANGES (GRAMS) DURING GESTATION

PAGE

GROUP :	1	2	3	4
DAY 15- 16 MEAN S.D./N	7. 3.3/ 6	7. 2.7/ 6	0. 0.0/ 0	0. 0.0/ 0
DAY 16- 20 MEAN S.D./N	65. 10.5/ 6	63. 7.8/ 6	0. 0.0/ 0	0. 0.0/ 0
DAY 6- 9 MEAN S.D./N	8. 9.6/ 6	-5. 10.2/ 6	0. 0.0/ 0	0. 0.0/ 0
DAY 9- 12 MEAN S.D./N	15. 6.7/ 6	20. 6.9/ 6	0. 0.0/ 0	0. 0.0/ 0
DAY 12- 16 MEAN S.D./N	26. 5.3/ 6	24. 12.9/ 6	0. 0.0/ 0	0. 0.0/ 0
DAY 6- 16 MEAN S.D./N	49. 11.9/ 6	40. 9.5/ 6	0. 0.0/ 0	0. 0.0/ 0
DAY 0- 20 MEAN S.D./N	147. 18.5/ 6	135. 19.5/ 6	0. 0.0/ 0	0. 0.0/ 0

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 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

PROJECT NO. []

TABLE 9
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 MEAN GRAVID UTERINE WEIGHTS AND NET BODY WEIGHT CHANGES (GRAMS)

PAGE 1

	GROUP:					
	1	2	3	4	5	6
INITIAL BODY WT.	243. 15.5 8	243. 9.4 8	248. 10.4 7	253. 8.5 8	NA	NA
TERMINAL BODY WT.	377. 29.7 8	383. 18.4 8	401. 13.6 7	402. 25.5 8	NA	NA
GRAVID UTERINE WT.	68.6 24.59 8	78.8 12.05 8	80.2 7.50 7	75.1 22.35 8	NA	NA
NET BODY WT.	308.8 15.92 8	304.1 13.08 8	320.5 16.91 7	326.9 21.40 8	NA	NA
NET BODY WT. CHANGE	65.4 16.29 8	61.6 7.37 8	72.9 13.65 7	74.1 16.22 8	NA	NA

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 50 MG/KG/DAY 4- 100 MG/KG/DAY 5- 500 MG/KG/DAY 6- 1000 MG/KG/DAY
 NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING A TWO-TAILED DUNNETT'S TEST
 NA = NO DAMS SURVIVED TO THE SCHEDULED NECROPSY

TABLE 9A
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 MEAN GRAVID UTERINE WEIGHTS AND NET BODY WEIGHT CHANGES (GRAMS)

PROJECT NO. []

	1		2		3		4	
INITIAL BODY WT.	MEAN	250.	254.	NA	NA	NA	NA	NA
	S.D.	7.6	14.3					
	N	6	6					
TERMINAL BODY WT.	MEAN	397.	388.	NA	NA	NA	NA	NA
	S.D.	21.4	25.7					
	N	6	6					
GRAVID UTERINE WT.	MEAN	77.1	75.7	NA	NA	NA	NA	NA
	S.D.	10.63	13.91					
	N	6	6					
NET BODY WT.	MEAN	320.1	312.6	NA	NA	NA	NA	NA
	S.D.	15.99	20.48					
	N	6	6					
NET BODY WT. CHANGE	MEAN	70.1	59.1	NA	NA	NA	NA	NA
	S.D.	13.78	12.67					
	N	6	6					

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 MG/KG/DAY
 NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP USING A TWO-TAILED DUNNETT'S TEST
 NA = NO DAMS SURVIVED TO THE SCHEDULED NECROPSY

TABLE 10
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY)

PROJECT NO. []

GROUP :	1	2	3	4	5	6
DAY 0- 6 MEAN	21.	21.	24.	23.	23.	22.
S.D./N	2.2/ 8	1.5/ 8	2.6/ 7	3.3/ 8	2.1/ 2	1.5/ 3
DAY 6- 7 MEAN	21.	19.	22.	21.	0.	0.
S.D./N	2.6/ 8	1.7/ 8	1.9/ 7	3.3/ 8	0.0/ 0	0.0/ 0
DAY 7- 8 MEAN	21.	21.	24.	22.	0.	0.
S.D./N	2.9/ 8	1.9/ 8	3.6/ 7	2.9/ 8	0.0/ 0	0.0/ 0
DAY 8- 9 MEAN	21.	20.	24.	23.	0.	0.
S.D./N	2.3/ 8	1.8/ 8	3.5/ 7	3.3/ 8	0.0/ 0	0.0/ 0
DAY 9- 10 MEAN	22.	22.	24.	23.	0.	0.
S.D./N	2.6/ 8	2.3/ 8	3.4/ 7	4.0/ 8	0.0/ 0	0.0/ 0
DAY 10- 11 MEAN	23.	21.	25.	24.	0.	0.
S.D./N	1.2/ 8	1.5/ 8	2.7/ 7	2.2/ 8	0.0/ 0	0.0/ 0
DAY 11- 12 MEAN	24.	26.	25.	26.	0.	0.
S.D./N	1.7/ 8	6.4/ 8	1.7/ 7	3.6/ 8	0.0/ 0	0.0/ 0
DAY 12- 13 MEAN	25.	24.	26.	26.	0.	0.
S.D./N	2.8/ 8	2.2/ 8	2.8/ 7	3.1/ 8	0.0/ 0	0.0/ 0
DAY 13- 14 MEAN	24.	23.	23.	24.	0.	0.
S.D./N	1.4/ 8	1.7/ 8	2.6/ 7	3.5/ 8	0.0/ 0	0.0/ 0
DAY 14- 15 MEAN	25.	23.	25.	25.	0.	0.
S.D./N	3.7/ 8	3.2/ 8	2.7/ 7	2.4/ 8	0.0/ 0	0.0/ 0

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 50 MG/KG/DAY 4- 100 MG/KG/DAY 5- 500 MG/KG/DAY 6- 1000 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 10
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY)

PROJECT NO. []

GROUP :	1	2	3	4	5	6
DAY 15-16 MEAN	23.	25.	25.	27.*	0.	0.
S.D./N	2.8/8	1.7/8	1.7/7	2.5/8	0.0/0	0.0/0
DAY 16-20 MEAN	27.	24.	27.	28.	0.	0.
S.D./N	2.8/8	4.4/8	1.9/7	2.1/8	0.0/0	0.0/0
DAY 6-9 MEAN	21.	20.	23.	22.	0.	0.
S.D./N	2.1/8	1.2/8	2.3/7	2.8/8	0.0/0	0.0/0
DAY 9-12 MEAN	23.	23.	25.	24.	0.	0.
S.D./N	1.5/8	2.3/8	2.0/7	3.0/8	0.0/0	0.0/0
DAY 12-16 MEAN	24.	24.	25.	26.	0.	0.
S.D./N	2.1/8	2.1/8	1.5/7	2.8/8	0.0/0	0.0/0
DAY 6-16 MEAN	23.	22.	24.	24.	0.	0.
S.D./N	1.5/8	1.4/8	1.7/7	2.6/8	0.0/0	0.0/0
DAY 0-20 MEAN	23.	22.	25.	25.	0.	0.
S.D./N	1.8/8	1.6/8	2.0/7	2.4/8	0.0/0	0.0/0

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 50 MG/KG/DAY 4- 100 MG/KG/DAY 5- 500 MG/KG/DAY 6- 1000 MG/KG/DAY
 * = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST
 NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

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TABLE 10A
A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY)

DAY	GROUP :	1	2	3	4
0-6	MEAN	22.	22.	19.	21.
	S.D./N	1.6/6	1.6/7	3.2/7	2.0/7
6-7	MEAN	20.	15.	0.	0.
	S.D./N	2.9/6	6.2/7	0.0/0	0.0/0
7-8	MEAN	23.	16.	0.	0.
	S.D./N	3.9/6	6.4/6	0.0/0	0.0/0
8-9	MEAN	22.	20.	0.	0.
	S.D./N	3.7/6	4.2/6	0.0/0	0.0/0
9-10	MEAN	24.	24.	0.	0.
	S.D./N	3.9/6	1.9/6	0.0/0	0.0/0
10-11	MEAN	23.	23.	0.	0.
	S.D./N	2.8/6	3.7/6	0.0/0	0.0/0
11-12	MEAN	23.	25.	0.	0.
	S.D./N	2.2/6	1.6/6	0.0/0	0.0/0
12-13	MEAN	24.	23.	0.	0.
	S.D./N	4.9/6	3.8/6	0.0/0	0.0/0
13-14	MEAN	24.	26.	0.	0.
	S.D./N	3.8/6	5.5/6	0.0/0	0.0/0
14-15	MEAN	28.	25.	0.	0.
	S.D./N	2.2/6	3.6/6	0.0/0	0.0/0

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 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 10A
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY)

PROJECT NO. []

GROUP :		1	2	3	4
DAY 15- 16	MEAN	26.	26.	0.	0.
	S.D./N	1.2/ 6	3.6/ 6	0.0/ 0	0.0/ 0
DAY 16- 20	MEAN	27.	27.	0.	0.
	S.D./N	1.9/ 6	2.1/ 6	0.0/ 0	0.0/ 0
DAY 6- 9	MEAN	22.	17.	0.	0.
	S.D./N	3.0/ 6	5.7/ 6	0.0/ 0	0.0/ 0
DAY 9- 12	MEAN	23.	24.	0.	0.
	S.D./N	2.0/ 6	2.2/ 6	0.0/ 0	0.0/ 0
DAY 12- 16	MEAN	26.	25.	0.	0.
	S.D./N	2.1/ 6	3.8/ 6	0.0/ 0	0.0/ 0
DAY 6- 16	MEAN	24.	22.	0.	0.
	S.D./N	1.5/ 6	2.7/ 6	0.0/ 0	0.0/ 0
DAY 0- 20	MEAN	24.	23.	0.	0.
	S.D./N	1.0/ 6	2.1/ 6	0.0/ 0	0.0/ 0

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 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

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PROJECT NO. [] TABLE 11
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/KG/DAY)

GROUP :	1	2	3	4	5	6
DAY 0-6 MEAN	82.	81.	89.	85.	87.	86.
S.D./N	5.2/8	4.3/8	8.5/7	8.9/8	10.6/2	5.5/3
DAY 6-7 MEAN	76.	70.	77.	72.	0.	0.
S.D./N	8.7/8	6.0/8	7.2/7	7.7/8	0.0/0	0.0/0
DAY 7-8 MEAN	76.	76.	83.	75.	0.	0.
S.D./N	8.1/8	7.6/8	9.9/7	8.4/8	0.0/0	0.0/0
DAY 8-9 MEAN	76.	74.	82.	78.	0.	0.
S.D./N	6.8/8	6.6/8	9.2/7	8.0/8	0.0/0	0.0/0
DAY 9-10 MEAN	76.	77.	81.	78.	0.	0.
S.D./N	7.4/8	7.3/8	8.6/7	9.4/8	0.0/0	0.0/0
DAY 10-11 MEAN	78.	75.	83.	79.	0.	0.
S.D./N	4.9/8	4.8/8	6.6/7	4.9/8	0.0/0	0.0/0
DAY 11-12 MEAN	81.	88.	81.	83.	0.	0.
S.D./N	5.3/8	24.6/8	6.8/7	7.0/8	0.0/0	0.0/0
DAY 12-13 MEAN	82.	80.	85.	82.	0.	0.
S.D./N	7.0/8	6.2/8	11.8/7	7.5/8	0.0/0	0.0/0
DAY 13-14 MEAN	78.	75.	74.	76.	0.	0.
S.D./N	4.9/8	4.8/8	7.7/7	7.5/8	0.0/0	0.0/0
DAY 14-15 MEAN	79.	73.	77.	77.	0.	0.
S.D./N	9.2/8	9.1/8	7.3/7	4.1/8	0.0/0	0.0/0

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 50 MG/KG/DAY 4- 100 MG/KG/DAY 5- 500 MG/KG/DAY 6- 1000 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

01

PROJECT NO. [] TABLE 11
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/KG/DAY)

GROUP :	1	2	3	4	5	6
DAY 15-16 MEAN	73.	77.	76.	80.	0.	0.
S.D./N	7.1/8	4.8/8	4.6/7	5.0/8	0.0/0	0.0/0
DAY 16-20 MEAN	78.	67.*	74.	75.	0.	0.
S.D./N	4.6/8	11.1/8	3.0/7	4.8/8	0.0/0	0.0/0
DAY 6-9 MEAN	76.	73.	81.	75.	0.	0.
S.D./N	6.2/8	4.0/8	6.0/7	6.1/8	0.0/0	0.0/0
DAY 9-12 MEAN	78.	80.	82.	79.	0.	0.
S.D./N	4.4/8	9.0/8	4.2/7	5.4/8	0.0/0	0.0/0
DAY 12-16 MEAN	78.	77.	78.	79.	0.	0.
S.D./N	4.1/8	5.4/8	4.2/7	5.3/8	0.0/0	0.0/0
DAY 6-16 MEAN	77.	77.	80.	78.	0.	0.
S.D./N	2.7/8	4.1/8	3.8/7	4.9/8	0.0/0	0.0/0
DAY 0-20 MEAN	78.	75.	80.	79.	0.	0.
S.D./N	2.5/8	3.6/8	4.1/7	3.9/8	0.0/0	0.0/0

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 50 MG/KG/DAY 4- 100 MG/KG/DAY 5- 500 MG/KG/DAY 6- 1000 MG/KG/DAY
 * = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST
 NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

52

TABLE 11A
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/KG/DAY)

GROUP :	1	2	3	4
DAY 0- 6 MEAN	81.	82.	75.	81.
S.D./N	6.2/ 6	3.8/ 7	10.5/ 7	5.6/ 7
DAY 6- 7 MEAN	70.	53.	0.	0.
S.D./N	10.2/ 6	20.8/ 7	0.0/ 0	0.0/ 0
DAY 7- 8 MEAN	79.	58.	0.	0.
S.D./N	13.0/ 6	19.9/ 6	0.0/ 0	0.0/ 0
DAY 8- 9 MEAN	76.	71.	0.	0.
S.D./N	11.7/ 6	12.0/ 6	0.0/ 0	0.0/ 0
DAY 9- 10 MEAN	81.	86.	0.	0.
S.D./N	13.8/ 6	4.0/ 6	0.0/ 0	0.0/ 0
DAY 10- 11 MEAN	78.	78.	0.	0.
S.D./N	10.9/ 6	9.7/ 6	0.0/ 0	0.0/ 0
DAY 11- 12 MEAN	75.	83.	0.	0.
S.D./N	7.9/ 6	5.7/ 6	0.0/ 0	0.0/ 0
DAY 12- 13 MEAN	78.	75.	0.	0.
S.D./N	13.1/ 6	9.2/ 6	0.0/ 0	0.0/ 0
DAY 13- 14 MEAN	77.	84.	0.	0.
S.D./N	10.5/ 6	13.0/ 6	0.0/ 0	0.0/ 0
DAY 14- 15 MEAN	86.	79.	0.	0.
S.D./N	9.4/ 6	9.8/ 6	0.0/ 0	0.0/ 0

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 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

03

TABLE 11A
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/KG/DAY)

PROJECT NO. []

	GROUP :			
	1	2	3	4
DAY 15- 16 MEAN S.D./N	78. 3.1/ 6	80. 7.6/ 6	0. 0.0/ 0	0. 0.0/ 0
DAY 16- 20 MEAN S.D./N	75. 3.8/ 6	76. 3.3/ 6	0. 0.0/ 0	0. 0.0/ 0
DAY 6- 9 MEAN S.D./N	75. 10.1/ 6	61. 18.2/ 6	0. 0.0/ 0	0. 0.0/ 0
DAY 9- 12 MEAN S.D./N	78. 7.8/ 6	82. 5.5/ 6	0. 0.0/ 0	0. 0.0/ 0
DAY 12- 16 MEAN S.D./N	80. 4.6/ 6	80. 8.7/ 6	0. 0.0/ 0	0. 0.0/ 0
DAY 6- 16 MEAN S.D./N	79. 3.7/ 6	75. 5.4/ 6	0. 0.0/ 0	0. 0.0/ 0
DAY 0- 20 MEAN S.D./N	77. 2.6/ 6	77. 3.3/ 6	0. 0.0/ 0	0. 0.0/ 0

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 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 12
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF MEAN FETAL DATA AT THE SCHEDULED NECROPSY

GROUP	SEX		VIABLE FETUSES	DEAD FETUSES	RESORPTIONS		IMPLANTATION LOSS		CORPORA LUTEA		PRE LOSS	FETAL WEIGHTS IN GRAMS	NO. OF GRAVID FEMALES
	M	F			EARLY	LATE	POST LOSS	SITES	LUTEA				
1	TOTAL	49	51	0	16	0	16	116	136	20	NA	8	
	MEAN	6.1	6.4	0.0	2.0	0.0	2.0	14.5	17.0	2.5	3.7		
	S.D.	2.75	2.92	0.00	1.85	0.00	1.85	5.26	2.78	4.44	0.29		
2	TOTAL	62	51	0	7	1	8	121	127	6	NA	8	
	MEAN	7.8	6.4	0.0	0.9	0.1	1.0	15.1	15.9	0.8	3.7		
	S.D.	2.96	1.92	0.00	0.99	0.35	0.93	2.17	2.75	1.16	0.19		
3	TOTAL	47	51	0	8	0	8	106	115	9	NA	7	
	MEAN	6.7	7.3	0.0	1.1	0.0	1.1	15.1	16.4	1.3	3.7		
	S.D.	2.63	2.87	0.00	1.21	0.00	1.21	1.57	1.90	1.50	0.27		
4	TOTAL	63	46	0	5	1	6	115	142	27	NA	8	
	MEAN	7.9	5.8	0.0	0.6	0.1	0.8	14.4	17.8	3.4	3.6		
	S.D.	2.70	2.82	0.00	1.06	0.35	1.16	4.10	2.31	3.38	0.27		

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

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

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL
 NA = NOT APPLICABLE

MEAN NUMBER OF VIABLE FETUSES COMPARED USING DUNNETT'S TEST;
 TOTAL NUMBER OF DEAD FETUSES COMPARED USING MANN-WHITNEY TEST;
 TOTAL NUMBER OF EARLY RESORPTIONS COMPARED USING MANN-WHITNEY TEST;
 TOTAL NUMBER OF LATE RESORPTIONS COMPARED USING MANN-WHITNEY TEST;
 SEX RATIO COMPARED USING CHI SQUARE TEST

TOTAL POST IMPLANTATION LOSS COMPARED USING MANN-WHITNEY TEST
 MEAN NUMBER OF IMPLANTATION SITES COMPARED USING DUNNETT'S TEST
 MEAN NUMBER OF CORPORA LUTEA COMPARED USING DUNNETT'S TEST
 FETAL WEIGHTS COMPARED USING DUNNETT'S TEST

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 50 MG/KG/DAY 4- 100 MG/KG/DAY 5- 500 MG/KG/DAY 6- 1000 MG/KG/DAY

PROJECT NO. [] TABLE 12A
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF MEAN FETAL DATA AT THE SCHEDULED NECROPSY

GROUP	SEX		VIABLE FETUSES	DEAD FETUSES	RESORPTIONS		IMPLANTATION LOSS		IMPLANTATION SITES	CORPORA LUTEA	PRE IMPLANTATION LOSS	FETAL WEIGHTS IN GRAMS	NO. OF GRAVID FEMALES
	M	F			EARLY	LATE	POST	LATE					
1	TOTAL	44	39	83	0	4	1	5	88	104	16	NA	6
	MEAN	7.3	6.5	13.8	0.0	0.7	0.2	0.8	14.7	17.3	2.7	3.6	
	S.D.	2.07	1.87	1.83	0.00	0.82	0.41	0.75	2.16	1.97	1.51	0.12	
2	TOTAL	34	47	81	0	2	0	2	83	98	15	NA	6
	MEAN	5.7	7.8	13.5	0.0	0.3	0.0	0.3	13.8	16.3	2.5	3.7	
	S.D.	1.97	1.17	2.26	0.00	0.52	0.00	0.52	2.48	1.21	3.39	0.34	

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

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

○) NONE SIGNIFICANTLY DIFFERENT FROM CONTROL
 ○) NA = NOT APPLICABLE

MEAN NUMBER OF VIABLE FETUSES COMPARED USING DUNNETT'S TEST; TOTAL POST IMPLANTATION LOSS COMPARED USING MANN-WHITNEY TEST
 TOTAL NUMBER OF DEAD FETUSES COMPARED USING MANN-WHITNEY TEST; MEAN NUMBER OF IMPLANTATION SITES COMPARED USING DUNNETT'S TEST
 TOTAL NUMBER OF EARLY RESORPTIONS COMPARED USING MANN-WHITNEY TEST; MEAN NUMBER OF CORPORA LUTEA COMPARED USING DUNNETT'S TEST
 TOTAL NUMBER OF LATE RESORPTIONS COMPARED USING MANN-WHITNEY TEST; FETAL WEIGHTS COMPARED USING DUNNETT'S TEST
 SEX RATIO COMPARED USING CHI SQUARE TEST

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 MG/KG/DAY

TABLE 13
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF MEAN FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)

PROJECT NO. []

GROUP NUMBER:	1	2	3	4	5	6
CORPORA LUTEA						
MEAN	17.0	15.9	16.4	17.8	NA	NA
S.D.	2.78	2.75	1.90	2.31		
N	8	8	7	8		
IMPLANTATION SITES						
MEAN	14.5	15.1	15.1	14.4	NA	NA
S.D.	5.26	2.17	1.57	4.10		
N	8	8	7	8		
VIABLE FETUSES (%)						
MEAN	87.7	93.5	92.8	94.8	NA	NA
S.D.	11.65	6.05	7.52	8.17		
N	8	8	7	8		
DEAD FETUSES (%)						
MEAN	0.0	0.0	0.0	0.0	NA	NA
S.D.	0.00	0.00	0.00	0.00		
N	8	8	7	8		
EARLY RESORPTIONS (%)						
MEAN	12.3	5.8	7.2	4.4	NA	NA
S.D.	11.64	6.48	7.52	7.54		
N	8	8	7	8		
LATE RESORPTIONS (%)						
MEAN	0.0	0.7	0.0	0.8	NA	NA
S.D.	0.00	1.98	0.00	2.37		
N	8	8	7	8		

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 50 MG/KG/DAY 4- 100 MG/KG/DAY 5- 500 MG/KG/DAY 6- 1000 MG/KG/DAY
 NA = NO DAMS SURVIVED TO THE SCHEDULED NECROPSY

TABLE 13
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF MEAN FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)

GROUP NUMBER:	1	2	3	4	5	6
TOTAL RESORPTIONS (%)						
MEAN	12.3	6.5	7.2	5.2	NA	NA
S.D.	11.64	6.05	7.52	8.17		
N	8	8	7	8		
PRE-IMPLANTATION LOSS (%)						
MEAN	15.2	4.2	7.4	19.3	NA	NA
S.D.	29.46	6.10	8.33	21.24		
N	8	8	7	8		
POST-IMPLANTATION LOSS (%)						
MEAN	12.3	6.5	7.2	5.2	NA	NA
S.D.	11.64	6.05	7.52	8.17		
N	8	8	7	8		
MALES (%)						
MEAN	49.2	54.0	48.2	58.7	NA	NA
S.D.	12.39	15.52	18.62	11.75		
N	8	8	7	8		
FEMALES (%)						
MEAN	50.8	46.0	51.8	41.3	NA	NA
S.D.	12.39	15.52	18.62	11.75		
N	8	8	7	8		
MALE FETAL WEIGHTS (g)						
MEAN	3.7	3.8	3.8	3.7	NA	NA
S.D.	0.31	0.19	0.22	0.33		
N	8	8	7	8		

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 50 MG/KG/DAY 4- 100 MG/KG/DAY 5- 500 MG/KG/DAY 6- 1000 MG/KG/DAY
 NA = NO DAMS SURVIVED TO THE SCHEDULED NECROPSY

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TABLE 13
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF MEAN FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)

GROUP NUMBER:	1	2	3	4	5	6
FEMALE FETAL WEIGHTS (g)						
MEAN	3.6	3.6	3.6	3.6	NA	NA
S.D.	0.24	0.20	0.30	0.21		
N	8	8	7	8		
COMBINED FETAL WEIGHTS (g)						
MEAN	3.7	3.7	3.7	3.6	NA	NA
S.D.	0.29	0.19	0.27	0.27		
N	8	8	7	8		

1- 0 MG/KG/DAY 2- 10 MG/KG/DAY 3- 50 MG/KG/DAY 4- 100 MG/KG/DAY 5- 500 MG/KG/DAY 6- 1000 MG/KG/DAY
 NA = NO DAMS SURVIVED TO THE SCHEDULED NECROPSY

PROJECT NO. []

TABLE 13A
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF MEAN FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)

GROUP NUMBER:	1	2	3	4
CORPORA LUTEA			NA	NA
MEAN	17.3	16.3		
S.D.	1.97	1.21		
N	6	6		
IMPLANTATION SITES			NA	NA
MEAN	14.7	13.8		
S.D.	2.16	2.48		
N	6	6		
VIABLE FETUSES (%)			NA	NA
MEAN	94.6	97.9		
S.D.	4.81	3.33		
N	6	6		
DEAD FETUSES (%)			NA	NA
MEAN	0.0	0.0		
S.D.	0.00	0.00		
N	6	6		
EARLY RESORPTIONS (%)			NA	NA
MEAN	4.5	2.2		
S.D.	5.29	3.36		
N	6	6		
LATE RESORPTIONS (%)			NA	NA
MEAN	0.9	0.0		
S.D.	2.29	0.00		
N	6	6		

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 MG/KG/DAY

NA = NO DAMS SURVIVED TO THE SCHEDULED NECROPSY

PROJECT NO. [] TABLE 13A
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF MEAN FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)

GROUP NUMBER:	1	2	3	4
TOTAL RESORPTIONS (%)				
MEAN	5.4	2.2	NA	NA
S.D.	4.81	3.36		
N	6	6		
PRE-IMPLANTATION LOSS (%)				
MEAN	15.3	14.4	NA	NA
S.D.	9.13	18.75		
N	6	6		
POST-IMPLANTATION LOSS (%)				
MEAN	5.4	2.2	NA	NA
S.D.	4.81	3.36		
N	6	6		
MALES (%)				
MEAN	53.0	40.8	NA	NA
S.D.	12.35	11.03		
N	6	6		
FEMALES (%)				
MEAN	47.0	59.2	NA	NA
S.D.	12.35	11.03		
N	6	6		
MALE FETAL WEIGHTS (g)				
MEAN	3.7	3.8	NA	NA
S.D.	0.10	0.34		
N	6	6		

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 MG/KG/DAY
 NA = NO DAMS SURVIVED TO THE SCHEDULED NECROPSY

TABLE 13A
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 SUMMARY OF MEAN FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)

GROUP NUMBER:	1	2	3	4
FEMALE FETAL WEIGHTS (g)				
MEAN	3.6	3.6	NA	NA
S.D.	0.13	0.34		
N	6	6		
COMBINED FETAL WEIGHTS (g)				
MEAN	3.6	3.7	NA	NA
S.D.	0.12	0.34		
N	6	6		

1- 0 MG/KG/DAY 2- 150 MG/KG/DAY 3- 250 MG/KG/DAY 4- 350 MG/KG/DAY

NA = NO DAMS SURVIVED TO THE SCHEDULED NECROPSY

PROJECT NO. []

TABLE 14
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 NUMBER OF FETUSES AND LITTERS WITH MALFORMATIONS - SUMMARY

DOSE GROUP:	FETUSES						LITTERS					
	1	2	3	4	5	6	1	2	3	4	5	6
NUMBER EXAMINED EXTERNALLY OMPHALOCELE	100	113	98	109	0	0	8	8	7	8	0	0
TOTAL NUMBER WITH MALFORMATIONS EXTERNAL :	0	1	0	0	0	0	0	1	0	0	0	0
1- 0 MG/KG/DAY	2- 10 MG/KG/DAY	3- 50 MG/KG/DAY	4- 100 MG/KG/DAY	5- 500 MG/KG/DAY	6- 1000 MG/KG/DAY							

TABLE 14A
A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
NUMBER OF FETUSES AND LITTERS WITH MALFORMATIONS - SUMMARY

PROJECT NO. []

	FETUSES				LITTERS			
	1	2	3	4	1	2	3	4
DOSE GROUP:								
NUMBER EXAMINED EXTERNALLY	83	81	0	0	6	6	0	0
NUMBER WITH FINDINGS	0	0	0	0	0	0	0	0
TOTAL NUMBER WITH MALFORMATIONS	0	0	0	0	0	0	0	0
EXTERNAL :								
1- 0 MG/KG/DAY	2- 150 MG/KG/DAY	3- 250 MG/KG/DAY	4- 350 MG/KG/DAY					

PROJECT NO. []

TABLE 15
A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
NUMBER OF FETUSES AND LITTERS WITH VARIATIONS - SUMMARY

DOSE GROUP:	FETUSES						LITTERS					
	1	2	3	4	5	6	1	2	3	4	5	6
NUMBER EXAMINED EXTERNALLY	100	113	98	109	0	0	8	8	7	8	0	0
NUMBER WITH FINDINGS	0	0	0	0	0	0	0	0	0	0	0	0
1- 0 MG/KG/DAY	4- 100 MG/KG/DAY						6- 1000 MG/KG/DAY					
2- 10 MG/KG/DAY	3- 50 MG/KG/DAY						5- 500 MG/KG/DAY					

PROJECT NO. []

TABLE 15A
 A DOSE R-F DEVELOPMENTAL TOXICITY STUDY OF FURFURAL IN RATS
 NUMBER OF FETUSES AND LITTERS WITH VARIATIONS - SUMMARY

PAGE 1

DAY 20

	DOSE GROUP:				FETUSES				LITTERS			
	1	2	3	4	1	2	3	4	1	2	3	4
NUMBER EXAMINED EXTERNALLY	83	81	0	0	6	6	0	0	0	0	0	0
NUMBER WITH FINDINGS	0	0	0	0	0	0	0	0	0	0	0	0
1- 0 MG/KG/DAY	2- 150 MG/KG/DAY				3- 250 MG/KG/DAY				4- 350 MG/KG/DAY			

II. PERSONNEL INVOLVED IN THE STUDY (continued)

5. Charlene M. Lindsey, M.A.
Manager of Technical Report Writing
6. Sally A. Keets, A.S.
Manager of Vivarium
7. Ronald E. Wilson, B.S.
Director of Informational Systems
8. Melinda L. Bowen
Group Supervisor - Developmental
and Reproductive Toxicology
9. Deborah A. Shoup, B.S.
Group Leader - Developmental,
Reproductive and Neurotoxicology
10. Kerin Clevidence, B.S.
Group Supervisor of Gross Pathology and
Developmental Toxicology Laboratory
11. Deborah L. Little
Manager of Quality Assurance
12. Loren W. Severs, M.S.
Manager of Analytical Chemistry
13. Daniel W. Sved, Ph.D.
Director of Metabolism and Analytical Chemistry
14. Carney B. Jackson, D.V.M., B.S. An. Sci., D.A.C.V.P., D.A.C.V.P.M.
Assistant Director of Pathology and Veterinary Medicine

III. STUDY SCHEDULE DATA

- A. Proposed Experimental Start Date: January 14, 1997
- B. Proposed Experimental Termination Date: February 7, 1997
- C. Proposed Audited Report Date: April, 1997

A Dose Range-Finding Study in Rats

IV. TEST ARTICLE DATA

- A. Identification: Furfural
- B. Lot Number: To be provided by Sponsor.
- C. Purity: To be provided by Sponsor.
- D. Stability: Stability of the neat test article in storage will be analytically determined by WIL Research Laboratories, Inc.
- E. Physical Description: To be documented by WIL Research Laboratories, Inc.
- F. Storage Conditions: Original container (air tight seal) at room temperature, in a dry well ventilated area protected from light.
- G. Reserve Samples: Retention samples will be collected and stored in accordance with standard operating procedures.
- H. Personnel Safety Data: Latex or nitrile gloves, eye protection, long sleeves (lab coat) and cartridge (organic) respirator are to be worn when handling this test article.

V. TEST SYSTEM

- A. Species: Rat
- B. Strain: Sprague-Dawley Crl:CD®BR
- C. Source: The Charles River Laboratories, Inc.
9801 Shaver Road
Portage, Michigan 49081
- D. Number on Study: Dose Range-Finding Study: 48 females. A sufficient number of sexually mature resident males of the same strain and source will be used to induce pregnancies.
- E. Body Weight Range: Minimum of 220 g at initiation of breeding
- F. Approximate Age: 80 to 120 days at the start of the in-life phase
- G. Identification System: Each rat will be uniquely identified by a Monel metal ear-tag displaying the animal number. Individual cage cards will be affixed to each cage and will display the animal number, group number, study number, dosage level, sex and the date of animal arrival and the start of the in-life phase.

V. TEST SYSTEM (continued)

H. Justification for Selection:

This species and strain of rat has been recognized to be appropriate for developmental toxicity studies. WIL Research Laboratories, Inc. has historical data on the background incidence of fetal malformations and developmental variations in this species from this same strain and source. This animal model has been proven susceptible to the effects of developmental toxicants.

VI. SPECIFIC MAINTENANCE SCHEDULE

A. Animal Housing

The rats will be individually housed (except during mating) in clean suspended wire-mesh cages in an environmentally controlled room during the study. The cages will be elevated above cage-board or other suitable material which will be changed at least three times each week. Nesting material will not be provided, as euthanization is scheduled prior to anticipated parturition. The cages will be subjected to routine cleaning at a frequency consistent with maintaining good animal health and Standard Operating Procedures. The facilities at WIL Research Laboratories, Inc. are fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International).

B. Environmental Conditions

Controls will be set to maintain temperature at $72^{\circ} \pm 4^{\circ}\text{F}$ and relative humidity between 30-70%. Air handling units will be set to provide approximately 10 fresh air changes per hour. Fluorescent lighting controlled by light timers will provide illumination for a 12-hour light/dark photoperiod (6:00 a.m. - 6:00 p.m.). Temperature and relative humidity will be recorded once daily.

C. Drinking Water

Tap water will be available *ad libitum*. Filters servicing the automatic watering system are changed regularly according to Standard Operating Procedures. The municipal water supplying the laboratory is analyzed according to WIL Standard Operating Procedures on a routine basis to assure that no contaminants are present in concentrations that would be expected to affect the outcome of the study.

D. Basal Diet

PMI Feeds, Inc.® Certified Rodent LabDiet® 5002 will be offered *ad libitum* during the study. Periodic analyses of the certified feed are performed by the manufacturer to ensure that heavy metals and pesticides are not present at concentrations that would be expected to affect the outcome of the study; results of the analyses are provided to WIL Research Laboratories, Inc. by the manufacturer. Feeders will be changed and sanitized once per week.

VII. EXPERIMENTAL DESIGN

A. Animal Receipt and Quarantine

Each rat will be inspected by a qualified technician upon receipt. Rats judged to be in good health and suitable as test animals will be immediately placed in quarantine for a minimum of 10 days. All rats will be initially weighed and permanently identified with a metal ear-tag. During the quarantine period each rat will be observed twice daily for changes in general appearance and behavior. Prior to the start of the in-life phase, those rats judged to be suitable test subjects will be identified.

B. Randomization

At the conclusion of the quarantine period, rats judged to be suitable test subjects and meeting acceptable body weight requirements will be cohabitated with a male. Females for which there is evidence of mating will be consecutively assigned in a block design to one control group and five test article groups of eight rats each.

C. Breeding Procedure

A female will be cohabitated with a male rat of the same strain and source in a suspended wire-mesh cage for mating. Detection of mating will be confirmed by evidence of a copulatory plug in the vagina or by a vaginal smear for sperm. After confirmation of mating, the female will be returned to an individual suspended wire-mesh cage (assigned to a group), and the day will be designated as day "0" of gestation.

D. Route and Rationale of Test Article Administration

The route of administration will be oral (gavage) since this is the intended route of clinical administration for the human. Historically, this route has been used extensively for studies of this nature. Sixteen-gauge stainless-steel dosing cannulas (Bio-Medical Feeding Needles, Popper and Sons, Inc., New Hyde Park, New York) will be used for the oral administration by gavage.

VII. EXPERIMENTAL DESIGN (continued)

E. Organization of Test Groups, Dosage Levels and Treatment Regimen

1. Organization of Test Groups

The dosage levels will be determined from results of previous studies and will be provided by the Sponsor Representative after consultation with the WIL Study Director. The following diagram presents the study group arrangement.

<u>Group Number</u>	<u>Test Article</u>	<u>Dosage Level (mg/kg/day)</u>	<u>Dosage Concentration (mg/ml)</u>	<u>Dosage Volume (ml/kg)</u>	<u>Number of Females</u>
1	Vehicle Control	0	0	5	8
2	Furfural	10	2	5	8
3	Furfural	50	10	5	8
4	Furfural	100	20	5	8
5	Furfural	500	100	5	8
6	Furfural	1000	200	5	8

2. Vehicle Control Article

The vehicle for the test article will be reverse osmosis treated water, sparged with nitrogen.

3. Treatment Regimen

The test and control articles will be administered as a single daily dose during the period of major organogenesis, gestation days 6 through 15. All rats will be dosed at approximately the same time each day.

4. Adjustment of Dosages

Individual dosages will be calculated based on each days body weight to provide the proper mg/kg/day dosage.

VII. EXPERIMENTAL DESIGN (continued)

F. Frequency, Method and Analysis of Test Article Preparations

1. Homogeneity, Stability and Periodic Analyses of Formulations of Test Article for Concentration

Homogeneity and stability of formulations of test article will be determined prior to the start of dosing. Batches of test suspension sufficient for eight animals at each of the selected dosage levels will be mixed. Based on the physical characteristics of the test article, appropriate methods will be used to ensure the best possible suspension of the test article in the vehicle. Dosing suspensions will be stored at room temperature for a period not to

exceed one week in duration. The study director or the deputy director will visually inspect the formulated suspensions prior to initiation of dosing. This visual inspection will be done to assure that the suspensions are visibly homogeneous and acceptable for dosing. If any special procedures are required for formulation, these procedures will be documented according to Good Laboratory Practices and presented in the final report of this study. While the test article formulations are being stirred in the storage containers, two aliquots (10 ml) from the control formulation and two aliquots (10 ml) each from the top, middle and bottom of each of the treated group formulations will be withdrawn for analysis. One of the two samples from each dose level and strata will be analyzed by the Analytical Chemistry Department at WIL Research Laboratories, Inc. to determine homogeneity. The remaining sample from each dose level and strata will be combined and stored under normal laboratory conditions for eight days, then analyzed to verify stability of the test article in the vehicle.

One 10 ml aliquot (one aliquot for the control group) will be taken during each weekly formulation (middle stratum) from the storage containers from all treatment groups. These samples will be analyzed for concentration.

2. Stability Assays of the Test Article

Storage stability of the neat test article will be determined concomitantly with the study. At initiation of administration, an approximate 1 g sample of the bulk test article will be submitted for analytical verification of identity and purity. An approximate 1 g sample of the test article will be submitted for analytical verification of identity and purity at conclusion of the dose administration period in the subsequent definitive developmental toxicity study

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VII. EXPERIMENTAL DESIGN (continued)

G. Maternal Observations During Gestation

1. Appearance and Behavior

Each rat will be observed twice daily for moribundity and mortality, once in the morning and once in the afternoon from gestation day 0 through 20. Clinical observations regarding general appearance and behavior will be recorded daily. Mortality and all signs of overt toxicity will be recorded on the day observed. Signs of toxicity will include, but are not limited to, changes in skin and fur appearance, eyes, mucous membranes, respiratory and circulatory system, autonomic and central nervous systems, somatomotor activity and behavior. During the treatment period, the rats will be observed also approximately one hour following dosing, and the observations will be recorded. Additional post-dose observation periods may be necessary and will be documented in the study records.

2. Body Weights

Individual body weights will be recorded on gestation days 0, 6-16 (daily) and 20.

3. Food Consumption

Individual food consumption will be recorded on gestation days 0, 6-16 (daily) and 20. Food intake will be reported as g/animal/day and g/kg/day for each corresponding interval of gestation.

4. Deaths and Animals Euthanized in Extremis

Females not surviving until the scheduled euthanization will be necropsied and the cause of death recorded, if possible. Rats not expected to survive to the next observation period (moribund) will be euthanized and subjected to a gross necropsy. The number and location of implantation sites and corpora lutea will be recorded. Tissues may be saved for histopathological examination as needed.

5. Abortions and Premature Deliveries

Females with evidence of abortion or premature delivery will be euthanized that day and necropsied. The number and location of implantation sites and corpora lutea will be recorded. Tissues may be saved for histopathological examination as needed.

VII. EXPERIMENTAL DESIGN (continued)

H. Scheduled Necropsy - Gestation Day 20

1. Laparohysterectomy and Macroscopic Examination

All surviving rats will be euthanized by carbon dioxide inhalation on gestation day 20. The abdominal, pelvic and thoracic cavities will be opened and the organs examined. The uterus of each dam will be excised and its adnexa trimmed. Gravid uterine weights will be obtained and recorded. Corpora lutea will be counted and noted. The uterus of each dam will be opened and the number of viable and nonviable fetuses, early and late resorptions and total number of implantation sites will be recorded. The individual uterine distribution will be documented using the following procedure. All implantation sites, including early and late resorptions, will be numbered in consecutive fashion beginning with the left distal uterine horn, noting the position of the cervix, and continuing from the proximal to the distal right uterine horn. Uteri which appear nongravid by macroscopic examination will be opened and placed in a 10% ammonium sulfide solution as described by Salewski(1) for detection of early implantation loss. Maternal tissues will be saved for histopathological examination in 10% neutral buffered formalin only as deemed necessary by the gross findings.

VII. EXPERIMENTAL DESIGN (continued)

2. Fetal Examination

Each viable fetus will be examined externally, sexed, weighed, euthanized by an intrathoracic injection of sodium pentobarbital and discarded. The findings will be recorded as either developmental variations or malformations. Selected specimens may be preserved at the discretion of the Study Director.

VIII. DURATION OF STUDY

The quarantine, breeding and gestation phases of the study will require approximately two months.

IX. STATISTICAL METHODS

All analyses will be two-tailed for a minimum significance level $p < 0.05$. All means will be presented with standard deviations. All statistical tests will be performed by a Digital Computer with appropriate programming as referenced below. The litter, rather than the fetus, will be considered as the experimental unit.

A. Maternal In-Life Data

Continuous data variables [mean maternal body weights (absolute and net), body weight gains (absolute and net) and food consumption of each interval] will be analyzed by a parametric one-way analysis of variance (ANOVA) to determine intragroup difference. If the results of the ANOVA are significant ($p < 0.05$), Dunnett's test (2) will be applied to the data to compare the treated groups to the control group.

B. Laparohysterectomy Data

The group mean numbers of corpora lutea, implantation sites, maternal gravid uterine weights and mean fetal weight (separately by sex, and combined) will be analyzed by a parametric one-way analysis of variance (ANOVA) and Dunnett's test(2) as described above. The mean litter proportions of prenatal data (% per litter of viable and nonviable fetuses, early and late resorptions, total resorptions, pre- and post-implantation loss and the fetal sex distribution) will be analyzed by the Kruskal-Wallis nonparametric ANOVA test (2) to determine intragroup difference. If the result of the ANOVA are significant ($p < 0.05$), the Mann-Whitney U-Test (2) will be applied to the data to compare the treated groups to the control group.

X. QUALITY ASSURANCE

The study will be audited by the WIL Quality Assurance Unit while in progress to assure compliance with the study protocol and protocol amendments, WIL Standard Operating Procedures and the appropriate provisions of U.S. EPA (40 CFR Parts 160 and 792) Good Laboratory Practice Regulations, the Japanese Ministry of Agriculture, Forestry and Fisheries (MAFF) Good Laboratory Practice Standards (59 NohSan No. 3850, August 10, 1984) and the Organization for Economic Co-Operation and Development (OECD) Good Laboratory Practice Regulations [C(81)30(Final)]. The raw data and draft report will be audited by the WIL Quality Assurance Unit prior to submission to the Sponsor's Representative to assure that the final report accurately describes the conduct and the findings of the study.

This study will not be included on the WIL regulated master schedule.

XI. RECORDS TO BE MAINTAINED

All original raw data records, as defined by WIL SOPs and the applicable GLPs, will be stored as described in Section XII. in the Archives at WIL Research Laboratories, Inc.

XII. WORK PRODUCT

Sponsor will have title to all documentation records, raw data, specimens and other work product generated during the performance of the study. All work product including raw paper data, magnetically encoded records and specimens will be retained at no charge for six months following issuance of the final report in the Archives at WIL Research Laboratories, Inc. Thereafter, WIL Research Laboratories will charge a quarterly archiving fee for retention of all work product. All work product will be stored in compliance with regulatory requirements.

XIII. REPORTS

The final report will contain a summary, test article data, methods and procedures, maternal and fetal data, WIL Historical Control Data (Charles River CrI:CD® BR Rats), the Analytical Chemistry Report and an interpretation and discussion of the study results. The final report will be comprehensive and shall define level(s) inducing toxic effects as well as "no-effect" level(s) under the condition of this investigation.

WIL Research Laboratories will provide one (1) copy of an Audited Draft Report, submitted in a timely manner upon completion of the study prior to issuance of the final report. One (1) revision will be permitted as part of the cost of the study, from which Sponsor's reasonable revisions and suggestions will be incorporated into the Final Report as appropriate. Additional changes or revisions may be made, at extra cost. It is expected that the Sponsor will review the draft report and provide comments to WIL within a two (2) month time frame following submission. WIL will submit the Final Report within one (1) month following receipt of comments. Two (2) copies of the Final Report (1 bound, 1 unbound) will be provided; requests for additional copies of the Final Report may result in additional charges.

XIV. ANIMAL WELFARE ACT COMPLIANCE

This study will comply with all applicable sections of the Final Rules of the Animal Welfare Act regulations (9 CFR). The Sponsor should make particular note of the following:

1. The Sponsor Representative's signature on this protocol documents for the Study Director the Sponsor's assurance that the study described in this protocol does not unnecessarily duplicate previous experiments.
2. Whenever possible, procedures used in this study have been designed to avoid or minimize discomfort, distress or pain to animals. All methods are described in this study protocol or in written laboratory Standard Operating Procedures.
3. Animals that experience severe or chronic pain or distress that cannot be relieved will be painlessly euthanized as deemed appropriate by the veterinary staff and Study Director. The Sponsor will be advised by the Study Director of all circumstances which could lead to this action in as timely a manner as possible.
4. Methods of euthanasia used during this study are in conformance with the above referenced regulation.

XV. PROTOCOL MODIFICATION

Modification of the protocol may be accomplished during the course of this investigation. However, no changes will be made in the study design without the verbal or written permission of the Sponsor. In the event that the Sponsor verbally requests or approves a change in the protocol, such changes will be made by appropriate documentation in the form of a protocol amendment. All alterations of the protocol and reasons for the modification(s) will be signed by the Study Director and the Sponsor Representative.

XVI. PROTOCOL APPROVAL

[_____]

01/02/97
Date

WIL Research Laboratories, Inc.
Ashland, OH 44805-9281

Mark D. Nemec
Mark D. Nemec, B.S.
Study Director

01/02/97
Date



Study Number: []

PROTOCOL AMENDMENT II

Sponsor: []

A. Title of Study:

A Dose Range-Finding Developmental Toxicity Study of Furfural in Rats

B. Protocol Modification:

1) **III. STUDY SCHEDULE DATA**

B. Proposed Experimental Termination Date: March 23, 1997

C. Proposed Audited Draft Report: June, 1997

2) **VII. EXPERIMENTAL DESIGN**

E. Organization of Test Groups, Dosage Levels and Treatment Regimen

1. Organization of Test Groups

The Sponsor has requested that the breeding phase for the study be re-initiated to further characterize the potential maternal and developmental toxicity of furfural over the dose range of 150-350 mg/kg/day.

The following diagram presents the study group arrangement. For the purposes of data acquisition this phase of the study will be designated as [] for computer entry.

<u>Group Number</u>	<u>Test Article</u>	<u>Dosage Level (mg/kg/day)</u>	<u>Dosage Concentration (mg/ml)</u>	<u>Dosage Volume (ml/kg)</u>	<u>Number of Females</u>
1	Vehicle Control	0	0	5	8
2	Furfural	150	30	5	8
3	Furfural	250	50	5	8
4	Furfural	350	70	5	8

C. Reason for Protocol Modification:

- 1) To document a change in the study schedule due to the requirement of additional testing as described below in item 2.
- 2) In the previous phase of study utilizing dose levels of 10, 50, 100, 500 and 1000 mg/kg/day, maternal mortality was noted at dose levels of 500 and 1000 mg/kg/day. No maternal or developmental toxicity was noted at dose levels of 10, 50 and 100 mg/kg/day. Therefore, the Sponsor has elected to further characterize the dose range between 100 and 500 mg/kg/day before proceeding to a definitive developmental toxicity study.

Approved By:

[]

3/4/97
Date

Prepared By:

WIL Research Laboratories, Inc.
Ashland, Ohio 44805-9281

WNL Neme
Mark D. Neme, B.S., D.A.B.T.
Study Director

2/24/97
Date



Study Number: []

PROTOCOL AMENDMENT III

Sponsor: []

A. Title of Study:

A Dose Range-Finding Developmental Toxicity Study of Furfural in Rats

B. Protocol Modification:

1) VII. EXPERIMENTAL DESIGN

F. Frequency, Method and Analysis of Test Article Preparations

1. Homogeneity, Stability and Periodic Analyses of Formulations of Test Article for Concentration

Analytical confirmation of formulations of test article for the 150, 250 and 350 mg/kg/day groups for concentration was performed on the first batch of formulations only.

C. Reason for Protocol Modification:

- 1) Protocol Amendment II, signed by the Study Director on February 24, 1997 defined the experimental approach for additional dose-range characterization (150, 250 and 350 mg/kg/day groups) but did not define the analytical chemistry requirements for this phase. Homogeneity and stability analyses were not repeated as these were established previously in the present study within an appropriate range of concentration.

Approved By:

[]

6-25-97

Date

Prepared By:

WIL Research Laboratories, Inc.
Ashland, Ohio 44805-9281

Mark D. Nemece
Mark D. Nemece, B.S., D.A.B.T.
Study Director

6/19/97

Date

APPENDIX A

References

1. Salewski (Köln), V.E. (1964) Farbemethode zum makroskopischen Nachweis von Implantationstellen am Uterus der Ratte. Naunyn - Schm. Archiv. für Exper. Pathologie und Pharm. 247:367.
2. BMDP (1979) Biomedical Computer Programs. (Dixon, W.J. and Brown, M.B., eds.) University of California Press, Berkeley, CA pp. 612, 780, 781.