FINAL REPORT

STUDY TITLE

A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS

EPA GUIDELINE NUMBER

40 CFR 798.4900

STUDY DIRECTOR

Donald G. Stump, Ph.D.

STUDY INITIATED ON

October 10, 1996

STUDY COMPLETED ON

May 30, 1997

PERFORMING LABORATORY

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

LABORATORY STUDY NUMBER

WIL-157016

SPONSOR PROJECT NUMBER

GP96-032

SPONSOR

A Developmental Toxicity Study of 313401 in Rats

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA 10(d)(1)(A), (B) or (C).

Director of Regulatory Affairs
(title)

-2-5222

A Developmental Toxicity Study of 313401 in Rats

COMPLIANCE STATEMENT

This study, designated WIL-157016, was conducted in compliance with the United States Environmental Protection Agency (EPA) Good Laboratory Practice Standards (40 CFR Part 160), October 16, 1989; the Japanese Ministry of Agriculture, Forestry and Fisheries (MAFF) Good Laboratory Practice Standards (59 NohSan No. 3850), August 10, 1984; the Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice [C(80) 30 (Final) Annex 2], 1981; the Standard Operating Procedures of WIL Research Laboratories, Inc.; and the protocol as approved by the sponsor. The protocol for this study was designed to be in accordance with the United States Environmental Protection Agency (EPA) Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Pesticide Assessment Guidelines (Subdivision F, series 83-3), 40 CFR 798.4900; the OECD Guidelines for Testing of Chemicals, Health Effects Test Guidelines, Section 414, May 12, 1981; and the Japanese MAFF Agricultural Chemical Laws and Regulations Testing Guidelines for Toxicology Studies (59 NohSan No. 4200), January 28, 1985.

Donald G. Stump

Donald G. Stump, Ph.D.
Study Director

5/30/97
Date

/97
ate

Applicant/Submitter

Date

A Developmental Toxicity Study of 313401 in Rats

FLAGGING STATEMENT

(This page was intentionally left blank; client will insert appropriate statement.)

A Developmental Toxicity Study of 313401 in Rats

TABLE OF CONTENTS

A Developmental Toxicity Study of 313401 in Rats

INDEX OF TABLES

A Developmental Toxicity Study of 313401 in Rats

I. SUMMARY

The potential maternal toxicity and developmental toxicity of 313401 were evaluated. The test article, 313401, in the vehicle, 1% carboxymethylcellulose (CMC)/0.1% polysorbate 80, was administered to three groups of 25 bred Crl:CD®(SD)BR rats once daily from gestation days 6 through 15. Dosage levels were 4, 16 and 32 mg/kg/day administered at a dose volume of 5 ml/kg. A concurrent control group composed of 25 bred females received the vehicle, 1% CMC/0.1% polysorbate 80, 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 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, soft tissue and skeletal malformations and variations.

All maternal animals survived to the scheduled necropsy on gestation day 20; no test article-related internal findings were observed. Clinical observations related to test article administration were not apparent at any dose level. A reduced mean body weight gain occurred in the 32 mg/kg/day group during gestation days 9-12 and 6-16. During the entire treatment period (gestation days 6-16), body weight gain in the 32 mg/kg/day group was 72% of the control group gain. Food consumption was inhibited in the 32 mg/kg/day group during gestation days 9-12, 12-16 and 6-16. Food consumption (g/animal/day) for the entire treatment period (gestation days 6-16) was reduced by 9% in the 32 mg/kg/day group when compared to the control group value.

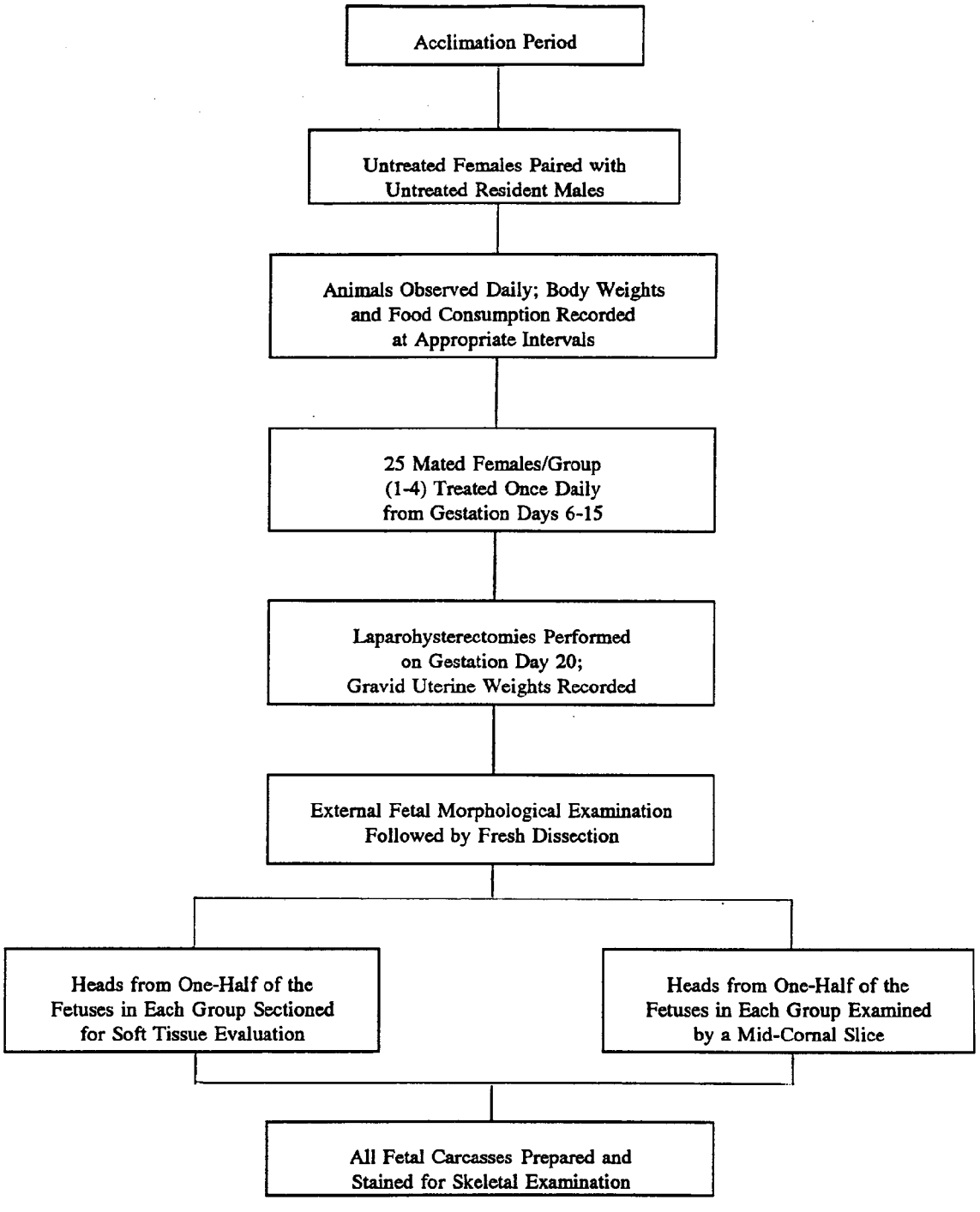
Fetal toxicity occurred in conjunction with the moderate maternal toxicity noted at a dose level of 32 mg/kg/day. A reduced mean fetal body weight was observed in the 32 mg/kg/day group. Intrauterine growth and survival were unaffected by test article administration at dose levels of 4 and 16 mg/kg/day. The malformations observed in the treated groups were considered to be spontaneous in origin. An increased incidence of one developmental variation, bent ribs, was observed in the 32 mg/kg/day group and was attributed to the test article.

In conclusion, no maternal toxicity or developmental toxicity was noted at dose levels of 4 and 16 mg/kg/day. Maternal toxicity was expressed at a dose level of 32 mg/kg/day by a reduced mean body weight gain during gestation days 9-12 and reduced food consumption during gestation days 9-12 and 12-16. Developmental toxicity was exhibited by a reduced mean fetal body weight in the 32 mg/kg/day group and by an increased incidence of one skeletal variant (bent ribs) in the 32 mg/kg/day group. Fetal toxicity occurred in conjunction with the moderate maternal toxicity previously noted at this dose level. Based on the results of this study, a dose level of 16 mg/kg/day was considered to be the NOAEL (no observable adverse effect level) for maternal toxicity and developmental toxicity.

II. OBJECTIVE

The objective of the study was to determine the potential maternal toxicity and developmental toxicity of 313401 in the Crl:CD®(SD)BR rat. The selected route of administration was oral since this is the intended route of clinical administration for the human. The animal model was selected on the basis of availability of historical control data and susceptibility of the species to known developmental toxicants.

III. STUDY DESIGN



IV. EXPERIMENTAL PROCEDURES

A. INTRODUCTION

The experimental phase of the study was initiated with the assignment of mated rats to treatment groups on December 17, 1996, and concluded with the last laparohysterectomy on January 10, 1997; the dosing period was from December 23, 1996, to January 5, 1997. Dose levels were selected based on the results of a preliminary range-finding study with 313401 (WIL-157015[1]).

B. TEST AND CONTROL ARTICLES

1. TEST ARTICLE IDENTIFICATION

The test article, 313401, was received from Griffin Corporation, Valdosta, Georgia, on October 3, 1996, as follows:

Identification	No. of Containers Received	Description
Sample: 313401 Expiration Date: 6/28/97 Lot No.: 22L-2 AN#: 9601474 [WIL Log No. 3170A]	1 Bottle Gross weight: 138.5 g	Light yellow powder

Stability and purity data for the test article were the responsibility of the sponsor. The test article was 93.297% pure. For the purposes of dose calculations, the test article was considered to be 100% 313401. The test article was stored at room temperature and was considered stable under these conditions. A Certificate of Analysis for the test article is presented in Appendix A. A one-gram reserve sample of the test article was taken on October 24, 1996, and stored in the Archives at WIL Research Laboratories, Inc.

2. VEHICLE CONTROL ARTICLE IDENTIFICATION

The vehicle control article utilized in preparation of the test mixtures was prepared using carboxymethylcellulose and polysorbate 80 received from Sigma Chemical Co., St. Louis, Missouri.

3. PREPARATION

The vehicle control article formulations were prepared as follows. A sufficient amount of 1% aqueous carboxymethylcellulose (1% CMC) was prepared by heating deionized water to approximately 70°C and adding an appropriate amount of carboxymethylcellulose powder. The mixture was then stirred until clear. The appropriate amount of polysorbate 80 was calculated to achieve a 0.1% solution and added to the 1% carboxymethylcellulose solution after removal of an identical amount of 1% CMC.

The appropriate amount of the test article, 313401, was weighed for each group into a tared, precalibrated, properly-labeled storage container. A sufficient amount of the vehicle was added to bring the volume in the container to the calibration mark. Each preparation was homogenized on a Polytron® PT 6000 for approximately 2-5 minutes. Formulations were placed on the Caframo™ overhead stirrers and the preparations were stirred continuously throughout the sampling and dispensing procedures. The formulations were divided into aliquots for daily dose administration. Daily aliquots were homogenized as needed.

Preparations for all dose groups were prepared weekly (December 23 and 30, 1996). The test article formulations were stored at room temperature. The dosing preparations were visually inspected for homogeneity by the study director on December 23, 1996, and were found to be acceptable for use.

4. ADMINISTRATION

The test mixtures were administered orally by gavage, via a 16-gauge stainless steel gavage cannula (Popper and Sons, Inc., New Hyde Park, New York 11040), as a single daily dose from gestation days 6 through 15. A dosage volume of 5 ml/kg was used for all dosage levels. The control animals received the vehicle, 1% CMC/0.1% polysorbate 80, on a comparable regimen at 5 ml/kg. Individual dosages were based on the most recently recorded body weights to provide the correct mg/kg dose. The following diagram presents the study group assignment:

Group Number	Test Article	Dosage Level (mg/kg/day)	Dosage Concentration (mg/ml)	Dosage Volume (ml/kg)	Number of Females
1	Vehicle	0	0	5	25
2	313401	4	0.8	5	25
3	313401	16	3.2	5	25
4	313401	32	6.4	5	25

5. SAMPLING AND ANALYSES

Prior to the initiation of dosing on December 10, 1996, duplicate 1-ml aliquots were collected from the middle stratum of the control group formulation and from the top, middle (four aliquots) and bottom strata of each treated group formulation. One set of these samples was analyzed for homogeneity. The second set of samples was combined and stored for 8-day stability verification. The results of homogeneity analysis for Groups 3 and 4 performed on December 10, 1996, were acceptable for use according to WIL Standard Operating Procedures. The homogeneity analysis of the Group 2 preparation on this date did not produce any usable data. The cause was determined to be related to the amount of acetonitrile in the secondary dilution. The Group 2 formulation was remade on December 11, 1996, and analyzed for homogeneity and 8-day stability on December 19, 1996. On December 18, 1996, an 8-day stability analysis was performed on the Group 3 and 4 formulations (prepared on December 10, 1996). On the days the dosing formulations were prepared (December 23 and 30, 1996), duplicate 1-ml aliquots were collected from the middle stratum of each dosing formulation, including the control, and analyzed for concentration. The methodology and results of these analyses are presented in Appendix B. The dosing formulations were homogeneous, stable for 8 days and contained the amounts of test article specified in the protocol.

C. ANIMAL RECEIPT AND ACCLIMATION

One hundred twenty-five sexually mature, virgin female rats, Crl:CD®(SD)BR, were received in good health from Charles River Laboratories, Inc., Portage, Michigan, on December 5, 1996. The animals were approximately 70 days old. Upon receipt, each female was observed by a qualified technician. The animals were

initially weighed on December 6, 1996. All animals were uniquely identified by a Monel metal eartag displaying the animal number and housed for 12 days for acclimation purposes. During the acclimation period, the animals were observed twice daily for mortality and moribundity.

D. ANIMAL HOUSING

Upon arrival and until pairing, all animals were individually housed in clean, wire-mesh cages suspended above cage-board. The animals were paired for mating in the home cage of the male. Following positive identification of mating, the females were returned to an individual suspended wire mesh cage; nesting material was not required as the females were euthanized prior to the date of expected parturition. Animals were maintained in accordance with the "Guide for the Care and Use of Laboratory Animals[2]." 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° ± 4°F and a relative humidity between 30% and 70%. Room temperature and relative humidity were recorded daily. Temperatures ranged from 71.1°F to 72.6°F and relative humidity ranged from 31.8% to 47.1% during the study period.

Light timers were calibrated to provide a 12-hour light/12-hour dark photoperiod. Air handling units were set to provide approximately 10 fresh air changes per hour.

G. ASSIGNMENT OF ANIMALS TO TREATMENT GROUPS AND BREEDING PROCEDURES

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

Positive evidence of mating was confirmed by the presence of a copulatory plug or the presence of sperm in a vaginal smear. Each mating pair was examined daily. The day on which evidence of mating was identified was termed day 0 of gestation and the animals were separated.

The experimental design for WIL-157016 consisted of three 313401 treated groups and one control group. The bred females were consecutively assigned in a block design to groups containing 25 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 25 females were placed into each group. Body weight values ranged from 223 g to 269 g on day 0 of gestation.

H. MATERNAL OBSERVATIONS DURING GESTATION

1. CLINICAL OBSERVATIONS AND SURVIVAL

All rats were observed twice daily for moribundity and mortality. Individual detailed clinical observations were recorded from day 0 through 20 of gestation (prior to test article administration during the dosing period). Animals were

observed for signs of toxicity approximately one hour following dosing. No significant findings were recorded at these observation periods, therefore, a table summarizing these data was not included in the report.

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 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 Salewski[3].

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

1. Group Mean Litter Basis:

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

2. Proportional Litter Basis:

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

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

J. FETAL MORPHOLOGICAL EXAMINATION

Each fetus was sexed, weighed and tagged for identification. Fetal tags contained the WIL study number, the female number and the fetus number. A detailed external examination of each fetus was conducted to include, but was not limited to, an examination of the eyes, palate and external orifices, and each finding was recorded. Crown-rump measurements were recorded for late resorptions, if present, and the tissues were discarded. Each fetus was examined viscerally by a modification of the Stuckhardt and Poppe[4] fresh dissection technique to include the heart and major blood vessels. The sex of each fetus was confirmed by internal examination. Fetal kidneys were examined and graded for renal papillae development by a method described in Woo and Hoar[5].

Heads from approximately one-half of the fetuses in each litter were placed in Bouin's fixative for subsequent soft-tissue examination by the Wilson[6] sectioning technique. The heads from the remaining one-half of the fetuses were examined by

a mid-coronal slice. All carcasses were eviscerated and fixed in 100% ethyl alcohol. Following fixation in alcohol, each fetus was macerated in potassium hydroxide and stained with Alizarin Red S by a method similar to that described by Dawson[7]. External, visceral and skeletal findings were recorded as developmental variations (alterations in anatomic structure that are considered to have no significant biological effects on animal health or 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 fetal developmental findings were summarized by: 1) presenting the incidence of a given finding both as a percentage of the number of fetuses and the number of litters available for examination in the group; and 2) considering the litter as the basic unit for comparison and calculating the number of affected fetuses in a litter on a proportional basis as follows:

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

$$a = \frac{\text{No. Viable Fetuses Affected/Litter}}{\text{No. Viable Fetuses/Litter}} \times 100$$

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 Dunnett's test[8]	Corpora Lutea, Total Implantations, Fetal Body Weights, Maternal Body Weights and Weight Changes, Maternal Net Body Weight Changes and Gravid Uterine Weights, Maternal Food Consumption
- Kruskal-Wallis test with Mann-Whitney U test[8]	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, 2

All animals survived to the scheduled necropsy on gestation day 20. No test article-related clinical findings were observed in the treated groups. Clinical signs in the treated groups, such as hair loss, scabbing and red material around the nose, occurred similarly in the control group, 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 3, 4, 5

Mean body weight gain in the 32 mg/kg/day group was similar to the control group value during the first three days of dosing (gestation days 6-9). The mean body weight gain for this group was reduced during gestation days 9-12. The difference from the control group value was statistically significant ($p<0.01$). During the remainder of the treatment period (gestation days 12-16), mean body weight gain in the 32 mg/kg/day group was similar to the control group value. Overall mean body weight gain during the entire treatment period (gestation days 6-16) in this group was statistically significantly ($p<0.01$) lower (72% of control) than the control group value. During the post-treatment period (gestation days 16-20), mean body weight gain in the 32 mg/kg/day group was slightly increased; the difference from the control group was statistically significant ($p<0.01$). Mean body weights in the 32 mg/kg/day group were generally comparable to the control group values throughout gestation; the only exceptions were significantly ($p<0.05$) reduced values on gestation days 14 and 15. A statistically significant ($p<0.01$) decrease in net body weight gain was noted for animals in the 32 mg/kg/day group. Mean gravid uterine weight and net body weight in this group were similar to the control group values.

The statistically significant effects on body weight data in the 32 mg/kg/day group when compared to the control group values are presented in the following table:

Body Weight Measurement	Gestation Days	Difference from Control	P Value
Body weight gain	9-12	lower	$p<0.01$
Body weight gain	6-16	lower	$p<0.01$
Body weight gain	16-20	higher	$p<0.01$
Body weight	14, 15	lower	$p<0.05$
Net body weight gain	20	lower	$p<0.01$

Mean body weights, body weight gains, net body weights, net body weight gains and gravid uterine weights in the 4 and 16 mg/kg/day groups were unaffected by test article administration. Sporadic statistically significant ($p<0.05$ or $p<0.01$) differences from the control group were noted and included lower mean body weight gain in the 16 mg/kg/day group during gestation days 9-12 and a lower mean body weight in this group on gestation day 14. However, a corresponding decrease in food consumption was not observed during gestation days 9-12, and the reduced body weight was attributed to the 5 g decrease in body weight relative to the control group on gestation day 6 (prior to the start of dosing). Therefore, no relationship to treatment was evident. All other values were similar to the control group values; none of the differences were statistically significant.

C. FOOD CONSUMPTION

Summary Data: Tables 6, 7

Food consumption in the 32 mg/kg/day group was comparable to that in the control group during the first three days of dosing (gestation days 6-9). Food consumption, evaluated as g/animal/day and g/kg/day, was slightly reduced in the 32 mg/kg/day group during the remainder of the treatment period (gestation days 9-12 and 12-16). The differences from the control group were generally statistically significant ($p<0.01$ or $p<0.05$). When the entire treatment period (gestation days 6-16) was evaluated, food consumption was slightly reduced in the 32 mg/kg/day group; the differences from the control group were statistically significant ($p<0.05$). During the post-treatment period (gestation days 16-20), food consumption in the 32 mg/kg/day group was slightly increased relative to the control group. The difference in g/kg/day values was statistically significant ($p<0.05$).

Food consumption was unaffected by test article administration at dose levels of 4 and 16 mg/kg/day. The only statistically significant ($p < 0.01$) difference from the control group was an increase in food consumption (g/kg/day) in the 16 mg/kg/day group during the post-treatment period (gestation days 16-20). All other values (g/animal/day and g/kg/day) in these groups were similar to the control group values.

D. NECROPSY DATA

At the scheduled necropsy on gestation day 20, no test article-related internal findings were observed at any dose level. One female (no. 59531) in the 4 mg/kg/day group had clear fluid contents in both uterine horns and was nongravid. Another female (no. 59587) in this group had dilated renal pelves. Female no. 59560 in the 16 mg/kg/day group had a cystic ovary. All other females were internally normal.

E. GESTATION DAY 20 LAPAROHYSTERECTOMY DATA

Summary Data: Tables 8, 9

Mean fetal body weight in the 32 mg/kg/day group (3.5 g) was slightly reduced when compared to the control group value (3.7 g), but was equal to the overall mean fetal body weight in the WIL historical control data (3.5 g). The difference between the concurrent control group and the 32 mg/kg/day group was statistically significant ($p < 0.05$). Viable litter size, fetal sex ratios, postimplantation loss and the mean numbers of corpora lutea and implantation sites in the 32 mg/kg/day group were similar to the control group values.

Intrauterine growth and survival were unaffected by test article administration at dose levels of 4 and 16 mg/kg/day. No statistically significant differences from the control group were observed.

F. FETAL MORPHOLOGICAL DATA

Summary Data: Tables 10, 11, 12, 13

The number of fetuses (litters) available for morphological evaluation were 338(25), 284(19), 330(24) and 377(25) in the control, 4, 16 and 32 mg/kg/day groups, respectively.

1. EXTERNAL MALFORMATIONS AND VARIATIONS

No external developmental malformations or variations were noted in fetuses at any dose level.

2. VISCERAL MALFORMATIONS AND VARIATIONS

No visceral developmental malformations or variations were noted in fetuses at any dose level.

3. SKELETAL MALFORMATIONS AND VARIATIONS

In the 16 mg/kg/day group, three fetuses from one litter (nos. 59537-01, -07 and -08) each had costal cartilage malformation. All of the malformations consisted of fused left costal cartilages (no. 1 to no. 2) prior to joining the sternum, no left costal cartilage in position no. 2 and the left half of sternebra no. 1 attached to the left half of sternebra no. 2. Fetus no. 59537-08 also had a vertebral malformation that consisted of fused right cervical arches (no. 6 to no. 7). No other skeletal malformations were observed.

Increased incidences of several skeletal developmental variations were observed in fetuses at dose levels of 16 and 32 mg/kg/day. These included the following. One skeletal variant, 14th rudimentary ribs, was noted in all dose groups, including the control group. However, the percentages in the 16 and 32 mg/kg/day groups (13.1 and 11.3% per litter, respectively) were increased when compared to the control group value (2.2% per litter). The differences from the control group were statistically significant ($p < 0.01$). Another skeletal variant, 14th full ribs, was noted only in the 16 and 32 mg/kg/day groups (1.0 and 1.2% per litter, respectively). The values for 14th rudimentary ribs and 14th full ribs in these groups were within the range of values in the WIL historical control data (0.0-39.3% and 0.0-1.3%, respectively). An increase in the incidence of bent ribs was noted in the 32 mg/kg/day group (6.7% per litter) when compared to the concurrent control group (0.8% per litter) and the maximum value in the WIL historical control data (4.6% per litter). It should be noted that for most of the fetuses in the 32 mg/kg/day group with bent ribs, the variation was slight, occurred bilaterally and affected various combinations of rib nos. 4 through 12. Other skeletal variants in the treated groups occurred similarly in the control

5214

group, were observed in a non dose-related manner, or were within the range of the WIL historical control data. No relationship to treatment was evident.

4. SUMMARY OF EXTERNAL, VISCERAL AND SKELETAL EXAMINATION

The only malformations observed during this study were in 3(1) fetuses (litters) in the 16 mg/kg/day group and were considered to be spontaneous in origin since no malformations were observed in the 32 mg/kg/day group. The only developmental variation attributed to treatment with the test article was an increase in the incidence of bent ribs in the 32 mg/kg/day group. The incidences of 14th rudimentary ribs and 14th full ribs were also increased in the 16 and 32 mg/kg/day group when compared to the concurrent control group values. However, no dose-related response was noted and the values were within the range of the WIL historical control data for these common developmental variations. In addition, no increase in the total number of developmental variations (% per litter) was observed at these dose levels, and no other evidence of developmental toxicity was observed in the 16 mg/kg/day group fetuses. Therefore, no relationship to treatment with the test article was evident. Other developmental variations in the treated groups were observed infrequently, at frequencies similar to those in the control group and/or at incidences that were within range of the WIL historical control data. When the total number of malformations and developmental variations were compared, on an incidence or proportional basis, no statistically significant differences from the control group were noted.

VI. DISCUSSION AND CONCLUSIONS

All maternal animals survived to the scheduled necropsy on gestation day 20. No clinical findings related to test article administration were observed at any dose level.

In the 32 mg/kg/day group, mean body weight gain and food consumption (g/animal/day and g/kg/day) were similar to the control group values during the first three days of dosing (gestation days 6-9). A statistically significant reduced mean body weight gain and slightly, but statistically significant reductions in food consumption occurred in this group during gestation days 9-12. Throughout the remainder of the treatment period (gestation days 12-16), mean body weight gain in the 32 mg/kg/day group was comparable to the control group value; however, food consumption remained slightly lower than that in the control group. When the entire treatment period (gestation days 6-16) was evaluated, mean body weight gain and food consumption in the 32 mg/kg/day group were significantly reduced relative to the control group values. During the post-treatment period (gestation days 16-20), mean body weight gain and food consumption in the 32 mg/kg/day group were slightly increased when compared to the control group values. Mean body weights in this group were generally similar to the control group values. A statistically significant decrease in mean net body weight gain was observed in the 32 mg/kg/day group. Mean net body weight and gravid uterine weight in this group were similar to the control group values. Mean body weights, body weight gains, net body weights, net body weight gains, gravid uterine weights and food consumption in the 4 and 16 mg/kg/day groups were unaffected by test article administration.

At the scheduled necropsy on gestation day 20, no test article-related internal findings were observed at any dose level.

Mean fetal body weight in the 32 mg/kg/day group was slightly reduced when compared to the control group value (statistically significant), but was within the range of the WIL historical control data. Viable litter size, fetal sex ratio, postimplantation loss and the numbers of corpora lutea and implantation sites in the 32 mg/kg/day group were unaffected by test article administration. Intrauterine growth and survival were not adversely affected at dose levels of 4 and 16 mg/kg/day.

Fetuses (litters) available for morphological evaluation numbered 338(25), 284(19), 330(24) and 377(25) in the control, 4, 16 and 32 mg/kg/day groups, respectively.

Malformations were observed in 0(0), 0(0), 3(1) and 0(0) fetuses (litters) in these same groups and were considered to be spontaneous in origin. An increased incidence of one developmental variation, bent ribs, was observed in the 32 mg/kg/day group and was attributed to the test article.

In conclusion, no maternal toxicity or developmental toxicity was noted at dose levels of 4 and 16 mg/kg/day. Maternal toxicity was expressed at a dose level of 32 mg/kg/day by a reduced mean body weight gain during gestation days 9-12 and reduced food consumption during gestation days 9-12 and 12-16. Developmental toxicity was exhibited by a reduced mean fetal body weight in the 32 mg/kg/day group and by an increased incidence of one skeletal variant (bent ribs) in the 32 mg/kg/day group. Fetal toxicity occurred in conjunction with the moderate maternal toxicity previously noted at this dose level. Based on the results of this study, a dose level of 16 mg/kg/day was considered to be the NOAEL (no observable adverse effect level) for maternal toxicity and developmental toxicity.

Donald G. Stump 5/30/97

Donald G. Stump, Ph.D. — Date
Study Director

VII. KEY STUDY PERSONNEL AND REPORT SUBMISSION

Submitted By:

Donald G. Stump, Ph.D.
Staff Toxicologist, Developmental
Reproductive and Neurotoxicology
Study Director

5/30/97
Date

Report Preparation:

Stephanie B. Gall, B.S.
Report Writer I

5/30/97
Date

Reviewed By:

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

5/30/97
Date

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

5/30/97
Date

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

5/30/97
Date

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

5/30/97
Date

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

VII. KEY STUDY PERSONNEL AND REPORT SUBMISSION (continued)

Study Supervisors:

Sally A. Keets, A.S.	Manager of Vivarium
Daniel W. Sved, Ph.D.	Director of Metabolism and Analytical Chemistry
Kerin Clevidence, B.S.	Group Supervisor of Gross Pathology and Developmental Toxicology Laboratory

VIII. QUALITY ASSURANCE UNIT STATEMENT

Date(s) of Inspection(s)	Phase Inspected	Date(s) Findings Reported to Study Director	Date(s) Findings Reported to Management
12/17/96	Clinical Observations and Body Weights	12/17/96	1/31/97
12/19/96	Animal Care & Equipment	12/19/96	1/31/97
12/23/96	Test Material Preparation/ Analysis	12/23/96	1/31/97
1/6/97	Laparohysterectomy/Viscerals	1/6/97	2/26/97
3/20, 21, 24 and 4/4/97	Study Records (I-1)	4/7/97	5/28/97
3/21, 24 and 4/4/97	Study Records (N-1)	4/4/97	5/28/97
4/24, 25 and 28, 29/97	Draft Report (w/o Analytical)	4/29/97	5/28/97
4/28, 29/97	Draft Report (Analytical)	4/29/97	5/28/97

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 amendments, with the following exception. The data located in Appendix A were the responsibility of the sponsor. 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 — 5/30/97

Deborah L. Little
Manager of Quality Assurance

Date

550

IX. REFERENCES

1. WIL-157015 (1997) A Dose Range-Finding Developmental Toxicity Study of 313401 in Rats. WIL Research Laboratories, Inc., Ashland, Ohio.

2. 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.

3. 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.

4. Stuckhardt, J.L. and Poppe, S.M. (1984) Fresh visceral examination of rat and rabbit fetuses used in teratogenicity testing. Teratogenesis, carcinogenesis and Mutagenesis 4:181-188.

5. Woo, D.C. and Hoar, R.M. (1972) Apparent hydronephrosis as a normal aspect of renal development in late gestation of rats: The effect of methyl salicylate. Teratology 6: 191-196.

6. Wilson, J.G. (1965) Embryological consideration in teratology. In: Teratology: Principles and Techniques. (Wilson, J.G. and Warkany, J., eds.) The University of Chicago Press, Chicago, Illinois, pp. 251-277.

7. Dawson, A.B. (1926) A note on the staining of cleared specimens with Alizarin Red S. Stain Technol. 1:123-124.

8. BMDP (1979) Biomedical Computer Programs. (Dixon, W.J. and Brown, M.B., eds.) University of California Press, Berkeley, CA, pp. 612, 780, 781.

A Developmental Toxicity Study of 313401 in Rats

TABLES 1-13

PROJECT NO.:WIL-157016

TABLE 1
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
SUMMARY OF MATERNAL SURVIVAL AND PREGNANCY STATUS

DOSE GROUP :	1		2		3		4	
	NO.	%	NO.	%	NO.	%	NO.	%
FEMALES ON STUDY	25		25		25		25	
FEMALES THAT ABORTED OR DELIVERED	0	0.0	0	0.0	0	0.0	0	0.0
FEMALES THAT DIED	0	0.0	0	0.0	0	0.0	0	0.0
FEMALES THAT ABORTED	0	0.0	0	0.0	0	0.0	0	0.0
NONGRAVID	0	0.0	0	0.0	0	0.0	0	0.0
GRAVID	0	0.0	0	0.0	0	0.0	0	0.0
FEMALES THAT WERE EUTHANIZED	0	0.0	0	0.0	0	0.0	0	0.0
NONGRAVID	0	0.0	0	0.0	0	0.0	0	0.0
GRAVID	0	0.0	0	0.0	0	0.0	0	0.0
FEMALES EXAMINED AT SCHEDULED NECROPSY	25	100.0	25	100.0	25	100.0	25	100.0
NONGRAVID	0	0.0	6	24.0	1	4.0	0	0.0
GRAVID	25	100.0	19	76.0	24	96.0	25	100.0
WITH RESORPTIONS ONLY	0	0.0	0	0.0	0	0.0	0	0.0
WITH VIABLE FETUSES	25	100.0	19	100.0	24	100.0	25	100.0
TOTAL FEMALES GRAVID	25	100.0	19	76.0	24	96.0	25	100.0

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY

553

PROJECT NO.:WIL-157016

TABLE 2 (DAILY EXAMINATIONS)
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
SUMMARY OF CLINICAL FINDINGS: TOTAL OCCURRENCE/NO. OF ANIMALS

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

TABLE RANGE:	12-17-96 TO 01-10-97			
GROUP:	1	2	3	4
NORMAL				
-NO SIGNIFICANT CLINICAL OBSERVATIONS	493/25	497/25	490/25	505/25
DISPOSITION				
-SENT TO LAB FOR SCHEDULED LAPAROHYSTERECTOMY; GESTATION DAY 20	25/25	25/25	25/25	25/25
BODY/INTEGUMENT				
-HAIR LOSS DORSAL HEAD	0/ 0	0/ 0	0/ 0	4/ 1
-SCABBING DORSAL HEAD	0/ 0	0/ 0	0/ 0	3/ 1
-HAIR LOSS RIGHT FORELIMB	28/ 3	17/ 3	31/ 6	9/ 3
-HAIR LOSS LEFT FORELIMB	29/ 3	20/ 3	30/ 6	8/ 3
-HAIR LOSS VENTRAL ABDOMINAL	0/ 0	8/ 1	1/ 1	0/ 0
-HAIR LOSS LEFT LATERAL ABDOMINAL AREA	0/ 0	0/ 0	0/ 0	5/ 1
-HAIR LOSS DORSAL THORACIC	0/ 0	4/ 1	0/ 0	0/ 0
-SCABBING DORSAL THORACIC	0/ 0	4/ 1	0/ 0	0/ 0
-HAIR LOSS RIGHT HINDLIMB	0/ 0	0/ 0	0/ 0	1/ 1
EYES/EARS/NOSE				
-DRIED RED MATERIAL AROUND NOSE	1/ 1	1/ 1	1/ 1	0/ 0
EXCRETA				
-SOFT STOOL	2/ 1	0/ 0	0/ 0	0/ 0

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY

PROJECT NO.:WIL-157016

TABLE 3
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
MEAN BODY WEIGHTS (GRAMS) DURING GESTATION

GROUP :		1	2	3	4
DAY 0	MEAN	245.	244.	242.	249.
	S.D./N	9.9/25	7.5/19	13.2/24	9.7/25
DAY 6	MEAN	280.	276.	275.	283.
	S.D./N	13.1/25	10.2/19	18.8/24	11.8/25
DAY 7	MEAN	281.	279.	277.	284.
	S.D./N	12.8/25	9.7/19	18.4/24	12.6/25
DAY 8	MEAN	285.	281.	281.	285.
	S.D./N	14.1/25	10.7/19	20.0/24	13.1/25
DAY 9	MEAN	286.	284.	283.	288.
	S.D./N	13.0/25	10.1/19	19.0/24	13.0/25
DAY 10	MEAN	292.	288.	286.	289.
	S.D./N	14.9/25	11.0/19	19.5/24	13.4/25
DAY 11	MEAN	299.	294.	292.	293.
	S.D./N	14.6/25	10.9/19	20.5/24	13.9/25
DAY 12	MEAN	305.	300.	296.	296.
	S.D./N	16.6/25	12.0/19	19.6/24	13.1/25
DAY 13	MEAN	309.	304.	299.	299.
	S.D./N	16.2/25	12.4/19	20.0/24	12.9/25
DAY 14	MEAN	315.	309.	303.*	302.*
	S.D./N	16.4/25	11.4/19	20.2/24	13.7/25

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 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

555

PROJECT NO.:WIL-157016

TABLE 3
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
MEAN BODY WEIGHTS (GRAMS) DURING GESTATION

GROUP :		1	2	3	4
DAY 15	MEAN	321.	317.	311.	308.*
	S.D./N	17.6/25	11.9/19	21.0/24	13.5/25
DAY 16	MEAN	330.	328.	321.	319.
	S.D./N	16.4/25	12.9/19	20.0/24	14.4/25
DAY 20	MEAN	393.	398.	387.	392.
	S.D./N	25.2/25	18.3/19	23.1/24	17.0/25

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 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

PROJECT NO.:WIL-157016

TABLE 4
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
MEAN BODY WEIGHT CHANGES (GRAMS) DURING GESTATION

GROUP :	1	2	3	4
DAY 0- 6 MEAN	35.	31.	33.	34.
S.D./N	6.5/25	8.0/19	9.5/24	7.0/25
DAY 6- 7 MEAN	1.	3.	2.	1.
S.D./N	2.7/25	3.8/19	3.2/24	3.4/25
DAY 7- 8 MEAN	4.	3.	4.	1.**
S.D./N	3.3/25	3.6/19	3.4/24	3.7/25
DAY 8- 9 MEAN	1.	3.	2.	3.
S.D./N	4.1/25	4.0/19	3.1/24	3.9/25
DAY 9- 10 MEAN	6.	4.	4.	2.**
S.D./N	3.5/25	2.7/19	3.5/24	3.7/25
DAY 10- 11 MEAN	7.	6.	6.	4.
S.D./N	4.2/25	3.3/19	4.1/24	3.3/25
DAY 11- 12 MEAN	6.	6.	4.	3.*
S.D./N	3.8/25	3.5/19	5.1/24	5.0/25
DAY 12- 13 MEAN	3.	4.	2.	3.
S.D./N	5.9/25	4.5/19	6.6/24	5.5/25
DAY 13- 14 MEAN	6.	6.	5.	3.
S.D./N	6.5/25	5.5/19	6.5/24	4.7/25
DAY 14- 15 MEAN	6.	8.	8.	5.
S.D./N	6.4/25	4.8/19	5.1/24	6.6/25

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY
* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
MEAN DIFFERENCES CALCULATED FROM INDIVIDUAL DIFFERENCES
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

PROJECT NO.:WIL-157016

TABLE 4
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
MEAN BODY WEIGHT CHANGES (GRAMS) DURING GESTATION

GROUP :	1	2	3	4
DAY 15- 16 MEAN	9.	11.	10.	11.
S.D./N	4.6/25	5.5/19	5.6/24	6.1/25
DAY 16- 20 MEAN	63.	70.	67.	73.**
S.D./N	14.2/25	8.8/19	8.8/24	7.4/25
DAY 6- 9 MEAN	7.	8.	8.	5.
S.D./N	3.1/25	4.0/19	3.7/24	4.5/25
DAY 9- 12 MEAN	19.	16.	14.**	8.**
S.D./N	6.0/25	4.7/19	5.2/24	5.5/25
DAY 12- 16 MEAN	24.	28.	24.	23.
S.D./N	7.4/25	3.7/19	7.3/24	7.5/25
DAY 6- 16 MEAN	50.	52.	46.	36.**
S.D./N	8.2/25	5.8/19	7.5/24	9.0/25
DAY 0- 20 MEAN	148.	154.	146.	143.
S.D./N	22.8/25	16.3/19	17.6/24	11.9/25

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
MEAN DIFFERENCES CALCULATED FROM INDIVIDUAL DIFFERENCES
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

SSf

PROJECT NO.:WIL-157016

TABLE 5
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
MEAN GRAVID UTERINE WEIGHTS AND NET BODY WEIGHT CHANGES (GRAMS)

	GROUP:	1	2	3	4
INITIAL BODY WT.	MEAN	245.	244.	242.	249.
	S.D.	9.9	7.5	13.2	9.7
	N	25	19	24	25
TERMINAL BODY WT.	MEAN	393.	398.	387.	392.
	S.D.	25.2	18.3	23.1	17.0
	N	25	19	24	25
GRAVID UTERINE WT.	MEAN	75.7	84.1	77.0	82.9
	S.D.	18.45	8.99	8.10	9.32
	N	25	19	24	24
NET BODY WT.	MEAN	317.1	314.1	310.2	308.7
	S.D.	19.85	12.82	22.75	15.51
	N	25	19	24	24
NET BODY WT. CHANGE	MEAN	71.9	69.8	68.6	59.3**
	S.D.	15.23	11.90	16.36	9.50
	N	25	19	24	24

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST

PROJECT NO.:WIL-157016

TABLE 6
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY)

GROUP :	1	2	3	4
DAY 0- 6 MEAN	22.	21.	22.	23.*
S.D./N	1.7/25	1.9/19	2.2/24	2.1/25
DAY 6- 7 MEAN	21.	21.	22.	23.
S.D./N	2.2/25	2.6/19	2.7/24	2.4/25
DAY 7- 8 MEAN	22.	22.	22.	21.
S.D./N	2.2/25	2.1/19	3.3/24	3.1/25
DAY 8- 9 MEAN	21.	21.	22.	22.
S.D./N	2.3/25	2.2/19	2.4/24	6.8/25
DAY 9- 10 MEAN	23.	21.	21.	21.
S.D./N	2.5/25	2.7/19	2.9/24	4.1/25
DAY 10- 11 MEAN	22.	22.	22.	21.*
S.D./N	2.2/25	1.9/19	2.7/24	2.7/25
DAY 11- 12 MEAN	25.	23.	23.	21.**
S.D./N	6.4/25	1.8/19	2.8/24	3.6/25
DAY 12- 13 MEAN	24.	24.	24.	24.
S.D./N	3.2/24	2.0/19	3.1/24	8.9/25
DAY 13- 14 MEAN	23.	23.	22.	20.**
S.D./N	2.2/25	2.2/19	2.2/24	4.1/25
DAY 14- 15 MEAN	23.	23.	23.	20.**
S.D./N	2.5/25	1.9/19	2.7/24	3.1/25

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY
* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

PROJECT NO.:WIL-157016

TABLE 6
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/ANIMAL/DAY)

GROUP :	1	2	3	4
DAY 15- 16 MEAN	25.	26.	26.	23.
S.D./N	2.6/25	2.1/19	3.0/24	6.0/25
DAY 16- 20 MEAN	24.	26.	27.	26.
S.D./N	4.7/25	1.4/19	3.3/24	2.5/25
DAY 6- 9 MEAN	21.	22.	22.	22.
S.D./N	1.7/25	1.8/19	2.5/24	2.7/25
DAY 9- 12 MEAN	23.	22.	22.	21.**
S.D./N	2.8/25	1.6/19	2.1/24	2.8/25
DAY 12- 16 MEAN	24.	24.	24.	22.**
S.D./N	2.4/25	1.1/19	2.4/24	3.1/25
DAY 6- 16 MEAN	23.	23.	23.	21.**
S.D./N	2.0/25	1.2/19	2.1/24	2.4/25
DAY 0- 20 MEAN	23.	23.	23.	23.
S.D./N	1.6/25	1.2/19	2.0/24	2.0/25

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

S2-1

PROJECT NO.:WIL-157016

TABLE 7
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/KG/DAY)

GROUP :	1	2	3	4
DAY 0- 6 MEAN	82.	81.	83.	87.*
S.D./N	5.1/25	6.8/19	5.0/24	6.7/25
DAY 6- 7 MEAN	76.	76.	78.	79.
S.D./N	7.0/25	9.0/19	7.3/24	7.3/25
DAY 7- 8 MEAN	77.	79.	80.	73.
S.D./N	6.8/25	6.0/19	7.6/24	9.2/25
DAY 8- 9 MEAN	74.	75.	77.	77.
S.D./N	6.5/25	7.0/19	5.9/24	24.2/25
DAY 9- 10 MEAN	78.	74.	74.	71.
S.D./N	6.7/25	8.6/19	8.7/24	14.0/25
DAY 10- 11 MEAN	76.	76.	77.	70.
S.D./N	5.3/25	6.5/19	8.0/24	9.2/25
DAY 11- 12 MEAN	83.	77.	78.	70.**
S.D./N	20.9/25	5.6/19	9.8/24	11.6/25
DAY 12- 13 MEAN	79.	79.	79.	79.
S.D./N	7.6/24	7.0/19	8.0/24	28.0/25
DAY 13- 14 MEAN	75.	74.	73.	67.**
S.D./N	5.9/25	6.9/19	5.9/24	12.3/25
DAY 14- 15 MEAN	73.	75.	75.	66.**
S.D./N	6.0/25	5.7/19	8.2/24	10.0/25

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY
* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

52-2

PROJECT NO.:WIL-157016

TABLE 7
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
MEAN FOOD CONSUMPTION DURING GESTATION (GRAMS/KG/DAY)

GROUP :	1	2	3	4
DAY 15- 16 MEAN	78.	79.	81.	74.
S.D./N	5.7/25	6.8/19	8.3/24	18.6/25
DAY 16- 20 MEAN	68.	73.	75.**	74.*
S.D./N	12.4/25	3.8/19	7.1/24	5.0/25
DAY 6- 9 MEAN	76.	77.	78.	77.
S.D./N	4.6/25	5.3/19	4.9/24	9.0/25
DAY 9- 12 MEAN	79.	76.	76.	71.**
S.D./N	7.6/25	4.8/19	6.4/24	9.2/25
DAY 12- 16 MEAN	77.	77.	78.	72.*
S.D./N	4.9/25	3.7/19	6.2/24	8.9/25
DAY 6- 16 MEAN	77.	77.	77.	73.**
S.D./N	4.7/25	3.1/19	4.7/24	7.2/25
DAY 0- 20 MEAN	76.	76.	78.	77.
S.D./N	4.2/25	3.3/19	4.2/24	5.3/25

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY
* = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.05 LEVEL USING A TWO-TAILED DUNNETT'S TEST
** = SIGNIFICANTLY DIFFERENT FROM CONTROL GROUP 1 AT 0.01 LEVEL USING A TWO-TAILED DUNNETT'S TEST
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

PROJECT NO.:WIL-157016

TABLE 8
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
SUMMARY OF MEAN FETAL DATA AT THE SCHEDULED NECROPSY

GROUP	SEX M	SEX F	VIABLE FETUSES	DEAD FETUSES	RESORPTIONS EARLY	RESORPTIONS LATE	POST IMPLANTATION LOSS	IMPLANTATION SITES	CORPORA LUTEA	PRE IMPLANTATION LOSS	FETAL WEIGHTS IN GRAMS	NO. OF GRAVID FEMALES
1 TOTAL	177	161	338	0	17	0	17	355	412	57	NA	25
MEAN	7.1	6.4	13.5	0.0	0.7	0.0	0.7	14.2	16.5	2.3	3.7	
S.D.	2.74	2.27	3.49	0.00	1.03	0.00	1.03	3.51	2.18	2.65	0.30	
2 TOTAL	132	152	284	0	6	0	6	290	326	36	NA	19
MEAN	6.9	8.0	14.9	0.0	0.3	0.0	0.3	15.3	17.2	1.9	3.7	
S.D.	2.12	2.05	1.72	0.00	0.58	0.00	0.58	1.45	1.89	1.85	0.16	
3 TOTAL	170	160	330	0	23	0	23	353	404	51	NA	24
MEAN	7.1	6.7	13.8	0.0	1.0	0.0	1.0	14.7	16.8	2.1	3.6	
S.D.	1.86	2.06	1.59	0.00	0.95	0.00	0.95	1.83	2.60	2.29	0.22	
4 TOTAL	206	171	377	0	19	0	19	396	428	32	NA	25
MEAN	8.2	6.8	15.1	0.0	0.8	0.0	0.8	15.8	17.1	1.3	3.5*	
S.D.	1.94	1.93	1.80	0.00	1.05	0.00	1.05	1.40	1.72	1.14	0.19	

* = SIGNIFICANTLY DIFFERENT FROM CONTROL AT 0.05 LEVEL
NA = NOT APPLICABLE

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

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY

PROJECT NO.:WIL-157016

TABLE 9
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
SUMMARY OF MEAN FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)

GROUP NUMBER:	1	2	3	4
CORPORA LUTEA				
MEAN	16.5	17.2	16.8	17.1
S.D.	2.18	1.89	2.60	1.72
N	25	19	24	25
IMPLANTATION SITES				
MEAN	14.2	15.3	14.7	15.8
S.D.	3.51	1.45	1.83	1.40
N	25	19	24	25
VIABLE FETUSES (%)				
MEAN	95.4	97.8	93.7	95.1
S.D.	6.89	4.09	5.71	6.60
N	25	19	24	25
DEAD FETUSES (%)				
MEAN	0.0	0.0	0.0	0.0
S.D.	0.00	0.00	0.00	0.00
N	25	19	24	25
EARLY RESORPTIONS (%)				
MEAN	4.6	2.2	6.3	4.9
S.D.	6.89	4.09	5.71	6.60
N	25	19	24	25
LATE RESORPTIONS (%)				
MEAN	0.0	0.0	0.0	0.0
S.D.	0.00	0.00	0.00	0.00
N	25	19	24	25

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY

PROPORTIONAL (%) DATA COMPARED USING THE KRUSKAL-WALLIS TEST
CORPORA LUTEA AND IMPLANTATION SITES COMPARED USING DUNNETT'S TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP

S25

PROJECT NO.:WIL-157016

TABLE 9
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
SUMMARY OF MEAN FETAL DATA AT SCHEDULED NECROPSY (% PER LITTER)

GROUP NUMBER:	1	2	3	4
TOTAL RESORPTIONS (%)				
MEAN	4.6	2.2	6.3	4.9
S.D.	6.89	4.09	5.71	6.60
N	25	19	24	25
PRE-IMPLANTATION LOSS (%)				
MEAN	14.2	10.4	11.6	7.2
S.D.	18.62	9.81	11.16	6.14
N	25	19	24	25
POST-IMPLANTATION LOSS (%)				
MEAN	4.6	2.2	6.3	4.9
S.D.	6.89	4.09	5.71	6.60
N	25	19	24	25
MALES (%)				
MEAN	50.0	46.4	51.6	54.7
S.D.	16.64	12.54	13.52	11.27
N	25	19	24	25
FEMALES (%)				
MEAN	50.0	53.6	48.4	45.3
S.D.	16.64	12.54	13.52	11.27
N	25	19	24	25
MALE FETAL WEIGHTS (g)				
MEAN	3.8	3.8	3.7	3.6
S.D.	0.31	0.20	0.21	0.20
N	24	19	24	25

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY

PROPORTIONAL (%) DATA COMPARED USING THE KRUSKAL-WALLIS TEST
FETAL WEIGHTS COMPARED USING DUNNETT'S TEST
NONE SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP

PROJECT NO.:WIL-157016

TABLE 9
A DEVELOPMENTAL TOXICITY STUDY OF 313401 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	3.5	3.4*
S.D.	0.31	0.17	0.20	0.19
N	25	19	24	25
COMBINED FETAL WEIGHTS (g)				
MEAN	3.7	3.7	3.6	3.5*
S.D.	0.30	0.16	0.22	0.19
N	25	19	24	25

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY
FETAL WEIGHTS COMPARED USING DUNNETT'S TEST
* = SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP AT THE 0.05 LEVEL

47

S-67

PROJECT NO.:WIL-157016

TABLE 10
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
NUMBER OF FETUSES AND LITTERS WITH MALFORMATIONS - SUMMARY

DAY 20

DOSE GROUP:	FETUSES 1	2	3	4	LITTERS 1	2	3	4
NUMBER EXAMINED EXTERNALLY	338	284	330	377	25	19	24	25
NUMBER WITH FINDINGS	0	0	0	0	0	0	0	0
NUMBER EXAMINED VISCERALLY	338	284	330	377	25	19	24	25
NUMBER WITH FINDINGS	0	0	0	0	0	0	0	0
NUMBER EXAMINED SKELETALLY	338	284	330	377	25	19	24	25
COSTAL CARTILAGE ANOMALY	0	0	3	0	0	0	1	0
VERTEBRAL ANOMALY WITH OR WITHOUT ASSOCIATED RIB ANOMALY	0	0	1	0	0	0	1	0
TOTAL NUMBER WITH MALFORMATIONS								
EXTERNAL :	0	0	0	0	0	0	0	0
SOFT TISSUE:	0	0	0	0	0	0	0	0
SKELETAL :	0	0	3	0	0	0	1	0
COMBINED :	0	0	3	0	0	0	1	0

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY

TABLE 11

PROJECT NO.:WIL-157016 A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS PAGE 1

MEAN LITTER PROPORTIONS OF MALFORMATIONS - SUMMARY

% PER LITTER DAY 20

DOSE GROUP:	1	2	3	4
NUMBER OF LITTERS EXAMINED EXTERNALLY	25	19	24	25
NUMBER OF LITTERS WITH FINDINGS	0	0	0	0

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY
NONE SIGNIFICANTLY DIFFERENT USING THE MANN-WHITNEY U TEST

PROJECT NO.:WIL-157016

TABLE 11
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
MEAN LITTER PROPORTIONS OF MALFORMATIONS - SUMMARY
% PER LITTER

DAY 20

DOSE GROUP:	1	2	3	4
NUMBER OF LITTERS EXAMINED VISCERALLY	25	19	24	25
NUMBER OF LITTERS WITH FINDINGS	0	0	0	0

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY
NONE SIGNIFICANTLY DIFFERENT USING THE MANN-WHITNEY U TEST

PROJECT NO.:WIL-157016

TABLE 11
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
MEAN LITTER PROPORTIONS OF MALFORMATIONS - SUMMARY
% PER LITTER

DAY 20

DOSE GROUP:		1	2	3	4
NUMBER OF LITTERS EXAMINED SKELETALLY		25	19	24	25
COSTAL CARTILAGE ANOMALY	MEAN	0.0	0.0	0.9	0.0
	S.D.	0.00	0.00	4.37	0.00
VERTEBRAL ANOMALY WITH OR WITHOUT ASSOCIATED RIB ANOMALY	MEAN	0.0	0.0	0.3	0.0
	S.D.	0.00	0.00	1.46	0.00

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY
NONE SIGNIFICANTLY DIFFERENT USING THE MANN-WHITNEY U TEST

PROJECT NO.:WIL-157016

TABLE 11
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
MEAN LITTER PROPORTIONS OF MALFORMATIONS - SUMMARY
% PER LITTER

DAY 20

DOSE GROUP:		1	2	3	4
NUMBER OF LITTERS EXAMINED		25	19	24	25
TOTAL MALFORMATIONS					
PERCENT PER LITTER WITH EXTERNAL MALFORMATIONS	MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
PERCENT PER LITTER WITH SOFT TISSUE MALFORMATIONS	MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
PERCENT PER LITTER WITH SKELETAL MALFORMATIONS	MEAN	0.0	0.0	0.9	0.0
	S.D.	0.00	0.00	4.37	0.00
TOTAL PERCENT PER LITTER WITH MALFORMATIONS	MEAN	0.0	0.0	0.9	0.0
	S.D.	0.00	0.00	4.37	0.00

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY
NONE SIGNIFICANTLY DIFFERENT USING THE MANN-WHITNEY U TEST

S-72

PROJECT NO.:WIL-157016

TABLE 12
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
NUMBER OF FETUSES AND LITTERS WITH VARIATIONS - SUMMARY

DAY 20

DOSE GROUP:	FETUSES 1	2	3	4	LITTERS 1	2	3	4
NUMBER EXAMINED EXTERNALLY	338	284	330	377	25	19	24	25
NUMBER WITH FINDINGS	0	0	0	0	0	0	0	0
NUMBER EXAMINED VISCERALLY	338	284	330	377	25	19	24	25
NUMBER WITH FINDINGS	0	0	0	0	0	0	0	0
NUMBER EXAMINED SKELETALLY	338	284	330	377	25	19	24	25
CERVICAL CENTRUM #1 OSSIFIED	68	44	52	74	18	15	19	21
14TH RUDIMENTARY RIB(S)	7	20	42	44	5	8	13	16
STERNEBRA(E) #5 AND/OR #6 UNOSSIFIED	20	11	22	32	11	7	11	14
14TH FULL RIB(S)	0	0	3	5	0	0	3	2
27 PRESACRAL VERTEBRAE	0	0	4	5	0	0	2	3
7TH CERVICAL RIB(S)	0	1	3	1	0	1	3	1
REDUCED OSSIFICATION OF THE VERTEBRAL ARCHES	0	0	0	1	0	0	0	1
REDUCED OSSIFICATION OF THE 13TH RIB(S)	5	1	3	2	3	1	2	2
BENT RIB(S)	3	5	3	24	1	4	2	7
HYOID UNOSSIFIED	4	5	5	11	3	4	4	6
STERNEBRA(E) MALALIGNED(SLIGHT OR MODERATE)	1	1	1	1	1	1	1	1
STERNEBRA(E) #1,#2,#3 AND/OR #4 UNOSSIFIED	1	2	0	1	1	2	0	1

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY

S 73

PROJECT NO.:WIL-157016

TABLE 13
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
MEAN LITTER PROPORTIONS OF VARIATIONS - SUMMARY
% PER LITTER

DAY 20

DOSE GROUP:	1	2	3	4
NUMBER OF LITTERS EXAMINED EXTERNALLY	25	19	24	25
NUMBER OF LITTERS WITH FINDINGS	0	0	0	0

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY
NONE SIGNIFICANTLY DIFFERENT USING THE MANN-WHITNEY U TEST

S-74

PROJECT NO.:WIL-157016

TABLE 13
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
MEAN LITTER PROPORTIONS OF VARIATIONS - SUMMARY
% PER LITTER

DAY 20

DOSE GROUP:	1	2	3	4
NUMBER OF LITTERS EXAMINED VISCERALLY	25	19	24	25
NUMBER OF LITTERS WITH FINDINGS	0	0	0	0

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY
NONE SIGNIFICANTLY DIFFERENT USING THE MANN-WHITNEY U TEST

PROJECT NO.:WIL-157016

TABLE 13
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
MEAN LITTER PROPORTIONS OF VARIATIONS - SUMMARY
% PER LITTER

DAY 20

DOSE GROUP:		1	2	3	4
NUMBER OF LITTERS EXAMINED SKELETALLY		25	19	24	25
CERVICAL CENTRUM #1 OSSIFIED	MEAN	21.2	16.0	15.8	19.4
	S.D.	22.48	19.77	14.00	16.77
14TH RUDIMENTARY RIB(S)	MEAN	2.2	6.6	13.1**	11.3**
	S.D.	4.86	10.14	17.36	14.78
STERNEBRA(E) #5 AND/OR #6 UNOSSIFIED	MEAN	5.3	3.8	6.6	8.5
	S.D.	8.03	5.69	8.29	9.37
14TH FULL RIB(S)	MEAN	0.0	0.0	1.0	1.2
	S.D.	0.00	0.00	2.71	4.68
27 PRESACRAL VERTEBRAE	MEAN	0.0	0.0	1.3	1.2
	S.D.	0.00	0.00	4.68	3.80
7TH CERVICAL RIB(S)	MEAN	0.0	0.4	1.0	0.3
	S.D.	0.00	1.64	2.71	1.43
REDUCED OSSIFICATION OF THE VERTEBRAL ARCHES	MEAN	0.0	0.0	0.0	0.3
	S.D.	0.00	0.00	0.00	1.25
REDUCED OSSIFICATION OF THE 13TH RIB(S)	MEAN	1.3	0.3	0.9	0.5
	S.D.	3.70	1.43	3.37	1.70
BENT RIB(S)	MEAN	0.8	2.0	0.8	6.3
	S.D.	3.75	4.38	2.80	12.68
HYOID UNOSSIFIED	MEAN	1.1	1.9	1.6	2.8
	S.D.	3.14	4.33	3.84	5.99

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY
** = SIGNIFICANTLY DIFFERENT FROM THE CONTROLS AT THE 0.01 LEVEL USING THE MANN-WHITNEY U TEST

PROJECT NO.:WIL-157016

TABLE 13
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
MEAN LITTER PROPORTIONS OF VARIATIONS - SUMMARY
% PER LITTER

DAY 20

DOSE GROUP:		1	2	3	4
NUMBER OF LITTERS EXAMINED SKELETALLY		25	19	24	25
STERNEBRA(E) MALALIGNED(SLIGHT OR MODERATE)	MEAN	0.2	0.4	0.3	0.3
	S.D.	1.00	1.64	1.57	1.25
STERNEBRA(E) #1,#2,#3 AND/OR #4 UNOSSIFIED	MEAN	0.2	0.8	0.0	0.2
	S.D.	1.18	2.45	0.00	1.18

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY
NONE SIGNIFICANTLY DIFFERENT USING THE MANN-WHITNEY U TEST

577

PROJECT NO.:WIL-157016

TABLE 13
A DEVELOPMENTAL TOXICITY STUDY OF 313401 IN RATS
MEAN LITTER PROPORTIONS OF VARIATIONS - SUMMARY
% PER LITTER

DAY 20

DOSE GROUP:		1	2	3	4
NUMBER OF LITTERS EXAMINED		25	19	24	25
TOTAL VARIATIONS					
PERCENT PER LITTER WITH EXTERNAL VARIATIONS	MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
PERCENT PER LITTER WITH SOFT TISSUE VARIATIONS	MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
PERCENT PER LITTER WITH SKELETAL VARIATIONS	MEAN	30.2	28.6	35.2	41.8
	S.D.	21.87	22.47	19.84	20.50
TOTAL PERCENT PER LITTER WITH VARIATIONS	MEAN	30.2	28.6	35.2	41.8
	S.D.	21.87	22.47	19.84	20.50

1- 0 MG/KG/DAY 2- 4 MG/KG/DAY 3- 16 MG/KG/DAY 4- 32 MG/KG/DAY
NONE SIGNIFICANTLY DIFFERENT USING THE MANN-WHITNEY U TEST

S-76