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Title Page

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DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

Sponsor: U.S. Army Medical Materiel
Development Activity

Test Article: WR238605 Succinate

Contract No.: DAMD17-92-C-2001

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Study Director

Barry S. Levine, D.Sc., D.A.B.T.

In-Life Phase Completed On

August 8, 1995

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<p>This study evaluated the developmental toxicity of WR238605 Succinate in time-mated New Zealand White (Pasteurella Free) female rabbits. Doses were 0, 2, 7 and 25 mg base/kg/day administered by gavage during gestation days (GD) 6 - 18 (GD0 = day of observed mating). A positive control group was administered retinol palmitate, 300 mg/kg/day, on GD9 and 10 by gavage. Due to an apparent dosage formulation analysis problem, the high dose was retested at the Sponsor's request. Doses of 0 or 25 mg base/kg/day were administered by gavage during GD6 - 18. Due to mortality and reduced food consumption, the dose was lowered to 16 mg base/kg/day on GD15 - 16 (the range of days reflects the study stagger start over two days). Maternal toxicity was observed in the initial 25 mg base/kg/day and retest 25/16 mg base/kg/day groups. Abortion and premature delivery occurred in the initial study concomitant with minimally reduced body weight and decreases in food consumption. In the retest, mortality or moribund sacrifice preceded by labored breathing or decreased activity, respectively, was seen at 25 mg base/kg/day; while abortion preceded by blood in the cage pan occurred at the lowered dose of 16 mg base/kg/day. Decreased body weight and/or reduced weight gain and severe reductions in food consumption were noted in the majority of animals in the retest group. In the 7 mg base/kg/day group, one animal aborted; however, there were no alterations in body weight or food consumption. Due to the increased incidence in the 25 and 25/16 mg base/kg/day groups, the abortion in the 7 mg base/kg/day group may be related to administration of WR238605 Succinate. There was no maternal toxicity at 2 mg base/kg/day. Neither embryotoxicity, fetotoxicity, nor teratogenicity was evident at any dose level in the initial or retest WR238605 Succinate-treated groups. Based on these data, the maternal NOEL was at or near 7 mg base/kg/day and the fetal NOEL was 25 mg base/kg/day. In the positive control group, embryotoxicity, fetotoxicity and overt teratogenicity were considered typical of exposure to retinol palmitate.</p>			
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STATEMENT OF COMPLIANCE

Study No. 156 entitled " Developmental Toxicity (Segment II) Study of WR238605 Succinate in Rabbits" was conducted in compliance with the Good Laboratory Practices regulations as published in 21 CFR 58, 40 CFR 160 and 40 CFR 792 in all material aspects.

The protocol for this study was approved by the UIC Animal Care Committee.

Signature

Study Director

Barry S. Levine, D.Sc., D.A.B.T.

Date

QUALITY ASSURANCE STATEMENT

STUDY TITLE: DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

STUDY NUMBER: 156

STUDY DIRECTOR: BARRY S. LEVINE

INITIATION DATE: 6/29/95

This study has been divided into a series of phases. Using a random sampling approach, Quality Assurance personnel monitors each of these phases over a series of studies. Procedures, equipment, documentation, etc., are examined in order to assure that the study is performed in accordance with the Good Laboratory Practice regulations of the Food and Drug Administration and the Environmental Protection Agency to assure that the study is conducted according to the protocol.

The following are the inspection dates, phases inspected, and report dates of QA inspections of the study.

INSPECT ON 6/29/94, TO STUDY DIR 6/29/94, TO MGMT 6/29/94
PHASES: PROTOCOL REVIEW
INSPECT ON 1/5/95, TO STUDY DIR 1/5/95, TO MGMT 1/10/95
PHASES: QUARANTINE
INSPECT ON 1/9/95, TO STUDY DIR 1/10/95, TO MGMT 1/11/95
PHASES: EAR TAGGING
INSPECT ON 2/3/95, TO STUDY DIR 2/3/95, TO MGMT 2/6/95
PHASES: EUTHANASIA, C-SECTION OBSERVATIONS AND CONFIRMATION
OF PREGNANCY
INSPECT ON 4/3-4/95, TO STUDY DIR 4/4/95, TO MGMT 4/16/95
PHASES: RAW DATA
INSPECT ON 11/1-2/94, TO STUDY DIR 11/2/94, TO MGMT 11/7/94
PHASES: RAW DATA
INSPECT ON 7/11/95, TO STUDY DIR 7/11/95, TO MGMT 7/13/95
PHASES: ANIMAL RECEIPT AND ROOM ENVIRONMENT
INSPECT ON 10/11-12/95, TO STUDY DIR 10/13/95, TO MGMT 10/13/95
PHASES: RAW DATA AND DRAFT REPORT FROM THE ANALYTICAL LAB
INSPECT ON 11/3/95, TO STUDY DIR 11/3/95, TO MGMT 11/10/95
PHASES: RAW DATA
INSPECT ON 11/3-6/95, TO STUDY DIR 11/6/95, TO MGMT 11/10/95
PHASES: DRAFT REPORT

Ronald Schwenke

QUALITY ASSURANCE

11/10/95

DATE

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Contract No.: DAMD17-92-C-2001
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Signature Page

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

TRL Chemical No.: 0720614

Sponsor: U.S. Army Medical Materiel
Development Activity
Fort Detrick
Frederick, MD 21702-5009

Test Article: WR238605 Succinate

Sponsor
Representative: George J. Schieferstein, Ph.D.

Testing Facility: TOXICOLOGY RESEARCH LABORATORY (TRL)
University of Illinois at Chicago (UIC)
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Barry S. Levine, D.Sc., D.A.B.T. Date
Study Director

Ashraf F. Youssef, M.D., Ph.D. Date
Reproductive Toxicologist

In-life Phase Initiation: January 2, 1995

Dosing Initiation: January 8, 1995

In-Life Completion: August 8, 1995

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1. SUMMARY

This study evaluated the embryo/fetal toxicity and the teratogenic potential of WR238605 Succinate in time-mated New Zealand White (Pasteurella Free) female rabbits. WR238605 Succinate is an 8-aminoquinoline derivative which has demonstrated antimalarial potential in preclinical studies. Doses were based on the results of a previously conducted dose range-finding study (UIC/TRL 155) where maternal toxicity (abortion, significant reductions in body weight and food consumption, and a significant increase in postimplantation loss due to a biological decrease in the number of viable fetuses and an increase in early resorptions) was evident at 32 mg base/kg/day and fetotoxicity (a significant decrease in body weight) was noted at the 32 mg base/kg/day dose level and to a lesser extent at the 16 and 8 mg base/kg/day dose levels.

In the present study, doses of 0, 2, 7, or 25 mg base/kg/day were administered by gavage to 20 rabbits/group during gestation days (GD) 6 - 18 (GD0 = day of observed mating). In addition, a positive control group of 20 rabbits was administered retinol palmitate, 300 mg/kg/day, on GD9 and 10 by gavage. Due to an apparent dosage formulation analysis problem, the high dose was retested at the Sponsor's request. Doses of 0 or 25 mg base/kg/day were administered by gavage to 20 rabbits/group during GD6 - 18. Due to mortality and reductions in food consumption, the dose was lowered to 16 mg base/kg/day on GD15 - 16 (the range of days reflects study stagger-start over two days). Animals in both aspects of the study were 6 - 6½ months old at the initiation of dosing (GD6). The weight range at the initiation of dosing (GD6) was 2.62 - 3.75 kg in the initial study and 2.96 - 4.33 kg in the retest of the high dose. Terminal necropsies were conducted on GD29.

The results of the initial study groups and the retest groups are summarized in Table 1. Maternal toxicity was observed in the initial 25 mg base/kg/day group, and included abortion (2/20) and premature delivery (1/20). A significant loss in body weight gain on GD9 contributed to a slight, but insignificant reduction in total body weight gain. Statistically significant decreases in food consumption were due to effects in these few animals. Maternal toxicity was also observed in the retest 25/16 mg base/kg/day group as exemplified by mortality (2/20), moribund sacrifice (2/20), and abortion (3/20). Statistically significant decreases in body weight and food consumption were attributed to reductions noted in the majority of animals in this retest group. There were no alterations in maternal reproductive indices or fetal parameters in any of the initial or retest WR238605 Succinate-treated groups.

One rabbit at 7 mg base/kg/day aborted but showed no other evidence of maternal toxicity. Based on the incidence of abortion in the 25 and 25/16 mg base/kg/day groups, this event may be related to administration of WR238605 Succinate. No evidence of maternal toxicity was seen in the 2 mg base/kg/day group. At the request of the Sponsor, skeletal evaluations were not conducted in fetuses in the initial 25 mg base/kg/day group. There was no embryotoxicity, fetotoxicity, or teratogenicity at any dose level. Based on the results of this study, the no-effect level (NOEL) for maternal toxicity of WR238605 Succinate in pregnant rabbits was at or near 7 mg base/kg/day, and the fetal NOEL was 25 mg base/kg/day.

Neither maternal nor fetal affects were seen in the vehicle control animals. Fetotoxicity and teratogenicity were noted in the positive control group. Slight, nonstatistically significant reductions were noted in uterine weight and fetal viability. A statistically significant increase in the number of early resorptions was accompanied by a nonsignificant reduction in the number of viable fetuses as well as nonsignificant increases in the percent postimplantation loss and total loss/litter. Statistically significant increases in the incidence of external, skeletal, and visceral fetal malformations were considered typical of retinol palmitate (e.g., cleft palate, micrognathia, microstomia). In addition, a statistically significant increase was noted in major blood vessel variations and the incidence of distended ureter.

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2. INTRODUCTION

This study was conducted to evaluate the embryo/fetal toxicity and the teratogenic potential of the test article in New Zealand White rabbits. WR238605 Succinate is an 8-aminoquinoline derivative which has demonstrated antimalarial potential in preclinical studies. WR238605 Succinate was discovered at WRAIR and is being developed as a prophylactic to replace primaquine. Previously conducted studies with this compound by the Toxicology Research Laboratory (UIC) include the following: 13-week oral toxicity studies with a 13-week recovery period in dogs and rats (UIC/TRL Nos. 097 and 098), and developmental toxicity study in rats (UIC/TRL No. 154). A 6-month toxicity study in rats (UIC/TRL No. 152) is ongoing. In addition, several *in vitro* mutagenicity tests (mouse lymphoma assay, chromosome aberrations in CHO cells, and a CHO/HGRPT assay) were performed via a subcontract by Microbiological Associates, Inc. (Task Order No. 10).

In the present study, the test article was administered at doses of 0, 2, 7, or 25 mg base/kg/day by gavage to time-mated females during GD6 - 18. The fetuses were delivered by Cesarean section on GD29. Due to an apparent dosage formulation analysis problem, the Sponsor requested a retest of the high dose with a concurrent vehicle control in a second group of time-mated females (20 rabbits/group). The dose of 25 mg base/kg/day was administered on GD6 - 14 or 15, but due to mortality and reduced food consumption, the dose was lowered to 16 mg base/kg/day on GD15 or 16 (the range of days reflects the study stagger start over two days). The dosing period ended on GD18, and the fetuses were delivered by Cesarean section on GD29. All viable fetuses in the initial and retest groups were examined for external anomalies using a stereomicroscope and for visceral anomalies using Staples' technique, then fixed in ethyl alcohol (95%). As directed by the Sponsor, fetuses from the initial 25 mg base/kg/day group were retained in ethyl alcohol and not evaluated for skeletal anomalies. All other fetuses from the initial study (0, 2, or 7 mg base/kg/day groups) and from the retest groups (0 or 25/16 mg base/kg/day) were examined skeletally.

All methods and procedures in this study were conducted in accordance with the Toxicology Research Laboratory, University of Illinois at Chicago and Pathology Associates Inc. Quality Assurance Programs designed to conform with FDA Good Laboratory Practices Regulations. No unforeseen circumstances affected the integrity of the study. The initial study was stagger-started over four days and was initiated on January 2, 1995 (observation of mating). Dosing was initiated (stagger-started) on January 8, 1995 (GD6), and the in-life portion was terminated on February 3, 1995 (GD29). The retest study was stagger-started over two days and was initiated on July 9, 1995 (observation of mating). Dosing was initiated (stagger-started) on July 15, 1995 (GD6), and the in-life portion was terminated on August 8, 1995 (GD29).

3. MATERIALS AND METHODS

3.1 Test Article

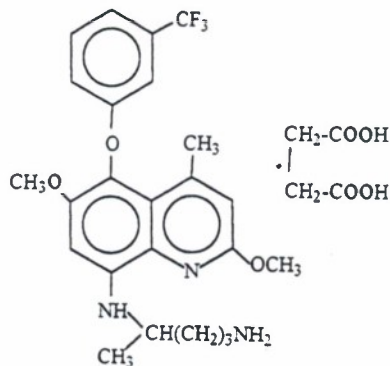
WR238605 Succinate (Bottle Lot No. BM12562), a pale yellow powder, was provided by the Sponsor. It was received in two shipments on July 21, 1994 and October 5, 1994 from Herner & Co. and was previously assigned an in-house chemical number (0720614). The chemical name of the test article is 8-[(4-amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethyl-phenoxy)quinoline succinate and the mole fraction of the base is 0.8. It was stored at 0 to 4°C and ambient humidity in the refrigerator, and was protected from light (the container was wrapped in aluminum foil). The chemical structure follows.

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The test article was initially identified by GC-MS and the purity was determined to be greater than 99.9%. The purity was re-determined following the completion of the in-life portion of the study. At that time, the purity was greater than 99.5%. Thus, the test article was stable under storage conditions.

Vitamin A (Retinol Palmitate, all-trans) was purchased from Sigma Co., St. Louis, MO. It was kept at 0 - 4° C at ambient humidity, and was protected from light in an amber bottle.

3.2 Animals

For the initial study, a total of one-hundred and twenty female New Zealand White (Pasteurella Free) rabbits were obtained from HRP, Inc., Denver, PA on January 3 & 6, 1995 (30 and 90 animals, respectively). The animals were 6 - 6½ months old upon arrival at the UIC AAALAC-accredited animal facility (date of birth 07/02/94). For the retest of the high dose, a total of forty-six female New Zealand White (Pasteurella Free) rabbits were obtained from HRP, Inc., Denver, PA on July 11, 1995. The animals were 6 - 6½ months old upon arrival at the UIC AAALAC-accredited animal facility (date of birth 01/07/95). Each animal was given an ear tag number by the supplier, and a separate study-unique number (ear-tag) upon arrival. This number appeared on a cage card visible on the front of each cage. The cage card additionally contained the study number, test article identification, treatment group number, dose level, and the assigned date of necropsy. Cage cards were color-coded as a function of treatment group. Animals were singly housed in stainless steel cages in a temperature (61 - 69°F) and humidity (30 - 70 %) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 0.32 m² area and 38 cm height, was adequate to house rabbits at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23. All animals were routinely transferred to clean cages every other week with weekly pan changes.

The animals were fasted on the day of arrival. They received approximately 25 g of High Fiber Certified Rabbit Chow #5325 (PMI Feeds, Inc., St. Louis, MO) on the second day, which was gradually increased over a few days to approximately 100 - 130 g/day. This regimen was recommended by the animal supplier (HRP, Inc.) to reduce the incidence of intestinal problems. On the days of measured food consumption, an exact amount of 130 g was provided. Due to severe reductions in food consumption observed in both the initial and retest high dose groups, and following consultation with the Clinical Veterinarian, food for one animal in the 25 mg base/kg/day group and all animals in the 25/16 mg base/kg/day groups was supplemented with hay cubes and/or loose hay (Cheeke, 1987). Additionally, several animals in the retest high dose group were gavaged once on GD 17 and 18 or GD 18 and 19 with a slurry of pelleted food in distilled water. Tap water from an automatic watering system in which the room distribution lines were flushed daily was provided *ad libitum* from arrival until

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termination. The water was not treated with additional chlorine or HCl. There are no known contaminants in the feed or water which were expected to influence the study. The results of the most current comprehensive chemical analyses of Chicago water performed by the City of Chicago are documented in files maintained by Quality Assurance.

3.3 Experimental Design

In the initial study, animals were mated on four consecutive days at the supplier's facility. The day of mating was considered GD0. The body weights on GD0 were obtained by the supplier after balance standardization. Of the 120 presumed pregnant rabbits which were received, 60, 30 and 30 were at GD1, GD2, and GD3, respectively, upon arrival at the animal facility. All animals were quarantined for at least 3 days before initiation of dosing (GD6). All animals were examined daily during the quarantine period, and were approved for use by the Clinical Veterinarian prior to being placed on test. One hundred animals (25 animals from each GD0 subset) were randomized into the following five groups on the basis of body weight to result in 20 animals/group. Dose levels were selected on the basis of a range-finding study (UIC/TRL Study No. 155) as follows:

<u>Group No.</u>	<u>Treatment</u>	<u>Dose Level</u> <u>(mg base/kg/day)</u>	<u>Number of</u> <u>Females*</u>
1	Vehicle	0	20
2	WR238605	2	20
3	WR238605	7	20
4	WR238605	25	20
5**	Vitamin A (Retinol Palmitate)	75,000 IU/kg/day (300 mg/kg/day)	20

* Presumed pregnant (observed mating)

** The positive control agent was administered orally at the specified dose on DG9 and 10 in deionized distilled water at a dosing volume of 1 ml/kg/day. It was prepared fresh on each day and was dispersed in the vehicle within 30 minutes of initiation of dosing.

As previously discussed, the high dose was retested in 20 presumed pregnant rabbits. Due to mortality and reduced food consumption, the dose was lowered to 16 mg base/kg/day on GD15 or 16 (the range of days reflects the study stagger-start over two days). The vehicle control was administered to a concurrent group of 20 presumed pregnant rabbits.

In the retest individual and summary tables, the study is identified as 156A as the initial study (156) could not be adjusted after initiation. Furthermore, in the report, the summary tables and appendices are identified as X for the initial study (156), and as X.1 for the retest (156A). Where appropriate, the appendices contains data from the initial study (X - Y) and the retest (X.1 - Y.1).

The test article was administered by gavage once daily during GD6 through 18. The dosing suspensions were administered at a dosing volume of 1 ml/kg. In the initial study, a stock

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test article suspension (20 mg/ml) was prepared once at the beginning of the study by suspending the appropriate quantity of the test article in the vehicle (aqueous 1% methylcellulose/0.2% Tween 80). Dosing formulations were then prepared once for the dosing period by diluting the stock to the appropriate concentration with additional vehicle. In the retest study, separate dosing formulations were prepared weekly, i.e., two sets during the dosing period. Each test article dosing suspension was prepared individually by adding the appropriate amount of WR238605 Succinate with the required volume of 1.0% methylcellulose/0.2% Tween 80 vehicle in a pre-calibrated beaker. The contents were mixed with an Omni-Mixer homogenizer for at least 5 minutes. All stock and dosing suspensions were kept at 0 - 4°C. Samples of the dosage formulations from the initial study were analyzed for test article concentration before the initiation of treatment and at the end of the dosing period. In week one of the retest, the dosage formulations were analyzed for test article concentration before use and after use. During the second week of dosing, when the dose was reduced from 25 to 16 mg base/kg/day, the high dose formulation was analyzed prior to use and midweek prior to dilution with additional vehicle to make the new formulation appropriate for a dose of 16 mg base/kg/day. This new formulation was analyzed prior to use and at the conclusion of the dosing period. Only samples within 10% of their intended concentration were used. Stability data obtained from a previous study (UIC/TRL Study No. 047) indicated that the dosing suspensions were stable for at least two weeks. Homogeneity data obtained from UIC/TRL Study No. 047 also demonstrated that the test article suspensions were homogeneous (coefficients of variation for sampling in the top, middle and bottom of several test suspensions were typically less than 4%).

Non-fasted body weights were recorded for all animals on GD0 (by the supplier), GD4 (for randomization), and on GD6 - 18, 24 and 29. Food consumption for all animals was measured during the following 24 hr intervals: GD7/8, 9/10, 11/12, 14/15, 17/18, 23/24 and 28/29. Clinical signs were observed and recorded approximately 1 - 2 hours post-dosing on the days of dosing and each morning following completion of the dosing period. Animals were also observed for moribundity/mortality in the morning and afternoon during the dosing and postdosing periods.

On GD29, all surviving rabbits were killed in random order by intravenous injection of sodium pentobarbital (50 mg/kg) via the marginal ear vein. The abdominal and thoracic cavities were opened by a ventral midline incision. The uterus was examined and weighed. In gravid animals, the number of *corpora lutea* on each ovary was recorded and the ovaries were discarded after evaluation. The gravid uterus was examined and weighed. The viability of the fetuses were checked *in utero*. A viable fetus was defined as one which responds to stimuli. A non-viable fetus was defined as a term fetus which does not respond to stimuli *in utero* or is not breathing. The number and location of fetuses, early resorption(s), late resorption(s) and the total number of implantation sites and their uterine distribution were documented using the following procedure. All implantation sites, including resorptions, were numbered in consecutive fashion beginning with the left distal uterine horn, and similarly with the right uterine horn noting the position of the cervix. An early resorption was defined as one in which it was not grossly evident that organogenesis had occurred. A late resorption was defined as one in which it was grossly evident that organogenesis had occurred. A fetus with evident autolysis was considered a late resorption. Following the cesarean section examination, the carcass of each dam was discarded.

Uteri from females that appeared nongravid were opened and placed in 10% ammonium sulfide solution for at least 10 minutes for detection of possible implantation sites. If implantation sites were detected, ovaries were evaluated as previously mentioned.

The number of fetuses in each litter was recorded. Each fetus was weighed and individually identified noting litter, uterine placement and study number. Subsequently, a morphological examination was performed. A detailed examination of each fetus was conducted to include the eyes, palate, head shape and extremities. Any abnormal finding was recorded.

All fetuses were euthanized by an intraperitoneal injection of a 40% solution of sodium pentobarbital (≈ 0.4 ml/fetus). All fetuses were examined for visceral anomalies and sexed internally employing the Staples' fresh tissue dissection techniques including a mid-sagittal section between the eyes (Staples, 1974). All fetuses were then eviscerated, skinned, and stored in 95% ethyl alcohol. As directed by the Sponsor, the fetuses from the initial 25 mg base/kg/day group were retained in 95% ethyl alcohol. The remaining fetal carcasses from all other groups were macerated in a 2% potassium hydroxide solution, stained with Alizarin Red S, then cleared in 25% glycerin as recommended by Dawson, and then the skeletons were examined for alterations (Dawson, 1926). Skeletal preparations were stored in 99.5% glycerin/0.5% phenol.

3.4 Statistical Analyses:

Maternal body weights, weight gains, uterine weights, and fetal body weights were analyzed by one-way analysis of variance. If a significant F ratio was obtained ($p \leq 0.05$), Dunnett's test was used for pair-wise comparisons to the vehicle control group.

Fetal abnormalities were statistically analyzed in terms of the litter as the experimental unit. Abnormalities included malformations in addition to variations. The proportions of litters with abnormalities were compared using Fisher's exact test. Male to female fetal sex ratios were compared using the Chi-square test.

Maternal food consumption data, early and late resorptions, non-viable fetuses, viable fetuses, *corpora lutea* (C.L.), implantations, preimplantation loss*, postimplantation loss**, and total implantation loss*** were compared using the Kruskal-Wallis test. If a significant effect was seen ($p \leq 0.05$), the Mann-Whitney U test was used for pair-wise comparisons to the vehicle control group.

$$\text{*Preimplantation loss} = [(\# \text{ C.L.} - \# \text{ implantations})/\# \text{ C.L.}] \times 100$$

$$\text{**Postimplantation loss} = [(\# \text{ implantations} - \# \text{ live fetuses})/\# \text{ implantations}] \times 100$$

$$\text{***Total implantation} = [(\text{C.L.} - \# \text{ live fetuses})/\# \text{ C.L.}] \times 100$$

Cesarian-section and fetal morphological data from pregnant animals that did not survive to the scheduled terminal sacrifice (i.e., animals found dead, sacrificed moribund, aborted, or premature delivery) were not included in the statistical analyses. Cesarian-section data from all animals were used to determine the incidence of pregnancy.

In addition to the written report, summary data tables of parameters and variability were transmitted to the Sponsor on magnetic media (computer diskette) in "ASCII" form. The transcribed data on disk were no longer considered GLP compliant.

4. RESULTS

4.1 Dosage Formulation Analysis

The results of dosage formulation analyses are shown in Table 2. The Analytical Chemistry Report is in Appendix 1.

All dosage formulations in the initial study and retest of the high dose group were within 10% of their target concentrations prior to and after use with the exception of the postdosing analysis of the initial study 25 mg base/kg/day dose level (25 mg base/ml). That postdose analysis was only within 48% of target concentration. Because of the limited amount of remaining dosage formulation, a repeat analysis could not be conducted. It is unclear, however, if the problem was with the formulation or in the sampling procedure of the formulation prior to analysis as the concentration was within 10% of target prior to use and subsequent stability testing demonstrated that 25 mg base/ml is stable for at least 2 weeks (Appendix 1).

4.2 Mortality/Clinical Signs

The summary of clinical signs of toxicity are in Tables 3 and 3.1. Individual signs are in Appendix 2 and 2.1.

In the initial 25 mg base/kg/day group, two animals aborted on GD23 or 25 (Nos. 575 and 580, respectively), and one animal delivered prematurely on GD29 (No. 565). No other clinical signs were observed in any dose level. In the 25 mg base/kg/day retest group, one animal (No. 625) displayed lethargy (noted in unscheduled observations) and was sacrificed moribund on GD10. Another animal (No. 624) had labored breathing and was found dead on GD13. Due to these mortalities and also because of reductions in food consumption noted in most of the animals in this group, the dose was lowered to 16 mg base/kg/day on GD15 or 16 (the range of days reflects the study stagger start). Moribund sacrifice, mortality, and abortions persisted accompanied by reductions in food consumption. One animal (No. 639) was sacrificed moribund on GD17. On GD22, another animal (No. 637) was found dead following clinical observations of blood in the cage pan. On GD23 and 25, two animals aborted (Nos. 622 and 630, respectively). Another animal (No. 631) in the 25/16 mg base/kg/day group is considered to have aborted, but the exact gestational day is unknown. This rabbit displayed blood in the cage pan on GD22 and 24 and body weight loss (340 g) on GD24. At the scheduled necropsy, implantation sites but no resorptions or fetuses were noted in this animal. Based on the gross morphology of the implantation sites, clinical observations, and severe body weight loss, it is assumed that this animal aborted on or near GD24 and cannibalized the fetal and placental material. In the retest 25 mg base/kg/day group, one animal (No. 627) also had blood in the cage pan on GD27 but no other clinical findings. One abortion (animal No. 558) occurred in the 7 mg base/kg/day group. Based on the incidence of abortions in the 25 and 25/16 mg base/kg/day dose groups, this observation may be related to administration of WR238605 succinate. No other findings were noted in the 2 or 7 mg base/kg/day groups, the positive control group, or the two concurrent vehicle control groups.

Two incidental mortalities occurred in the initial 25 mg base/kg/day group. One animal (No. 570) was sacrificed moribund on GD12 due to a broken back. Another animal (No. 576) found dead on GD19 had necropsy findings consistent with misintubation.

4.3 Maternal Body Weights

The summaries of maternal body weights and weight gains are in Tables 4 and 4.1 and 5 and 5.1, respectively. Individual data are contained in Appendix 3.

Body weights were generally unaffected by treatment with the exception of a statistically significant reduction in body weight gain (weight loss) which occurred on GD9. This loss contributed to a slight, but insignificant reduction in total body weight gain.

In the retest 25/16 mg base/kg/day group, maternal body weights and/or body weight gains were periodically lower than the concurrent vehicle control from GD13 - 18, i.e., through the end of the dosing period. Statistically significant body weight losses (i.e., negative body weight gains) were noted on GD13, 15, and 17 and contributed to an insignificant reduction in total body weight gain. These body weight changes occurred in the majority of animals in the 25/16 mg base/kg/day group.

Administration of 2 or 7 mg base/kg/day of WR238605 Succinate, the positive control, or the concurrent vehicle control had no effect on body weight.

4.4 Food Consumption

The summaries of mean daily food consumption are in Tables 6 and 6.1. Individual food consumption data are contained in Appendix 4.

In the initial 25 mg base/kg/day group, significant reductions in food consumption were noted on GD15, 18, 24, and 29. Generally, these reductions were noted in animals that aborted or delivered prematurely. In the retest 25/16 mg base/kg/day group, significantly reduced food consumption was noted on GD12, 15, and 18, although biologically relevant reductions also occurred on GD10 and 29. The reductions in food consumption occurred in the majority of animals in the 25/16 mg base/kg/day group.

Food consumption was unaffected in the 2 or 7 mg base/kg/day groups, the positive control group, or in either concurrent vehicle control.

4.5 Cesarean-Section and Maternal Gross Observations

The summary of cesarean-section data is in Table 7. The Teratology Report is in Appendix 5.

In the initial study, the pregnancy rates were 75% in the low dose group, 80% in the mid and high dose groups, and 90% in the concurrent vehicle control and positive control groups. The pregnancy rate was 95% in the retest 25/16 mg base/kg/day and concurrent vehicle control groups. No biologically meaningful changes were observed in any of the reproductive indices in the WR238605 Succinate-treated groups in either the initial study or in the retest of the high dose.

In the positive control group, a statistically significant increase in the number of early resorptions was accompanied by a nonsignificant reduction in the number of viable fetuses as well as nonsignificant increases in the percentages of postimplantation loss and total loss/litter. These intrauterine losses resulted in a nonsignificant reduction in uterine weight.

4.6 Fetal Observations

The summary of fetal observation is in Table 7. The Teratology Report is in Appendix 5.

Administration of WR238605 Succinate did not affect fetal weight in any group. Fetuses in the 2 or 7 mg base/kg/day groups did not show any biologically meaningful increases in external, visceral, or skeletal malformations or variations. No meaningful alterations in external or visceral development occurred in fetuses in the initial 25 mg base/kg/day group. At the direction of the Sponsor, fetuses in the initial 25 mg base/kg/day group were not evaluated for skeletal anomalies. An incidental but significant decrease in the total numbers of litters with variations occurred in the initial 25 mg base/kg/day group. Fetuses in the retest 25 mg base/kg/day group were fully evaluated. There were no meaningful alterations in external, visceral, or skeletal development in this group.

Administration of retinol palmitate had no effect on fetal weight. Statistically significant increases in the incidence of external, skeletal, and visceral malformations were considered typical of retinol palmitate (e.g., cleft palate, micrognathia, microstomia). The incidence of two developmental variations (major blood vessel variations and distended ureters) was also significantly increased in the positive control group compared to the concurrent vehicle control.

5. DISCUSSION/CONCLUSION

This study evaluated the embryo/fetal toxicity and the teratogenic potential of WR238605 Succinate in time-mated New Zealand White (Pasteurella Free) female rabbits. Doses of 0, 2, 7, or 25 mg base/kg/day were administered by gavage to 20 rabbits/group during gestation days (GD) 6 - 18 (GD0 = day of observed mating). In addition, a positive control group of 20 rabbits was administered retinol palmitate, 300 mg/kg/day, on GD9 and 10 by gavage. Due to an apparent dosage formulation analysis problem, the high dose was retested at the Sponsor's request. Doses of 0 or 25 mg base/kg/day were administered by gavage to 20 rabbits/group during GD6 - 18. Due to mortality and reduced food consumption, the dose was lowered to 16 mg base/kg/day on gestation day 15 or 16 (the range of days reflects the study stagger start over two days). The results of the initial study and the retest of the high dose group are summarized in Table 1.

Maternal toxicity was seen primarily in the initial 25 mg base/kg/day group and in the retest 25/16 mg base/kg/day group. In the initial study, administration of 25 mg base/kg/day resulted in two abortions and one premature delivery. A significant loss in body weight on GD9 contributed to a slight, but insignificant reduction in total body weight gain. Significant reductions in food consumption were attributed to reductions which occurred primarily in the animals that aborted or delivered prematurely. Maternal toxicity was also observed in the retest 25/16 mg base/kg/day group as exemplified by mortality (2/20), moribund sacrifice (2/20), and abortion (3/20). Statistically significant decreases in body weight and food consumption were reflective of decreases noted in the majority of animals in this retest group. One rabbit at 7 mg base/kg/day aborted, but showed no other evidence of maternal toxicity. Based on the incidence of abortion in the 25 and 25/16 mg base/kg/day groups, this event may be related to administration of WR238605 Succinate.

There was no indication of embryotoxicity, fetotoxicity, or teratogenicity in any WR238605 Succinate-treated group. There were no alterations in any maternal reproductive indices, fetal weights or viability, or pre- and postimplantation parameters. External and visceral fetal evaluations did not reveal any effects of treatment. There were no meaningful alterations in skeletal

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development in fetuses in the 2 and 7 mg base/kg/day groups. At the direction of the Sponsor, fetuses in the initial 25 mg base/kg/day group were not evaluated for skeletal anomalies. Fetal skeletal evaluations conducted in the retest 25/16 mg base/kg/day group were comparable to the concurrent vehicle control. Based on these results, the maternal NOEL in this study was at or near 7 mg base/kg/day, and the fetal NOEL was 25 mg base/kg/day.

Neither maternal nor fetal effects were seen in the vehicle control animals. Fetotoxicity and teratogenicity were noted in the positive control group. Slight, nonstatistically significant reductions were noted in uterine weight and fetal viability. A statistically significant increase in the number of early resorptions was accompanied by a nonsignificant reduction in the number of viable fetuses as well as nonsignificant increases in the percent postimplantation loss and total loss/litter. Statistically significant increases in the incidence of external, skeletal, and visceral fetal malformations were considered typical of retinol palmitate (e.g., cleft palate, micrognathia, microstomia). In addition, a statistically significant increase was noted in major blood vessel variations and the incidence of distended ureter.

6. REFERENCES

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7. PERSONNEL

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Report preparation was assisted by Dr. Debra Kirchner, Ms. Soudabeh Soura and Mr. Mukesh Pitroda.

8. ARCHIVES

All raw data, documentation, specimens, test article reserves, and the final report are archived at the University of Illinois at Chicago, Toxicology Research Laboratory, Department of Pharmacology, 1940 W. Taylor St., Chicago, IL 60612.

Table 1

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

Summary of Toxic Responses

Dose Level (mg base/kg/day)	WR238605 Succinate (Initial Study)				Retinol Palmitate	WR238605 Succinate (Retest)	
	0	2	7	25	300 ^a	0	25/16 ^b
Number of Females Pregnant (Non-pregnant)	20 (2)	20 (5)	20 (4)	20 (4)	20(2)	20 (1)	20 (1)
Early Pregnancy Termination (Cause)	0	0	1(AB)	1(FD) ^c 1(MS) ^c 2(AB) 1(PD)	0	0	2 (FD) 2 (MS) 3 (AB)
Clinical Signs	-	NE	NE	NE	NE	-	1 (DA) 1 (LB) 3 (BCP)
Maternal Body Weight Gain	-	NE	NE	d	NE	-	↓
Food Consumption	-	NE	NE	↓	NE	-	↓
Uterine Weight	-	NE	NE	NE	↓	-	NE
Early Resorptions	-	NE	NE	NE	↑	-	NE
Postimplantation Loss	-	NE	NE	NE	↓	-	NE
Decrease in Fetal Body Weight (♂/♀)	-	NE/NE	NE/NE	NE/NE	NE/NE	-	NE/NE
Viable Fetuses	-	NE	NE	NE	↓	-	NE
Total Loss/Litter	-	NE	NE	NE	↑	-	NE
External Malformations	-	NE	NE	NE	↑	-	NE
Skeletal Malformations	-	NE	NE	d	↑	-	NE
Visceral Malformations	-	NE	NE	NE	↑	-	NE

CONCLUSIONS

This study evaluated the developmental toxicity of WR238605 Succinate in time-mated New Zealand White (Pasteurella Free) female rabbits. Doses were 0, 2, 7 and 25 mg base/kg/day administered by gavage during gestation days (GD) 6 - 18 (GD0 = day of observed mating). A positive control group was administered retinol palmitate, 300 mg/kg/day, on GD9 and 10 by gavage. Due to an apparent dosage formulation analysis problem, the high dose was retested at the Sponsor's request. Doses of 0 or 25 mg base/kg/day were administered by gavage during GD6 - 18. Due to mortality and reduced food consumption, the dose was lowered to 16 mg base/kg/day on GD15 - 16 (the range of days reflects the study stagger start over two days). Maternal toxicity was observed in the initial 25 mg base/kg/day and retest 25/16 mg base/kg/day groups. Abortion and premature delivery occurred in the initial study concomitant with minimally reduced body weight and decreases in food consumption. In the retest, mortality or moribund sacrifice preceded by labored breathing or decreased activity, respectively, was seen at 25 mg base/kg/day; while abortion preceded by blood in the cage pan occurred at the lowered dose of 16 mg base/kg/day. Decreased body weight and/or reduced weight gain and severe reductions in food consumption were noted in the majority of animals in the retest group. In the 7 mg base/kg/day group, one animal aborted; however, there were no alterations in body weight or food consumption. Due to the increased incidence in the 25 and 25/16 mg base/kg/day groups, the abortion in the 7 mg base/kg/day group may be related to administration of WR238605 Succinate. There was no maternal toxicity at 2 mg base/kg/day. Neither embryotoxicity, fetotoxicity, nor teratogenicity was evident at any dose level in the initial or retest WR238605 Succinate-treated groups. Based on these data, the maternal NOEL was at or near 7 mg base/kg/day and the fetal NOEL was 25 mg base/kg/day. In the positive control group, embryotoxicity, fetotoxicity and overt teratogenicity were considered typical of exposure to retinol palmitate.

NE = No effect
FD = Found dead
MS = Moribund sacrifice
AB = Abortion
PD = Premature delivery
DA = Decreased Activity
LB = Labored Breathing
BCP = Blood in Cage Pan

^amg/kg/day on GD9 and GD10

^bDose was lowered from 25 to 16 mg base/kg/day on GD 15 or 16 (range of days reflects study stagger-start over two days)

^cNot related to treatment

^dSkeletal evaluations were not conducted in the initial 25 mg base/kg/day group

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Table 2

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

Dosage Formulation Analysis* - Initial Study

Target Concentration (mg base/ml)	Predose Week 1	% Target	Target Concentration (mg base/ml)	Postdose Week 2	% Target
0	0	-	0	0	-
2	1.98 ± 0.01	99.0	2	2.03 ± 0.02	101.5
7	6.91 ± 0.01	98.7	7	7.95 ± 0.03	113.6
25	25.43 ± 0.03	101.7	25	12.05 ± 0.06	48.2

Dosage Formulation Analysis* - Retest

Target Concentration (mg base/ml)	Predose Week 1	% Target	Target Concentration (mg base/ml)	Postdose Week 1	% Target
0	0	-	0	0	-
25	25.56 ± 0.10	102.2	25	26.60 ± 0.38	106.4
Target Concentration (mg base/ml)	Predose Week 2	% Target	Target Concentration (mg base/ml)	Postdose Mid-Week 2	% Target
0	0	-	-	-	-
25	23.98 ± 0.03	95.9	25	25.49 ± 0.51	102.0
Target Concentration (mg base/ml)	Predose Mid-Week 2	% Target	Target Concentration (mg base/ml)	Postdose Week 2	% Target
-	-	-	0	0	-
16	16.50 ± 0.25	103.1	16	16.20 ± 0.05	101.3

*Mean ± standard deviation for triplicate runs.

Table 3

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

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 SUMMARY OF CLINICAL SIGNS

STUDY: 156

SEX: FEMALE

	DOSE: (mg base/kg/day)					300 (mg/kg/day) ^a
	0	2	7	25		
GROUP:	1-F	2-F	3-F	4-F	5-F	
Scheduled Sacrifice	20	20	19	15	20	
Animal Found Dead	0	0	0	1	0	
Sacrificed Moribund	0	0	0	1	0	
Aborted/Sacrificed	0	0	1	2	0	
Premature Delivery/Sacrifice	0	0	0	1	0	
Total Number of Animals	20	20	20	20	20	

^aRetinol Palmitate given on GD9 and GD10 only

Table 3.1

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

SUMMARY OF CLINICAL SIGNS

STUDY: 156A

SEX: FEMALE

DOSE: (mg base/kg/day)	0	25/16 ^a
GROUP:	1-F	2-F

Scheduled Sacrifice	20	14
Animal Found Dead	0	2
Sacrificed Moribund	0	2
Aborted/Sacrificed	0	2
Decreased Activity	0	1
Labored Breathing	0	1
Blood found in cage pan	0	3
Total Number of Animals	20	20

^aThe high dose was reduced from 25 mg base/kg/day to 16 mg base/kg/day on GD15 - GD16 (the range of days reflects study stagger-start over 2 days)

Table 4
 DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

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SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 156

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day)	GROUP:				
		0 1-F	2 2-F	7 3-F	25 4-F	300 (mg/kg/day) ^a 5-F
DAY 0	MEAN	3.26	3.25	3.23	3.20	3.21
	S.D.	0.327	0.320	0.376	0.354	0.301
	N	18	15	16	16	18
DAY 5	MEAN	3.13	3.16	3.09	3.11	3.13
	S.D.	0.299	0.296	0.297	0.308	0.309
	N	18	15	16	16	18
DAY 6	MEAN	3.14	3.14	3.07	3.09	3.10
	S.D.	0.333	0.290	0.290	0.330	0.289
	N	18	15	16	16	17
DAY 7	MEAN	3.15	3.18	3.10	3.08	3.12
	S.D.	0.351	0.288	0.302	0.339	0.296
	N	18	15	16	16	17
DAY 8	MEAN	3.17	3.20	3.11	3.11	3.15
	S.D.	0.328	0.292	0.292	0.348	0.297
	N	18	15	16	16	18
DAY 9	MEAN	3.19	3.20	3.12	3.07	3.15
	S.D.	0.320	0.296	0.299	0.326	0.294
	N	18	15	16	16	18
DAY 10	MEAN	3.21	3.22	3.13	3.10	3.14
	S.D.	0.315	0.295	0.300	0.316	0.297
	N	18	15	16	16	18
DAY 11	MEAN	3.23	3.24	3.16	3.12	3.15
	S.D.	0.315	0.312	0.305	0.321	0.292
	N	18	15	16	16	18
DAY 12	MEAN	3.25	3.26	3.18	3.16	3.16
	S.D.	0.303	0.299	0.297	0.319	0.293
	N	18	15	16	15	18
DAY 13	MEAN	3.26	3.28	3.21	3.20	3.20
	S.D.	0.313	0.311	0.304	0.322	0.288
	N	18	15	16	15	18

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aRetinol Palmitate given on GD9 and GD10 only

Table 4 (contd.)
 DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 156

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0	2	7	25	300 (mg/kg/day) ^a
		1-F	2-F	3-F	4-F	5-F
DAY 14	MEAN	3.30	3.30	3.26	3.22	3.24
	S.D.	0.304	0.315	0.297	0.321	0.297
	N	18	15	16	15	18
DAY 15	MEAN	3.33	3.31	3.25	3.24	3.26
	S.D.	0.293	0.340	0.298	0.327	0.290
	N	18	15	16	15	18
DAY 16	MEAN	3.34	3.36	3.29	3.26	3.27
	S.D.	0.298	0.346	0.335	0.338	0.308
	N	18	15	16	15	18
DAY 17	MEAN	3.36	3.35	3.29	3.25	3.27
	S.D.	0.305	0.325	0.325	0.328	0.306
	N	18	15	16	15	18
DAY 18	MEAN	3.36	3.32	3.28	3.24	3.26
	S.D.	0.302	0.314	0.308	0.323	0.292
	N	18	15	16	15	18
DAY 24	MEAN	3.44	3.45	3.39	3.28	3.35
	S.D.	0.281	0.296	0.279	0.323	0.303
	N	18	15	16	13	18
DAY 29	MEAN	3.50	3.48	3.39	3.29	3.41
	S.D.	0.304	0.300	0.283	0.412	0.304
	N	18	15	15	12	18

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aRetinol Palmitate given on GD9 and GD10 only

Table 4.1

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 156A

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day)	GROUP:	
		0	25/16 ^a
		1-F	2-F
DAY 0	MEAN	3.80	3.68
	S.D.	0.319	0.266
	N	19	19
DAY 5	MEAN	3.60	3.57
	S.D.	0.352	0.329
	N	19	19
DAY 6	MEAN	3.53	3.51
	S.D.	0.355	0.310
	N	19	19
DAY 7	MEAN	3.54	3.50
	S.D.	0.339	0.320
	N	19	19
DAY 8	MEAN	3.55	3.48
	S.D.	0.344	0.299
	N	19	19
DAY 9	MEAN	3.55	3.48
	S.D.	0.343	0.302
	N	19	19
DAY 10	MEAN	3.55	3.48
	S.D.	0.342	0.304
	N	19	19
DAY 11	MEAN	3.56	3.47
	S.D.	0.341	0.317
	N	19	18
DAY 12	MEAN	3.59	3.47
	S.D.	0.341	0.323
	N	19	18
DAY 13	MEAN	3.63	3.48
	S.D.	0.367	0.333
	N	19	17

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aThe high dose was reduced from 25 mg base/kg/day to 16 mg base/kg/day on GD15 - GD16 (the range of days reflects study stagger-start over 2 days)

Table 4.1 (contd.)
 DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 156A

SEX: FEMALE

PERIOD		DOSE: (mg base/kg/day) 0		25/16 ^a
		GROUP: 1-F		2-F
DAY 14	MEAN	3.65	3.47	
	S.D.	0.370	0.351	
	N	19	17	
DAY 15	MEAN	3.69	3.46	
	S.D.	0.360	0.362	
	N	19	17	
DAY 16	MEAN	3.70	3.43*	
	S.D.	0.384	0.369	
	N	19	17	
DAY 17	MEAN	3.70	3.38*	
	S.D.	0.380	0.365	
	N	19	16	
DAY 18	MEAN	3.72	3.38*	
	S.D.	0.394	0.374	
	N	19	16	
DAY 24	MEAN	3.76	3.55	
	S.D.	0.363	0.395	
	N	19	14	
DAY 29	MEAN	3.83	3.66	
	S.D.	0.386	0.392	
	N	19	13	

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aThe high dose was reduced from 25 mg base/kg/day to 16 mg base/kg/day on GD15 - GD16 (the range of days reflects study stagger-start over 2 days)

Table 5
 DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 156

SEX: FEMALE

PERIOD ^a	DOSE: (mg base/kg/day)	GROUP:				
		0 1-F	2 2-F	7 3-F	25 4-F	300 (mg/kg/day) ^c 5-F
DAY 7 ^b	MEAN	0.01	0.05	0.03	0.00	0.02
	S.D.	0.068	0.057	0.052	0.046	0.059
	N	18	15	16	16	17
DAY 8	MEAN	0.02	0.02	0.01	0.02	0.03
	S.D.	0.070	0.049	0.049	0.046	0.047
	N	18	15	16	16	17
DAY 9	MEAN	0.02	0.01	0.01	-0.04*	0.00
	S.D.	0.051	0.036	0.049	0.056	0.039
	N	18	15	16	16	18
DAY 10	MEAN	0.02	0.01	0.01	0.03	-0.01
	S.D.	0.054	0.025	0.037	0.027	0.043
	N	18	15	16	16	18
DAY 11	MEAN	0.01	0.02	0.03	0.02	0.01
	S.D.	0.049	0.046	0.051	0.036	0.047
	N	18	15	16	16	18
DAY 12	MEAN	0.02	0.02	0.02	0.02	0.01
	S.D.	0.042	0.047	0.056	0.045	0.037
	N	18	15	16	15	18
DAY 13	MEAN	0.02	0.02	0.03	0.04	0.04
	S.D.	0.039	0.047	0.044	0.047	0.039
	N	18	15	16	15	18
DAY 14	MEAN	0.04	0.02	0.05	0.02	0.04
	S.D.	0.030	0.028	0.036	0.043	0.021
	N	18	15	16	15	18
DAY 15	MEAN	0.03	0.01	-0.01	0.02	0.02
	S.D.	0.044	0.101	0.033	0.041	0.031
	N	18	15	16	15	18
DAY 16	MEAN	0.02	0.05	0.03	0.02	0.01
	S.D.	0.051	0.108	0.064	0.033	0.034
	N	18	15	16	15	18

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^a Successive periods

^b Baseline is day 6

^c Retinol Palmitate given on GD9 and GD10 only

Table 5 (contd.)
 DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 156

SEX: FEMALE

PERIOD ^a	DOSE: (mg base/kg/day) GROUP:	2		7	25	300 (mg/kg/day) ^b
		1-F	2-F	3-F	4-F	5-F
DAY 17	MEAN	0.02	-0.01	0.00	-0.01	0.00
	S.D.	0.055	0.057	0.031	0.055	0.023
	N	18	15	16	15	18
DAY 18	MEAN	-0.01	-0.03	0.00	-0.02	0.00
	S.D.	0.037	0.103	0.047	0.054	0.040
	N	18	15	16	15	18
DAY 24	MEAN	0.08	0.13	0.11	0.05	0.08
	S.D.	0.064	0.095	0.059	0.124	0.047
	N	18	15	16	13	18
DAY 29	MEAN	0.06	0.03	0.03	0.00	0.06
	S.D.	0.081	0.047	0.061	0.203	0.060
	N	18	15	15	12	18
TOTAL GAIN	MEAN	0.36	0.34	0.33	0.23	0.30
	S.D.	0.111	0.102	0.073	0.232	0.131
	N	18	15	15	12	17

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aSuccessive periods

^bRetinol Palmitate given on GD9 and GD10 only

Table 5.1
 DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 156A

SEX: FEMALE

PERIOD^a DOSE: (mg base/kg/day) 0 25/16^c
 GROUP: 1-F 2-F

DAY	MEAN	0	25/16 ^c
DAY 7 ^b	MEAN	0.01	-0.01
	S.D.	0.061	0.035
	N	19	19
DAY 8	MEAN	0.01	-0.02
	S.D.	0.053	0.048
	N	19	19
DAY 9	MEAN	0.01	0.00
	S.D.	0.034	0.052
	N	19	19
DAY 10	MEAN	0.00	0.00
	S.D.	0.037	0.054
	N	19	19
DAY 11	MEAN	0.02	-0.01
	S.D.	0.048	0.036
	N	19	18
DAY 12	MEAN	0.02	0.01
	S.D.	0.046	0.058
	N	19	18
DAY 13	MEAN	0.04	-0.01*
	S.D.	0.038	0.055
	N	19	17
DAY 14	MEAN	0.02	-0.01
	S.D.	0.039	0.079
	N	19	17
DAY 15	MEAN	0.05	-0.01*
	S.D.	0.056	0.058
	N	19	17
DAY 16	MEAN	0.01	-0.03
	S.D.	0.047	0.054
	N	19	17

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aSuccessive periods

^bBaseline is day 6

^cThe high dose was reduced from 25 mg base/kg/day to 16 mg base/kg/day on GD15 - GD16 (the range of days reflects study stagger-start over 2 days)

Table 5.1 (contd.)
 DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 156A

SEX: FEMALE

PERIOD ^a	DOSE: (mg base/kg/day)	GROUP:	
		0	25/16 ^b
		1-F	2-F
DAY 17	MEAN	0.00	-0.03*
	S.D.	0.034	0.039
	N	19	16
DAY 18	MEAN	0.01	0.01
	S.D.	0.034	0.056
	N	19	16
DAY 24	MEAN	0.04	0.11
	S.D.	0.049	0.159
	N	19	14
DAY 29	MEAN	0.07	0.07
	S.D.	0.041	0.061
	N	19	13
TOTAL GAIN	MEAN	0.30	0.18
	S.D.	0.115	0.315
	N	19	13

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^a Successive periods

^b The high dose was reduced from 25 mg base/kg/day to 16 mg base/kg/day on GD15 - GD16 (the range of days reflects study stagger-start over 2 days)

Table 6

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

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SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 156

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day) 0 GROUP:	2		7	25	300 (mg/kg/day) ^a
		1-F	2-F	3-F	4-F	5-F
DAY 8	INTAKE (g)	130	130	130	130	130
	S.D.	0.0	0.0	0.0	0.0	0.0
	N	18	15	15	16	17
DAY 10	INTAKE (g)	130	130	129	130	130
	S.D.	0.0	0.0	2.5	0.0	0.0
	N	18	15	16	16	18
DAY 12	INTAKE (g)	130	126	130	130	130
	S.D.	0.0	14.2	0.0	0.0	0.0
	N	18	15	16	15	18
DAY 15	INTAKE (g)	130	130	129	118*	124
	S.D.	0.0	0.0	5.3	34.9	23.5
	N	18	15	16	15	18
DAY 18	INTAKE (g)	130	130	130	108*	130
	S.D.	0.0	0.0	0.0	45.7	0.0
	N	18	15	16	15	18
DAY 24	INTAKE (g)	130	130	130	119*	130
	S.D.	0.0	0.0	0.0	24.7	0.0
	N	18	15	16	13	18
DAY 29	INTAKE (g)	130	127	130	116*	123
	S.D.	0.0	11.6	0.0	35.3	21.5
	N	18	15	15	12	18

* P less than .05

Statistical Analysis by Kruskal-Wallis test and Mann-Whitney U test

^aRetinol Palmitate given on GD9 and GD10 only

Table 6.1

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 156A

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day)	25/16 ^a	
		GROUP: 0 1-F	2-F
DAY 8	INTAKE (g)	130	129
	S.D.	0.0	3.7
	N	19	19
DAY 10	INTAKE (g)	127	117
	S.D.	11.5	33.1
	N	19	19
DAY 12	INTAKE (g)	129	107*
	S.D.	4.4	47.0
	N	19	18
DAY 15	INTAKE (g)	127	69*
	S.D.	7.4	61.6
	N	19	17
DAY 18	INTAKE (g)	129	68*
	S.D.	5.7	61.0
	N	19	16
DAY 24	INTAKE (g)	129	115
	S.D.	3.0	35.5
	N	19	14
DAY 29	INTAKE (g)	128	120
	S.D.	8.9	36.1
	N	19	13

* P less than .05 Statistical Analysis by Kruskal-Wallis test and Mann-Whitney U test

^aThe high dose was reduced from 25 mg base/kg/day to 16 mg base/kg/day on GD15 - GD16 (the range of days reflects study stagger-start over 2 days)

Table 7
 DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS
 Summary of Cesarean-Section Data and Fetal Evaluations

	WR238605 Succinate (Initial Study)				Retinol Palmitate	WR238605 Succinate (Retest)	
	0	2	7	25		0	25/16 ^b
Dose Level (mg base/kg/day)	0	2	7	25	300 ^a	0	25/16 ^b
Females Pregnant/On Study	18/20	15/20	16/20	16/20	18/20	19/20	19/20
Early Pregnancy Termination/Term Litters	0/18	0/15	1/15	5/11	0/18 ^a	0/19	7/12
Uterine Weight (g)	419.87 ± 93.59	390.14 ± 98.68	384.83 ± 64.81	413.08 ± 113.41	345.68 ± 98.58	448.58 ± 111.11	477.93 ± 80.05
Early Resorptions (No.)	0.3 ± 0.6	0.1 ± 0.4	0.4 ± 0.7	0.4 ± 0.5	1.4 ± 0.5 ^d	0.2 ± 0.4	0.4 ± 0.8
Viable Fetuses (No.)	7.8 ± 1.8	8.1 ± 2.5	7.4 ± 1.2	7.8 ± 1.6	5.7 ± 2.7	8.1 ± 2.5	9.5 ± 1.7
Postimplantation loss (%)	6.0 ± 8.2	1.7 ± 4.5	6.1 ± 10.1	7.5 ± 6.1	22.9 ± 30.9	6.3 ± 7.3	4.2 ± 7.8
Total Implantation Loss (%)	11.8 ± 12.5	12.5 ± 17.2	13.8 ± 15.4	12.3 ± 9.7	28.8 ± 30.3	17.2 ± 19.0	7.8 ± 10.1
Fetal Body Weight (g) ^e	39.02 ± 5.97	35.84 ± 4.19	36.72 ± 4.34	36.23 ± 3.79	41.92 ± 5.62	39.42 ± 6.24	35.80 ± 4.89
- Males							
- Females	38.74 ± 5.76	35.47 ± 5.71	37.60 ± 6.70	36.44 ± 5.97	39.10 ± 4.53	38.49 ± 4.91	35.00 ± 4.51
Litters with External Malformations (%)	0 (0)	0 (0)	0 (0)	0 (0)	13 (72.2) ^f	0 (0)	0 (0)
Litters with Skeletal Malformations (%)	2 (11.1)	4 (26.6)	5 (31.3)	8	15 (83.3) ^f	2 (10.5)	2 (10.5)
Litters with Visceral Malformations (%)	0 (0)	1 (6.66)	0 (0)	0 (0)	9 (50.0) ^f	2 (10.5)	0 (0)

^amg/kg/day on GD9 and GD10

^bDose lowered from 25 to 16 mg base/kg/day on GD15 or 16 (the range of days reflects study stagger start over two days)

^cOf 18 term litters, 17 litters were examined because 1 litter had 100% resorptions

^dStatistically significant from vehicle control group using Kruskal-Wallis/Mann-Whitney U Test (p ≤ 0.05)

^eData indicate mean of the total litter means

^fStatistically significant from vehicle control group using the Fisher's Exact Test (p ≤ 0.05)

^gSkeletal evaluations were not conducted in the initial 25 mg base/kg/day group

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APPENDIX 1
Analytical Chemistry Report

Part I: Identity, Purity and Stability Study of WR238605**Objective**

The objective of this study was to confirm the identity, and establish the purity and stability of WR238605.

Identification**GC-MS System**

Gas Chromatograph: Hewlett-Packard Model 5890 Series II

Mass Selective Detector: Hewlett-Packard Model 5970

Analytical Column: 30 m x 0.25 mm ID, DB-1 with a 3 micron film thickness.

GC Parameters: Injector temp. 250°C, oven temp. 70°C initial, 270°C final, 15°C/minute ramp, carrier gas - helium, flow rate 2 ml/minute, split ratio 10:1

Procedure

Subject sample (WR238605 succinate) was submitted by the Toxicology Research Laboratory. The sample was dissolved in hexane:ethanol (4:1) to a concentration of 0.8 µg base/ml and a 2 µl aliquot was injected on the column. The MSD scanned from 40 amu to 475 amu at a rate of 1 scan per second.

Results - GC-MS

The mass spectrum indicates a molecular ion m/e 463 (M⁺ free base) and m/e 405 [M⁺ free base minus (CH₂)₃ NH₂]. This pattern is consistent with the structural formula and corresponds to the finding by SRI International (see SRI International Report No. 469, May 9, 1994).

The mass spectrum of the WR238605 sample was previously reported (see Analytical Chemistry Report of UIC/TRL Study No. 097 and Study No. 098 from August 19, 1993) and it is shown in Figure 1.

Purity**Experimental**

The subject sample (WR238605 succinate) was supplied by the Toxicology Research Laboratory and stored at 4°C ± 2°C when it was not being analyzed.

Description

A fine powder having a yellow cast and no obvious odor.

Spectrum

An ultraviolet spectrum (Figure 2) recorded on a Spectra Physics multiwavelength detector interfaced with an IBM Personal Data System 2 was obtained from a 1.2 mg base/ml solution of WR238605 prepared in mobile phase. The sample was found to absorb at 218 and 268 nm.

HPLC System

Solvent Delivery System:	Perkin-Elmer Series 3B Pump
Injector:	Rheodyne 7125 with 20 μ l sample loop
Analytical Column:	Bondclone 10 μ C ₁₈ , 300 mm x 3.9 mm (Phenomenex)
Detector:	Kratos, Spectroflow 773 UV, 268 nm
Integrator:	Perkin-Elmer, LCI-100
Mobile Phase:	9 ml of 85% o-phosphoric acid and 6.8 g of sodium acetate per liter of a mixture of methanol:water (75:25, v/v), flow 1.5 ml/minute

Procedure

Six solutions of WR238605 were prepared as follows. Twenty five mg of WR238605 succinate sample was weighed into a 25 ml volumetric flask. The sample was dissolved in and the volume brought to mark with mobile phase. A 20 μ l aliquot of each solution was immediately chromatographed at 268 nm.

Calculation of Results

Quantitations were based on the assumption of equal detector response per unit weight of all UV-absorbing components. Areas of WR238605 and other detectable components in the subject sample chromatograms were employed in the following equation to calculate the percentage of WR238605 present in the sample:

$$\% \text{PURITY} = (\text{area of WR238605} / \text{total area}) \times 100$$

D R A F T

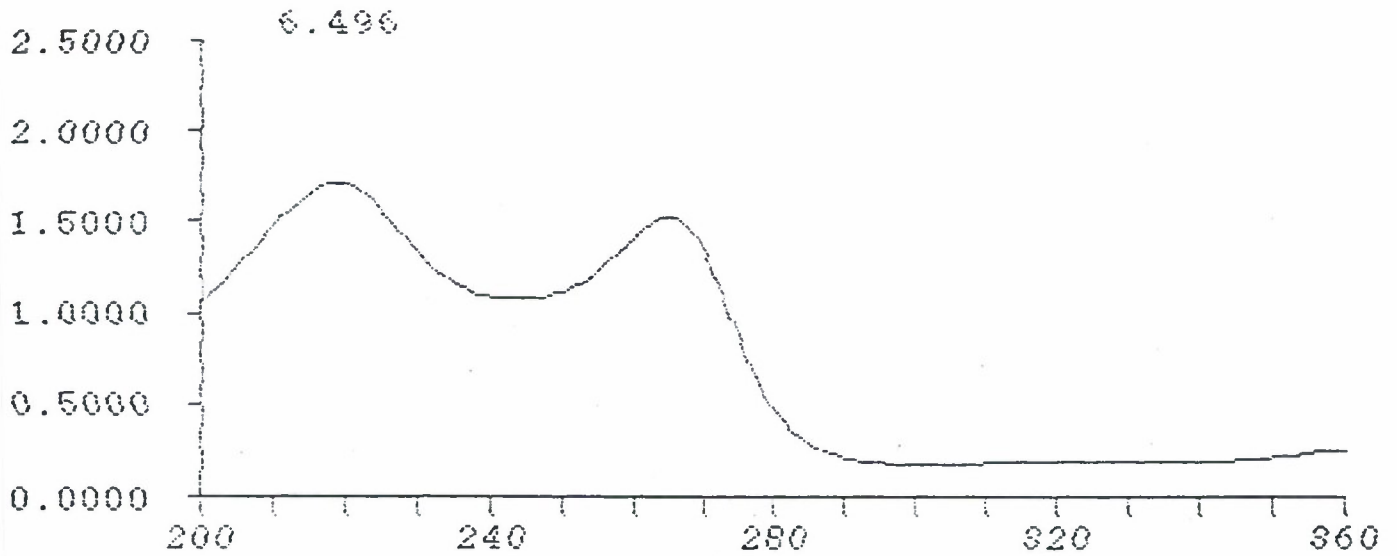
Results

Typical chromatograms are shown in Figure 3. The subject samples were found to contain less than 1% of one UV-absorbing impurity (268 nm). Percent purity of initial WR238605 sample was found to be 99.94%, standard deviation - 0.03%, terminal 99.52% \pm 0.21%. The assay results are presented in Tables 1 and 2.

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FIGURE 2

ULTRAVIOLET SPECTRUM OF WR238605

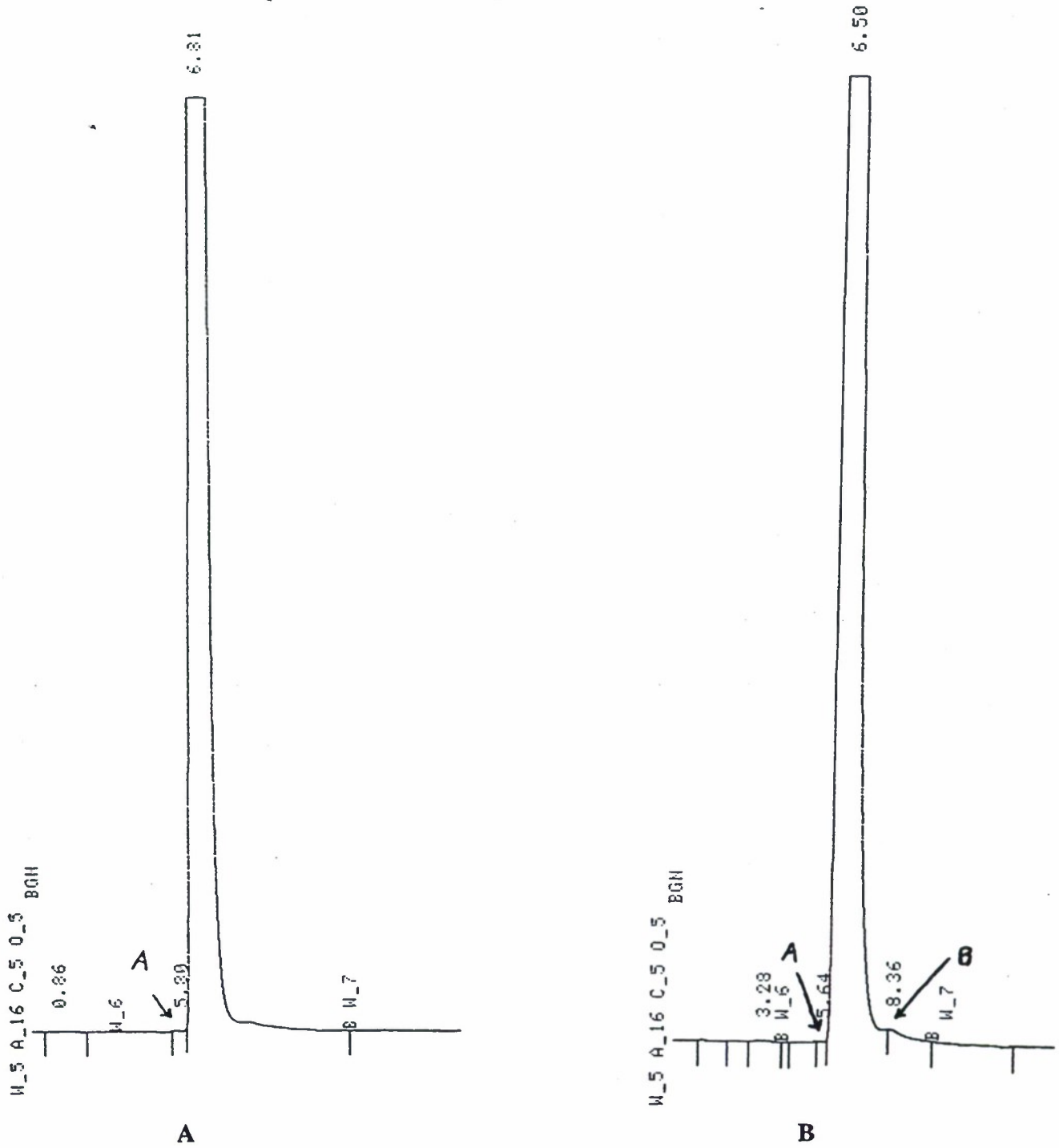


Spectra Display: \FOCUS\WR238X.BPF

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FIGURE 3

CHROMATOGRAMS OF WR238605 SAMPLE, CONC. 0.80 MG BASE/ML, 268 NM,
A - INITIAL SAMPLE, B - TERMINAL SAMPLE



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Table 1
Purity Data for WR238605
Initial Sample

Solutions

Peak Identity	1	2	3	4	5	6
A	2538	3016	3422	2779	1450	2402
WR238605	20379994	20424860	20440788	20542162	20364232	20464028
Total Area	20398037	20437514	20460042	20547597	20369243	20467969
% Purity	99.91	99.94	99.90	99.97	99.97	99.98

% Purity - 99.94 ± 0.03

Table 2

Purity Data for WR238605
Terminal Sample

Solutions

Peak Identity	1	2	3	4	5	6
A	5571	1	1743	2792	2890	-
B	81818	111201	108637	133756	97545	-
WR238605	21209642	21198802	21123542	21199894	21095026	21150796
Total Area	21312265	21326153	21243192	21336441	21204674	21164619
% Purity	99.52	99.40	99.44	99.36	99.48	99.93

1 - peak not integrated

% Purity - 99.52 ± 0.21

Part II: Stability and Homogeneity Study of WR238605 in 1% Methylcellulose/0.2% Tween 80

Introduction

One suspension of WR238605 (25 mg base/ml target) in 1% methylcellulose/0.2% Tween 80 was submitted by the Toxicology Research Laboratory for a stability and homogeneity study. The suspension was stored at 4°C (\pm 2°C) and sample aliquots were analyzed over an eight day period. Homogeneity was shown by comparing the mean (\pm S.D.) sample concentration at three levels.

Analytical Method

The suspension sample was analyzed by high performance liquid chromatography by a previously described analytical method (see Analytical Chemistry Report in UIC/TRL Study No. 098 from August 19, 1993, Part I).

Sample Preparation

A suspension of WR238605 was submitted by the Toxicology Research Laboratory and stored under refrigeration. It was allowed to warm to room temperature and mixed prior to diluting. Three aliquots (1 ml) were withdrawn from the suspension using a 1 cc syringe and transferred to three 25 ml volumetric flasks. Each 1 ml aliquot was withdrawn from a different level within the suspension analyzed (top, middle and bottom third). The content of each volumetric flask was thoroughly mixed and diluted to mark with mobile phase. A 1 ml aliquot from each volumetric flask was transferred to three individual 25 ml volumetric flasks and diluted to mark with the mobile phase. The final dilution was 1:625.

Three 1 ml aliquots were diluted, as previously described and analyzed immediately to determine baseline level of WR238605 (one from the top, one from the middle and one from the bottom third). Subsequent analyses were performed 4 and 8 days later.

Calculations

A standard curve was run at the beginning of each day assay. Controls and samples were then randomly assayed. The standard curve was reanalyzed following all samples and controls. Final concentrations for controls and samples were determined using a composite standard curve. The composite standard curve was determined by linear least squared regression analysis of the peak areas for WR238605 as a function of concentration. Data sets from both standard curves (beginning and end of each days assay run) were used in developing the composite standard curve.

WR238605 concentrations (mg base/ml) for controls and samples were determined using the following equation:

$$\text{WR238605 conc.} = (Y-B)/M \times (\text{d.f.}/1000)$$

- Y - peak area
B - Y-intercept from regression analysis of composite standard curve
M - slope from regression analysis of composite standard curve
d.f. - dilution factor

Data Analysis

The stability of WR238605 in 1% methylcellulose/0.2% Tween 80, stored at 4°C, was assessed by examining the percentage change from baseline concentration at each time interval. A change from the baseline concentration of greater than 10% was considered to represent a significant loss of potency.

Homogeneity was shown by comparing the mean (\pm S.D.) sample concentration at three levels, within a single suspension, from which the dilution aliquots were taken.

Results

The results of the stability testing of WR238605 in 1% methylcellulose/0.2% Tween 80 are summarized in Table 3 and Figure 4. There was no loss of potency greater than 10% in the WR238605 suspension at 4 and 8 days after preparation (day 0).

For homogeneity testing, three samples were drawn after mixing from each of the different levels (top, middle and bottom third of the suspension). Table 4 shows the mean (\pm S.D.) concentrations of WR238605 in samples drawn from the top, middle and bottom third of the suspensions in each stability sample. These results demonstrate the suspension to be homogenous.

Table 3
Stability of WR238605 Suspension
(storage at 4°C)

	Time (days)		
	0	4	8
Mean WR238605 Conc. [mg base/ml]	26.99	26.42	26.53
Standard Deviation	0.23	0.30	0.38
Percentage of Baseline Conc.	100	97.89	98.30

FIGURE 4

Stability of WR238605 at 4°C

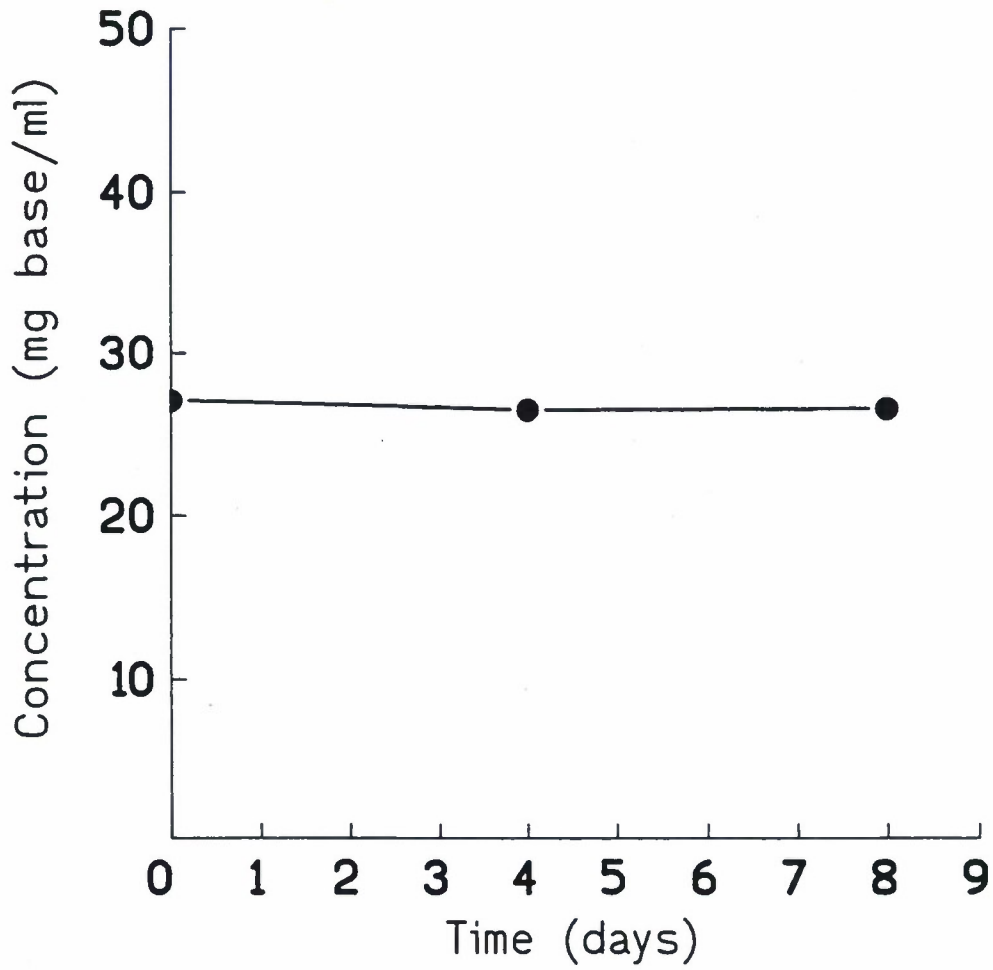


Table 4

WR238605 Concentrations (mg base/ml) in Samples Drawn From The Upper, Middle and Bottom Thirds of Stability Suspension Stored at 4°C

TOP-THIRD (mg base/ml \pm S.D.)	26.41 \pm 0.32
MIDDLE-THIRD (mg base/ml \pm S.D.)	26.66 \pm 0.46
BOTTOM-THIRD (mg base/ml \pm S.D.)	26.86 \pm 0.31

Part III: Dosing Formulations Analysis of WR238605 in 1% Methylcellulose/0.2% Tween 80

Introduction

Samples from Study No. 156 were submitted by the Toxicology Research Laboratory to the Drug Disposition Research Laboratory for the quantitation of WR238605 in dosing formulations. Samples were received on January 6, 1995, January 23, 1995, July 14, 1995, July 21, 1995, July 25, 1995 and July 28, 1995. All samples submitted were analyzed by high performance liquid chromatography by a previously described analytical method (see report UIC/TRL Study No. 098 from August 19, 1993, Part I).

Results

Results of dosing formulations for Study No. 156 are found in Table 5. The three dosage formulations used in the initial study conducted in January 1995 were within 10% of their target concentrations prior to dosing. At the end of the dosing period, the high dose level formulation was only about 50% of its target value. The low dose level formulation was acceptable, however a slight increase of about 13.6% over target was noted in the mid dose formulation.

In the repeat study, all dosage formulations were within 10% of their target concentrations before and after use.

Table 5

Results of Dosing Formulations Analysis for Study No. 156

Sample ID	Target Concentration (mg base/ml)	Mean Concentration ± S.D. (mg base/ml)	
		Jan. 6, 1995	Jan. 23, 1995
WHITE	0	0	0
YELLOW	2.0	1.9801 ± 0.0099	2.0301 ± 0.0167
ORANGE	7.0	6.9056 ± 0.0136	7.9534 ± 0.0333
GREEN	25.0	25.4255 ± 0.0341	12.0507 ± 0.0589

July 14, 1995 Week 1 (Predose)

Sample ID	Target Concentration (mg base/ml)	Mean Concentration ± S.D. (mg base/ml)
WHITE	0	0
RED	25.0	25.5636 ± 0.0970

July 21, 1995

Sample ID	Target Concentration (mg base/ml)	Mean Concentration ± S.D. (mg base/ml)	
		Week 1 (Postdose)	Week 2 (Predose)
WHITE	0	0	0
RED	25.0	26.5989 ± 0.3786	23.9835 ± 0.0280

Sample ID	Target Concentration (mg base/ml)	Mean Concentration ± S.D. (mg base/ml)	
		Mid week 2 ^a	Week 2 (Postdose) ^b
WHITE	0	NA	0
RED	25.0	25.4850 ± 0.5078 ^c	NA
LIGHT RED	16.0	16.5026 ± 0.2511 ^d	16.1989 ± 0.0464

see next page

- a - July 25, 1995
- b - July 28, 1995
- c - Postdose
- d - Predose

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APPENDIX 2

Individual Maternal Clinical Signs

Initial Study: 2-2 through 2-14
Retest: 2.1-1 through 2.1-7

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

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INDIVIDUAL CLINICAL SIGNS

STUDY: 156
DAY 6-DAY 29

GROUP: 1-F
DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
501	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
502	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
503	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
504	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
505	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
506	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
507	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
508	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
509	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
510	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
511	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
512	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
513	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 156
DAY 6-DAY 29

GROUP: 1-F
DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
514	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
515	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
516	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
517	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
518	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
519	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
520	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 156
DAY 6-DAY 29

GROUP: 2-F
DOSE: 2 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
521	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
522	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
523	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
524	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
525	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
526	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
527	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
528	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
529	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
530	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
531	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
532	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
533	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 156
DAY 6-DAY 29

GROUP: 2-F
DOSE: 2 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
534	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
535	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
536	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
537	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
538	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
539	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
540	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 156
 DAY 6-DAY 29

GROUP: 3-F
 DOSE: 7 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
541	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
542	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
543	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
544	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
545	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
546	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
547	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
548	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
549	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
550	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
551	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
552	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
553	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 156
DAY 6-DAY 29

GROUP: 3-F
DOSE: 7 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
554	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
555	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
556	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
557	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
558	Aborted/Sacrific Normal			DAY 25 DAY 6-DAY 24
559	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
560	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 156
 DAY 6-DAY 29

GROUP: 4-F
 DOSE: 25 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
561	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
562	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
563	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
564	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
565	Normal Premature Delivery/Sacrifice			DAY 6-DAY 28 DAY 29
566	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
567	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
568	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
569	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
570	Normal Sacrificed Moribund			DAY 6-DAY 11 DAY 12
571	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
572	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
573	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 156
 DAY 6-DAY 29

GROUP: 4-F
 DOSE: 25 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
574	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
575	Aborted/Sacrificed Normal			DAY 23 DAY 6-DAY 22
576	Animal Found Dead Normal			DAY 19 DAY 6-DAY 18
577	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
578	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
579	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
580	Aborted/Sacrificed Normal			DAY 25 DAY 6-DAY 24

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 156
 DAY 6-DAY 29

GROUP: 5-F
 DOSE: 300 (mg/kg/day)^a

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
581	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
582	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
583	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
584	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
585	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
586	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
587	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
588	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
589	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
590	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
591	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
592	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
593	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29

^aRetinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 156
DAY 6-DAY 29

GROUP: 5-F
DOSE: 300 (mg/kg/day)^a

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
594	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
595	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
596	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
597	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
598	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
599	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
600	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29

^aRetinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 156

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0 1-F	2 2-F	7 3-F	25 4-F	300 (mg/kg/day) ^a 5-F
DAY 6						
No. Observed		20	20	20	20	0
Normal		20 100%	20 100%	20 100%	20 100%	0
DAY 7						
No. Observed		20	20	20	20	0
Normal		20 100%	20 100%	20 100%	20 100%	0
DAY 8						
No. Observed		20	20	20	20	0
Normal		20 100%	20 100%	20 100%	20 100%	0
DAY 9						
No. Observed		20	20	20	20	20
Normal		20 100%	20 100%	20 100%	20 100%	20 100%
DAY 10						
No. Observed		20	20	20	20	20
Normal		20 100%	20 100%	20 100%	20 100%	20 100%
DAY 11						
No. Observed		20	20	20	20	20
Normal		20 100%	20 100%	20 100%	20 100%	20 100%
DAY 12						
No. Observed		20	20	20	20	20
Sacrificed Moribund		0	0	0	1 5%	0
Normal		20 100%	20 100%	20 100%	19 95%	20 100%
DAY 13						
No. Observed		20	20	20	19	20
Normal		20 100%	20 100%	20 100%	19 100%	20 100%
DAY 14						
No. Observed		20	20	20	19	20
Normal		20 100%	20 100%	20 100%	19 100%	20 100%
DAY 15						
No. Observed		20	20	20	19	20
Normal		20 100%	20 100%	20 100%	19 100%	20 100%

^aRetinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INCIDENCE OF OBSERVATION

STUDY: 156

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	2	7	25	300 (mg/kg/day) ^a
		1-F	2-F	3-F	4-F	5-F
DAY 16						
No. Observed		20	20	20	19	20
Normal		20 100%	20 100%	20 100%	19 100%	20 100%
DAY 17						
No. Observed		20	20	20	19	20
Normal		20 100%	20 100%	20 100%	19 100%	20 100%
DAY 18						
No. Observed		20	20	20	19	20
Normal		20 100%	20 100%	20 100%	19 100%	20 100%
DAY 19						
No. Observed		20	20	20	19	20
Animal Found Dead		0	0	0	1 5%	0
Normal		20 100%	20 100%	20 100%	18 95%	20 100%
DAY 20						
No. Observed		20	20	20	18	20
Normal		20 100%	20 100%	20 100%	18 100%	20 100%
DAY 21						
No. Observed		20	20	20	18	20
Normal		20 100%	20 100%	20 100%	18 100%	20 100%
DAY 22						
No. Observed		20	20	20	18	20
Normal		20 100%	20 100%	20 100%	18 100%	20 100%
DAY 23						
No. Observed		20	20	20	18	20
Aborted/Sacrificed		0	0	0	1 6%	0
Normal		20 100%	20 100%	20 100%	17 94%	20 100%
DAY 24						
No. Observed		20	20	20	17	20
Normal		20 100%	20 100%	20 100%	17 100%	20 100%

^aRetinol Palmitate given on DG9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 156

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day)					300 (mg/kg/day) ^a
	GROUP:	0 1-F	2 2-F	7 3-F	25 4-F	
DAY 25						
No. Observed		20	20	20	17	20
Aborted/Sacrificed		0	0	1 5%	1 6%	0
Normal		20 100%	20 100%	19 95%	16 94%	20 100%
DAY 26						
No. Observed		20	20	19	16	20
Normal		20 100%	20 100%	19 100%	16 100%	20 100%
DAY 27						
No. Observed		20	20	19	16	20
Normal		20 100%	20 100%	19 100%	16 100%	20 100%
DAY 28						
No. Observed		20	20	19	16	20
Normal		20 100%	20 100%	19 100%	16 100%	20 100%
DAY 29						
No. Observed		20	20	19	16	20
Scheduled Sacrifice		20 100%	20 100%	19 100%	15 94%	20 100%
Premature Delivery/Sacrifice		0	0	0	1 6%	0

^aRetinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 156A
DAY 6-DAY 29

GROUP: 1-F
DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
601	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
602	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
603	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
604	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
605	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
606	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
607	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
608	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
609	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
610	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
611	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
612	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
613	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 156A
DAY 6-DAY 29

GROUP: 1-F
DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
614	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
615	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
616	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
617	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
618	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
619	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
620	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 156A
 DAY 6-DAY 29

GROUP: 2-F
 DOSE: 25/16^a (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
621	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
622	Aborted/Sacrificed Normal			DAY 23 DAY 6-DAY 22
623	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
624	Animal Found Dead Labored Breathing Normal			DAY 13 DAY 12 DAY 6-DAY 11
625	Decreased Activity Normal Sacrificed Moribund			DAY 10 DAY 6-DAY 9 DAY 10
626	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
627	Blood found in cage pan Normal Normal Scheduled Sacrifice			DAY 27 DAY 6-DAY 26 DAY 28 DAY 29
628	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
629	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
630	Aborted/Sacrificed Normal			DAY 25 DAY 6-DAY 24
631	Blood found in cage pan Blood found in cage pan Normal Normal Normal Scheduled Sacrifice			DAY 22 DAY 24 DAY 6-DAY 21 DAY 23 DAY 25-DAY 28 DAY 29

^aThe high dose was reduced from 25 mg base/kg/day to 16 mg base/kg/day on GD15 - GD16 (the range of days reflects study stagger start over 2 days)

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 156A
 DAY 6-DAY 29

GROUP: 2-F
 DOSE: 25/16^a (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
632	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
633	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
634	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
635	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
636	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
637	Blood found in cage pan Animal Found Dead Normal			DAY 21 DAY 22 DAY 6-DAY 20
638	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
639	Normal Sacrificed Moribund			DAY 6-DAY 16 DAY 17
640	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

^aThe high dose was reduced from 25 mg base/kg/day to 16 mg base/kg/day on GD15 - GD16 (the range of days reflects study stagger start over 2 days)

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 156A

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day)	
	0	25/16 ^a
	GROUP:	
	1-F	2-F
DAY 6		
No. Observed	20	20
Normal	20 100%	20 100%
DAY 7		
No. Observed	20	20
Normal	20 100%	20 100%
DAY 8		
No. Observed	20	20
Normal	20 100%	20 100%
DAY 9		
No. Observed	20	20
Normal	20 100%	20 100%
DAY 10		
No. Observed	20	20
Sacrificed Moribund	0	1 5%
Normal	20 100%	19 95%
Decreased Activity	0	1 5%
DAY 11		
No. Observed	20	19
Normal	20 100%	19 100%
DAY 12		
No. Observed	20	19
Normal	20 100%	18 95%
Labored Breathing	0	1 5%
DAY 13		
No. Observed	20	19
Animal Found Dead	0	1 5%
Normal	20 100%	18 95%
DAY 14		
No. Observed	20	18
Normal	20 100%	18 100%

^aThe high dose was reduced from 25 mg base/kg/day to 16 mg base/kg/day on GD15 - GD16 (the range of days reflects study stagger-start over 2 days)

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INCIDENCE OF OBSERVATION

STUDY: 156A

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day)		25/16 ^a	
	GROUP:	0	1-F	2-F
DAY 15				
No. Observed		20	18	
Normal		20 100%	18 100%	
DAY 16				
No. Observed		20	18	
Normal		20 100%	18 100%	
DAY 17				
No. Observed		20	18	
Sacrificed Moribund		0	1	6%
Normal		20 100%	17	94%
DAY 18				
No. Observed		20	17	
Normal		20 100%	17	100%
DAY 19				
No. Observed		20	17	
Normal		20 100%	17	100%
DAY 20				
No. Observed		20	17	
Normal		20 100%	17	100%
DAY 21				
No. Observed		20	17	
Normal		20 100%	16	94%
Blood found in cage pan		0	1	6%
DAY 22				
No. Observed		20	17	
Animal Found Dead		0	1	6%
Normal		20 100%	15	88%
Blood found in cage pan		0	1	6%
DAY 23				
No. Observed		20	16	
Aborted/Sacrificed		0	1	6%
Normal		20 100%	15	94%

^aThe high dose was reduced from 25 mg base/kg/day to 16 mg base/kg/day on GD15 - GD16 (the range of days reflects study stagger start over 2 days)

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 156A

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day)		25/16 ^a	
	GROUP:	0	1-F	2-F
DAY 24				
No. Observed		20		15
Normal		20 100%	14	93%
Blood found in cage pan		0	1	7%
DAY 25				
No. Observed		20		15
Aborted/Sacrificed		0	1	7%
Normal		20 100%	14	93%
DAY 26				
No. Observed		20		14
Normal		20 100%	14	100%
DAY 27				
No. Observed		20		14
Normal		20 100%	13	93%
Blood found in cage pan		0	1	7%
DAY 28				
No. Observed		20		14
Normal		20 100%	14	100%
DAY 29				
No. Observed		20		14
Scheduled Sacrifice		20 100%	14	100%

^aThe high dose was reduced from 25 mg base/kg/day to 16 mg base/kg/day on GD15 - GD16 (the range of days reflects study stagger-start over 2 days)

DRAFT

APPENDIX 3

Individual Maternal Body Weight and Weight Gain Data

Initial Study: 3-2 through 3-21

Retest: 3.1-1 through 3.1-8

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 156

GROUP: 1-F
 DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	DAY 0	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
501	3.74	3.45	3.55	3.60	3.56	3.63	3.60	3.61	3.62	3.64	3.66	3.67
502	--	--	--	--	--	--	--	--	--	--	--	--
503	2.84	2.69	2.62	2.64	2.62	2.66	2.64	2.69	2.71	2.71	2.73	2.77
504	3.14	3.08	3.12	3.12	3.09	3.15	3.14	3.08	3.20	3.23	3.29	3.23
505	3.09	3.00	2.98	3.06	3.13	3.11	3.09	3.17	3.21	3.18	3.20	3.26
506	3.11	3.02	2.96	2.96	2.94	2.94	3.02	3.03	3.02	3.03	3.09	3.07
507	3.11	3.03	3.16	3.20	3.22	3.15	3.17	3.25	3.29	3.26	3.28	3.35
508	3.63	3.48	3.57	3.50	3.57	3.56	3.54	3.61	3.59	3.60	3.62	3.61
509	2.91	2.81	2.79	2.81	2.80	2.84	2.84	2.82	2.86	2.88	2.93	2.96
510	3.85	3.66	3.62	3.67	3.69	3.73	3.71	3.76	3.74	3.78	3.79	3.81
511	3.07	2.88	2.92	2.97	3.00	3.00	3.04	3.03	3.06	3.05	3.10	3.13
512	2.89	2.77	2.63	2.43	2.69	2.86	2.91	2.90	2.95	2.92	3.00	3.07
513	--	--	--	--	--	--	--	--	--	--	--	--
514	3.23	3.22	3.33	3.29	3.25	3.22	3.39	3.31	3.42	3.40	3.44	3.53
515	3.08	3.04	3.19	3.11	3.15	3.14	3.19	3.16	3.18	3.28	3.30	3.40
516	3.09	3.03	2.98	3.06	3.04	3.10	3.05	3.07	3.07	3.11	3.11	3.14
517	3.15	2.94	2.87	2.91	2.91	2.92	2.97	3.04	3.01	3.09	3.10	3.17
518	3.51	3.36	3.33	3.38	3.40	3.45	3.46	3.44	3.45	3.50	3.52	3.55
519	3.28	3.17	3.17	3.17	3.25	3.27	3.22	3.28	3.28	3.26	3.38	3.36
520	3.90	3.74	3.75	3.77	3.75	3.77	3.81	3.80	3.77	3.84	3.85	3.82
MEAN	3.26	3.13	3.14	3.15	3.17	3.19	3.21	3.23	3.25	3.26	3.30	3.33
S.D.	0.327	0.299	0.333	0.351	0.328	0.320	0.315	0.315	0.303	0.313	0.304	0.293
N	18	18	18	18	18	18	18	18	18	18	18	18

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 156

GROUP: 1-F
 DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL # DAY 16 DAY 17 DAY 18 DAY 24 DAY 29

501	3.72	3.78	3.78	3.71	3.85
502	--	--	--	--	b
503	2.80	2.80	2.78	2.94	3.00
504	3.29	3.26	3.23	3.33	3.38
505	3.32	3.38	3.37	3.47	3.42
506	3.10	3.09	3.08	3.23	3.35
507	3.32	3.40	3.34	3.42	3.54
508	3.60	3.61	3.67	3.79	3.89
509	2.94	2.94	2.98	3.13	3.18
510	3.85	3.79	3.80	3.92	3.97
511	3.11	3.08	3.11	3.23	3.34
512	3.06	3.10	3.12	3.15	3.07
513	--	--	--	--	b
514	3.45	3.59	3.51	3.51	3.72
515	3.30	3.41	3.39	3.42	3.29
516	3.19	3.13	3.17	3.17	3.20
517	3.24	3.24	3.23	3.37	3.46
518	3.57	3.60	3.56	3.63	3.68
519	3.44	3.49	3.46	3.59	3.66
520	3.87	3.85	3.87	3.93	3.98

MEAN	3.34	3.36	3.36	3.44	3.50
S.D.	0.298	0.305	0.302	0.281	0.304
N	18	18	18	18	18

--: Data Unavailable

b: Scheduled Sacrifice

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 156

GROUP: 2-F
 DOSE: 2 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	DAY 0	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
521	3.16	3.08	3.04	3.16	3.08	3.08	3.06	3.08	3.15	3.16	3.22	3.25
522	2.87	2.98	2.85	2.93	3.03	2.94	2.95	2.87	3.03	2.95	2.95	3.03
523	3.03	3.00	3.01	3.05	2.97	3.02	2.99	3.05	3.04	3.09	3.10	3.11
524	--	--	--	--	--	--	--	--	--	--	--	--
525	--	--	--	--	--	--	--	--	--	--	--	--
526	3.07	2.94	2.92	2.94	2.96	2.96	3.00	2.98	3.02	3.04	3.05	3.09
527	3.79	3.78	3.66	3.66	3.68	3.68	3.68	3.71	3.72	3.67	3.77	3.80
528	--	--	--	--	--	--	--	--	--	--	--	--
529	3.27	3.14	3.05	3.13	3.18	3.18	3.22	3.28	3.29	3.34	3.34	3.38
530	3.85	3.57	3.63	3.77	3.81	3.83	3.84	3.88	3.91	3.92	3.93	3.99
531	3.05	3.04	2.90	3.00	3.06	3.09	3.13	3.16	3.17	3.20	3.22	3.22
532	3.13	3.05	3.09	3.08	3.09	3.14	3.12	3.18	3.16	3.16	3.21	3.26
533	3.14	3.09	3.07	3.10	3.12	3.15	3.19	3.11	3.15	3.20	3.22	3.27
534	2.96	2.99	3.12	3.06	3.12	3.13	3.16	3.16	3.19	3.18	3.22	2.87
535	2.98	2.75	2.82	2.85	2.83	2.85	2.85	2.88	2.89	2.89	2.91	2.91
536	3.70	3.61	3.58	3.62	3.62	3.61	3.63	3.69	3.67	3.78	3.79	3.81
537	--	--	--	--	--	--	--	--	--	--	--	--
538	3.59	3.45	3.42	3.39	3.42	3.44	3.45	3.49	3.48	3.56	3.55	3.58
539	--	--	--	--	--	--	--	--	--	--	--	--
540	3.19	2.94	2.90	3.00	3.02	2.97	3.02	3.05	3.02	3.04	3.07	3.09
MEAN	3.25	3.16	3.14	3.18	3.20	3.20	3.22	3.24	3.26	3.28	3.30	3.31
S.D.	0.320	0.296	0.290	0.288	0.292	0.296	0.295	0.312	0.299	0.311	0.315	0.340
N	15	15	15	15	15	15	15	15	15	15	15	15

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 156

GROUP: 2-F
 DOSE: 2 (mg base/kg/day)

SEX: FEMALE

ANIMAL # DAY 16 DAY 17 DAY 18 DAY 24 DAY 29

521	3.29	3.25	3.25	3.34	3.42
522	2.98	2.94	2.99	3.11	3.22
523	3.18	3.09	3.10	3.16	3.16
524	--	--	--	--	b
525	--	--	--	--	b
526	3.08	3.08	3.08	3.24	3.27
527	3.76	3.76	3.75	3.88	3.87
528	--	--	--	--	b
529	3.43	3.41	3.41	3.57	3.61
530	4.04	4.00	3.99	4.01	4.11
531	3.22	3.29	3.27	3.37	3.32
532	3.22	3.29	3.27	3.38	3.45
533	3.31	3.30	3.33	3.47	3.46
534	3.24	3.27	3.23	3.40	3.44
535	2.93	2.93	2.94	3.05	3.09
536	4.02	3.87	3.86	3.88	3.87
537	--	--	--	--	b
538	3.60	3.61	3.22	3.65	3.72
539	--	--	--	--	b
540	3.13	3.15	3.08	3.20	3.19

MEAN	3.36	3.35	3.32	3.45	3.48
S.D.	0.346	0.325	0.314	0.296	0.300
N	15	15	15	15	15

--: Data Unavailable

b: Scheduled Sacrifice

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 156

GROUP: 3-F
 DOSE: 7 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	DAY 0	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
541	--	--	--	--	--	--	--	--	--	--	--	--
542	--	--	--	--	--	--	--	--	--	--	--	--
543	2.91	2.83	2.85	2.93	2.86	2.85	2.86	2.90	2.96	2.97	2.95	2.98
544	2.91	3.01	2.90	2.95	3.01	2.89	2.84	2.94	2.94	3.05	3.14	3.09
545	2.93	2.86	2.76	2.74	2.80	2.80	2.85	2.92	2.87	2.87	2.92	2.94
546	3.27	3.14	3.10	3.14	3.16	3.16	3.15	3.14	3.20	3.23	3.28	3.27
547	4.03	3.78	3.68	3.77	3.76	3.80	3.82	3.87	3.85	3.88	3.86	3.89
548	3.18	3.10	3.09	3.10	3.11	3.08	3.08	3.07	3.12	3.06	3.15	3.11
549	3.02	2.88	2.92	2.86	2.90	3.01	3.00	3.01	3.08	3.15	3.21	3.19
550	3.10	2.97	2.94	3.03	2.97	3.02	2.99	3.01	3.06	3.03	3.09	3.10
551	--	--	--	--	--	--	--	--	--	--	--	--
552	2.87	2.78	2.79	2.79	2.80	2.81	2.83	2.84	2.87	2.87	2.92	2.93
553	3.02	2.87	3.00	3.01	3.04	3.04	3.12	3.13	3.00	3.07	3.13	3.13
554	3.23	3.12	3.08	3.17	3.10	3.14	3.11	3.17	3.21	3.24	3.27	3.30
555	3.07	3.06	3.10	3.02	3.08	3.06	3.13	3.05	3.15	3.23	3.24	3.28
556	4.01	3.74	3.75	3.75	3.76	3.75	3.77	3.77	3.76	3.82	3.85	3.85
557	2.98	2.84	2.79	2.83	2.93	2.91	2.97	2.96	2.95	3.01	3.08	3.01
558	3.67	3.24	3.27	3.33	3.34	3.38	3.38	3.52	3.51	3.56	3.67	3.62
559	3.46	3.16	3.16	3.21	3.20	3.22	3.22	3.25	3.29	3.30	3.35	3.34
560	--	--	--	--	--	--	--	--	--	--	--	--
MEAN	3.23	3.09	3.07	3.10	3.11	3.12	3.13	3.16	3.18	3.21	3.26	3.25
S.O.	0.376	0.297	0.290	0.302	0.292	0.299	0.300	0.305	0.297	0.304	0.297	0.298
N	16	16	16	16	16	16	16	16	16	16	16	16

---: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 156

GROUP: 3-F
 DOSE: 7 (mg base/kg/day)

SEX: FEMALE

ANIMAL # DAY 16 OAY 17 OAY 18 OAY 24 DAY 29

541	--	--	--	--	b
542	--	--	--	--	b
543	2.91	2.93	3.00	3.18	3.17
544	3.13	3.16	3.19	3.32	3.30
545	2.96	3.00	3.00	3.06	3.14
546	3.27	3.26	3.26	3.50	3.41
547	3.98	4.00	3.96	3.96	4.08
548	3.13	3.13	3.13	3.25	3.24
549	3.20	3.23	3.17	3.27	3.33
550	3.09	3.09	3.10	3.23	3.32
551	--	--	--	--	b
552	2.93	2.94	2.92	3.03	3.07
553	3.16	3.15	3.26	3.33	3.32
554	3.31	3.32	3.27	3.37	3.43
555	3.42	3.33	3.30	3.38	3.46
556	3.88	3.85	3.84	3.89	3.96
557	3.05	3.06	3.04	3.24	3.17
558	3.82	3.81	3.75	3.84	e
559	3.33	3.30	3.34	3.46	3.48
560	--	--	--	--	b

MEAN	3.29	3.29	3.28	3.39	3.39
S.D.	0.335	0.325	0.308	0.279	0.283
N	16	16	16	16	15

--: Data Unavailable b: Scheduled Sacrifice e: Aborted/Sacrificed

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 156

GROUP: 4-F

SEX: FEMALE

DOSE: 25 (mg base/kg/day)

ANIMAL #	DAY 0	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
561	--	--	--	--	--	--	--	--	--	--	--	--
562	--	--	--	--	--	--	--	--	--	--	--	--
563	2.79	2.75	2.72	2.76	2.74	2.68	2.73	2.72	2.79	2.81	2.86	2.87
564	--	--	--	--	--	--	--	--	--	--	--	--
565	3.05	2.98	2.91	2.92	2.95	2.94	2.96	2.99	3.05	3.05	3.11	3.13
566	3.32	3.27	3.16	3.21	3.24	3.27	3.28	3.31	3.29	3.31	3.36	3.33
567	4.11	3.79	3.81	3.78	3.87	3.72	3.78	3.81	3.86	3.90	3.88	3.94
568	2.89	3.12	2.92	2.93	3.00	2.92	2.93	3.04	2.94	3.08	3.02	3.12
569	2.94	2.88	2.82	2.69	2.79	2.77	2.83	2.85	2.87	2.93	2.95	3.00
570	2.92	2.84	2.74	2.73	2.70	2.74	2.76	2.80	d	d	d	d
571	3.15	3.00	3.01	3.01	3.05	3.06	3.06	3.07	3.10	3.22	3.21	3.23
572	2.91	2.82	2.83	2.79	2.82	2.78	2.85	2.85	2.86	2.87	2.91	2.93
573	2.92	2.96	2.92	2.90	2.86	2.86	2.89	2.85	2.92	2.98	2.97	3.02
574	3.28	3.05	3.11	3.07	3.06	2.93	3.01	2.99	3.03	2.99	3.02	3.02
575	3.18	3.07	3.17	3.14	3.24	3.13	3.16	3.23	3.27	3.30	3.34	3.34
576	3.34	3.21	3.19	3.20	3.21	3.18	3.20	3.25	3.22	3.25	3.29	3.28
577	--	--	--	--	--	--	--	--	--	--	--	--
578	3.07	2.84	2.88	2.94	2.93	2.94	2.98	2.98	2.96	2.99	3.04	2.98
579	3.69	3.60	3.67	3.71	3.72	3.66	3.65	3.65	3.65	3.74	3.84	3.90
580	3.60	3.57	3.55	3.57	3.55	3.53	3.53	3.54	3.57	3.57	3.53	3.51
MEAN	3.20	3.11	3.09	3.08	3.11	3.07	3.10	3.12	3.16	3.20	3.22	3.24
S.D.	0.354	0.308	0.330	0.339	0.348	0.326	0.316	0.321	0.319	0.322	0.321	0.327
N	16	16	16	16	16	16	16	16	15	15	15	15

--: Data Unavailable d: Sacrificed Moribund

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 156

GROUP: 4-F
 DOSE: 25 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	DAY 16	DAY 17	DAY 18	DAY 24	DAY 29
561	--	--	--	--	b
562	--	--	--	--	b
563	2.87	2.85	2.85	2.94	3.04
564	--	--	--	--	b
565	3.16	3.13	3.10	3.10	2.48
566	3.34	3.34	3.34	3.39	3.53
567	3.97	3.86	3.86	4.04	4.13
568	3.08	3.16	3.11	3.27	3.33
569	2.99	2.94	3.02	3.17	3.15
570	d	d	d	d	d
571	3.23	3.21	3.22	3.33	3.32
572	2.92	2.94	2.91	3.00	3.05
573	3.02	3.08	3.07	3.11	3.12
574	3.05	3.06	3.03	3.12	3.23
575	3.43	3.44	3.44	e	e
576	3.31	3.24	3.14	c	c
577	--	--	--	--	b
578	3.05	3.06	3.13	3.22	3.33
579	3.94	4.01	4.00	3.84	3.81
580	3.52	3.44	3.31	3.06	e
MEAN	3.26	3.25	3.24	3.28	3.29
S.D.	0.338	0.328	0.323	0.323	0.412
N	15	15	15	13	12

--: Data Unavailable

b: Scheduled Sacrifice

c: Animal Found Dead

d: Sacrificed Moribund

e: Aborted/Sacrificed

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 156		GROUP: 5-F						SEX: FEMALE				
		DOSE: 300 (mg/kg/day) ^a										
ANIMAL #	DAY 0	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
581	3.07	3.10	3.08	3.05	3.09	3.06	3.04	3.05	3.05	3.12	3.17	3.17
582	3.02	2.97	3.01	2.93	2.95	2.95	2.93	2.93	2.93	2.97	3.00	3.06
583	3.18	3.06	3.06	3.10	3.10	3.07	3.09	3.04	3.13	3.11	3.15	3.21
584	2.89	2.85	2.89	2.84	2.87	2.86	2.88	2.82	2.86	2.86	2.92	2.98
585	3.27	3.12	--	--	3.35	3.25	3.09	3.20	3.19	3.29	3.34	3.36
586	3.13	3.04	2.98	3.04	3.03	3.06	3.04	3.11	3.11	3.16	3.22	3.21
587	2.95	2.78	2.73	2.83	2.84	2.90	2.89	2.93	2.94	2.97	2.96	2.98
588	3.07	3.00	2.93	2.98	3.10	3.10	3.07	3.05	3.08	3.11	3.12	3.11
589	3.57	3.55	3.46	3.50	3.53	3.55	3.54	3.57	3.60	3.57	3.64	3.68
590	3.82	3.62	3.51	3.53	3.62	3.59	3.64	3.58	3.61	3.65	3.70	3.71
591	3.21	3.04	3.07	3.10	3.10	3.11	3.10	3.12	3.10	3.16	3.20	3.28
592	3.28	3.34	3.31	3.26	3.34	3.33	3.33	3.31	3.30	3.34	3.41	3.45
593	--	--	--	--	--	--	--	--	--	--	--	--
594	2.84	2.72	2.72	2.70	2.76	2.75	2.77	2.84	2.78	2.80	2.84	2.84
595	2.96	3.02	2.98	3.10	3.02	2.96	2.97	3.02	3.11	3.24	3.26	3.30
596	--	--	--	--	--	--	--	--	--	--	--	--
597	3.36	2.70	2.69	2.73	2.72	2.75	2.74	2.71	2.73	2.77	2.78	2.82
598	3.07	3.48	3.43	3.46	3.47	3.47	3.50	3.51	3.51	3.50	3.53	3.56
599	3.94	3.77	3.67	3.75	3.75	3.78	3.77	3.77	3.77	3.80	3.84	3.81
600	3.23	3.10	3.14	3.07	3.14	3.19	3.16	3.15	3.13	3.17	3.20	3.19
MEAN	3.21	3.13	3.10	3.12	3.15	3.15	3.14	3.15	3.16	3.20	3.24	3.26
S.D.	0.301	0.309	0.289	0.296	0.297	0.294	0.297	0.292	0.293	0.288	0.297	0.290
N	18	18	17	17	18	18	18	18	18	18	18	18

--: Data Unavailable

^aRetinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 156

GROUP: 5-F
 DOSE: 300 (mg/kg/day)^a

SEX: FEMALE

ANIMAL #	DAY 16	DAY 17	DAY 18	DAY 24	DAY 29
581	3.21	3.22	3.21	3.29	3.43
582	3.01	3.01	3.00	3.13	3.20
583	3.24	3.22	3.22	3.34	3.39
584	2.92	2.88	2.86	2.88	2.86
585	3.40	3.42	3.41	3.47	3.59
586	3.23	3.25	3.21	3.40	3.46
587	3.01	2.99	3.01	3.07	3.17
588	3.11	3.08	3.12	3.29	3.34
589	3.69	3.70	3.68	3.79	3.71
590	3.79	3.78	3.64	3.74	3.90
591	3.27	3.26	3.28	3.34	3.37
592	3.43	3.45	3.49	3.55	3.65
593	--	--	--	--	b
594	2.83	2.84	2.85	2.86	2.89
595	3.31	3.33	3.33	3.38	3.49
596	--	--	--	--	b
597	2.82	2.82	2.85	2.91	2.99
598	3.60	3.57	3.59	3.68	3.70
599	3.83	3.79	3.79	3.86	3.86
600	3.17	3.21	3.21	3.29	3.40
MEAN	3.27	3.27	3.26	3.35	3.41
S.D.	0.308	0.306	0.292	0.303	0.304
N	18	18	18	18	18

--: Data Unavailable b: Scheduled Sacrifice

^aRetinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 156

GROUP: 1-F
 DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	DAY 7 ^b	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 16	DAY 17
501	0.05	-0.04	0.07	-0.03	0.01	0.01	0.02	0.02	0.01	0.05	0.06
502	--	--	--	--	--	--	--	--	--	--	--
503	0.02	-0.02	0.04	-0.02	0.05	0.02	0.00	0.02	0.04	0.03	0.00
504	0.00	-0.03	0.06	-0.01	-0.06	0.12	0.03	0.06	-0.06	0.06	-0.03
505	0.08	0.07	-0.02	-0.02	0.08	0.04	-0.03	0.02	0.06	0.06	0.06
506	0.00	-0.02	0.00	0.08	0.01	-0.01	0.01	0.06	-0.02	0.03	-0.01
507	0.04	0.02	-0.07	0.02	0.08	0.04	-0.03	0.02	0.07	-0.03	0.08
508	-0.07	0.07	-0.01	-0.02	0.07	-0.02	0.01	0.02	-0.01	-0.01	0.01
509	0.02	-0.01	0.04	0.00	-0.02	0.04	0.02	0.05	0.03	-0.02	0.00
510	0.05	0.02	0.04	-0.02	0.05	-0.02	0.04	0.01	0.02	0.04	-0.06
511	0.05	0.03	0.00	0.04	-0.01	0.03	-0.01	0.05	0.03	-0.02	-0.03
512	-0.20	0.26	0.17	0.05	-0.01	0.05	-0.03	0.08	0.07	-0.01	0.04
513	--	--	--	--	--	--	--	--	--	--	--
514	-0.04	-0.04	-0.03	0.17	-0.08	0.11	-0.02	0.04	0.09	-0.08	0.14
515	-0.08	0.04	-0.01	0.05	-0.03	0.02	0.10	0.02	0.10	-0.10	0.11
516	0.08	-0.02	0.06	-0.05	0.02	0.00	0.04	0.00	0.03	0.05	-0.06
517	0.04	0.00	0.01	0.05	0.07	-0.03	0.08	0.01	0.07	0.07	0.00
518	0.05	0.02	0.05	0.01	-0.02	0.01	0.05	0.02	0.03	0.02	0.03
519	0.00	0.08	0.02	-0.05	0.06	0.00	-0.02	0.12	-0.02	0.08	0.05
520	0.02	-0.02	0.02	0.04	-0.01	-0.03	0.07	0.01	-0.03	0.05	-0.02
MEAN	0.01	0.02	0.02	0.02	0.01	0.02	0.02	0.04	0.03	0.02	0.02
S.D.	0.068	0.070	0.051	0.054	0.049	0.042	0.039	0.030	0.044	0.051	0.055
N	18	18	18	18	18	18	18	18	18	18	18

---: Data Unavailable

^aSuccessive periods

^bBaseline is day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 156

GROUP: 1-F
 DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	DAY 18	DAY 24	DAY 29	TOTAL GAIN
501	0.00	-0.07	0.14	0.30
502	--	--	b	--
503	-0.02	0.16	0.06	0.38
504	-0.03	0.10	0.05	0.26
505	-0.01	0.10	-0.05	0.44
506	-0.01	0.15	0.12	0.39
507	-0.06	0.08	0.12	0.38
508	0.06	0.12	0.10	0.32
509	0.04	0.15	0.05	0.39
510	0.01	0.12	0.05	0.35
511	0.03	0.12	0.11	0.42
512	0.02	0.03	-0.08	0.44
513	--	--	b	--
514	-0.08	0.00	0.21	0.39
515	-0.02	0.03	-0.13	0.10
516	0.04	0.00	0.03	0.22
517	-0.01	0.14	0.09	0.59
518	-0.04	0.07	0.05	0.35
519	-0.03	0.13	0.07	0.49
520	0.02	0.06	0.05	0.23
MEAN	-0.01	0.08	0.06	0.36
S.D.	0.037	0.064	0.081	0.111
N	18	18	18	18

--: Data Unavailable b: Scheduled Sacrifice

^aSuccessive periods

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 156

GROUP: 2-F

SEX: FEMALE

DOSE: 2 (mg base/kg/day)

ANIMAL #	DAY 7 ^b	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 16	DAY 17
521	0.12	-0.08	0.00	-0.02	0.02	0.07	0.01	0.06	0.03	0.04	-0.04
522	0.08	0.10	-0.09	0.01	-0.08	0.16	-0.08	0.00	0.08	-0.05	-0.04
523	0.04	-0.08	0.05	-0.03	0.06	-0.01	0.05	0.01	0.01	0.07	-0.09
524	--	--	--	--	--	--	--	--	--	--	--
525	--	--	--	--	--	--	--	--	--	--	--
526	0.02	0.02	0.00	0.04	-0.02	0.04	0.02	0.01	0.04	-0.01	0.00
527	0.00	0.02	0.00	0.00	0.03	0.01	-0.05	0.10	0.03	-0.04	0.00
528	--	--	--	--	--	--	--	--	--	--	--
529	0.08	0.05	0.00	0.04	0.06	0.01	0.05	0.00	0.04	0.05	-0.02
530	0.14	0.04	0.02	0.01	0.04	0.03	0.01	0.01	0.06	0.05	-0.04
531	0.10	0.06	0.03	0.04	0.03	0.01	0.03	0.02	0.00	0.00	0.07
532	-0.01	0.01	0.05	-0.02	0.06	-0.02	0.00	0.05	0.05	-0.04	0.07
533	0.03	0.02	0.03	0.04	-0.08	0.04	0.05	0.02	0.05	0.04	-0.01
534	-0.06	0.06	0.01	0.03	0.00	0.03	-0.01	0.04	-0.35	0.37	0.03
535	0.03	-0.02	0.02	0.00	0.03	0.01	0.00	0.02	0.00	0.02	0.00
536	0.04	0.00	-0.01	0.02	0.06	-0.02	0.11	0.01	0.02	0.21	-0.15
537	--	--	--	--	--	--	--	--	--	--	--
538	-0.03	0.03	0.02	0.01	0.04	-0.01	0.08	-0.01	0.03	0.02	0.01
539	--	--	--	--	--	--	--	--	--	--	--
540	0.10	0.02	-0.05	0.05	0.03	-0.03	0.02	0.03	0.02	0.04	0.02
MEAN	0.05	0.02	0.01	0.01	0.02	0.02	0.02	0.02	0.01	0.05	-0.01
S.D.	0.057	0.049	0.036	0.025	0.046	0.047	0.047	0.028	0.101	0.108	0.057
N	15	15	15	15	15	15	15	15	15	15	15

--: Data Unavailable

^aSuccessive periods

^bBaseline is day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 156

GROUP: 2-F
 DOSE: 2 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OAY 18	OAY 24	OAY 29	TOTAL GAIN
521	0.00	0.09	0.08	0.38
522	0.05	0.12	0.11	0.37
523	0.01	0.06	0.00	0.15
524	--	--	b	--
525	--	--	b	--
526	0.00	0.16	0.03	0.35
527	-0.01	0.13	-0.01	0.21
528	--	--	b	--
529	0.00	0.16	0.04	0.56
530	-0.01	0.02	0.10	0.48
531	-0.02	0.10	-0.05	0.42
532	-0.02	0.11	0.07	0.36
533	0.03	0.14	-0.01	0.39
534	-0.04	0.17	0.04	0.32
535	0.01	0.11	0.04	0.27
536	-0.01	0.02	-0.01	0.29
537	--	--	b	--
538	-0.39	0.43	0.07	0.30
539	--	--	b	--
540	-0.07	0.12	-0.01	0.29
MEAN	-0.03	0.13	0.03	0.34
S.D.	0.103	0.095	0.047	0.102
N	15	15	15	15

--: Data Unavailable b: Scheduled Sacrifice

^aSuccessive periods

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 156

GROUP: 3-F

SEX: FEMALE

DOSE: 7 (mg base/kg/day)

ANIMAL #	DAY 7 ^b	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 16	DAY 17
541	--	--	--	--	--	--	--	--	--	--	--
542	--	--	--	--	--	--	--	--	--	--	--
543	0.08	-0.07	-0.01	0.01	0.04	0.06	0.01	-0.02	0.03	-0.07	0.02
544	0.05	0.06	-0.12	-0.05	0.10	0.00	0.11	0.09	-0.05	0.04	0.03
545	-0.02	0.06	0.00	0.05	0.07	-0.05	0.00	0.05	0.02	0.02	0.04
546	0.04	0.02	0.00	-0.01	-0.01	0.06	0.03	0.05	-0.01	0.00	-0.01
547	0.09	-0.01	0.04	0.02	0.05	-0.02	0.03	-0.02	0.03	0.09	0.02
548	0.01	0.01	-0.03	0.00	-0.01	0.05	-0.06	0.09	-0.04	0.02	0.00
549	-0.06	0.04	0.11	-0.01	0.01	0.07	0.07	0.06	-0.02	0.01	0.03
550	0.09	-0.06	0.05	-0.03	0.02	0.05	-0.03	0.06	0.01	-0.01	0.00
551	--	--	--	--	--	--	--	--	--	--	--
552	0.00	0.01	0.01	0.02	0.01	0.03	0.00	0.05	0.01	0.00	0.01
553	0.01	0.03	0.00	0.08	0.01	-0.13	0.07	0.06	0.00	0.03	-0.01
554	0.09	-0.07	0.04	-0.03	0.06	0.04	0.03	0.03	0.03	0.01	0.01
555	-0.08	0.06	-0.02	0.07	-0.08	0.10	0.08	0.01	0.04	0.14	-0.09
556	0.00	0.01	-0.01	0.02	0.00	-0.01	0.06	0.03	0.00	0.03	-0.03
557	0.04	0.10	-0.02	0.06	-0.01	-0.01	0.06	0.07	-0.07	0.04	0.01
558	0.06	0.01	0.04	0.00	0.14	-0.01	0.05	0.11	-0.05	0.20	-0.01
559	0.05	-0.01	0.02	0.00	0.03	0.04	0.01	0.05	-0.01	-0.01	-0.03
560	--	--	--	--	--	--	--	--	--	--	--
MEAN	0.03	0.01	0.01	0.01	0.03	0.02	0.03	0.05	-0.01	0.03	0.00
S.D.	0.052	0.049	0.049	0.037	0.051	0.056	0.044	0.036	0.033	0.064	0.031
N	16	16	16	16	16	16	16	16	16	16	16

---: Data Unavailable

^aSuccessive periods

^bBaseline is day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 156

GROUP: 3-F
 DOSE: 7 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OAY 18	OAY 24	OAY 29	TOTAL GAIN
541	--	--	b	--
542	--	--	b	--
543	0.07	0.18	-0.01	0.32
544	0.03	0.13	-0.02	0.40
545	0.00	0.06	0.08	0.38
546	0.00	0.24	-0.09	0.31
547	-0.04	0.00	0.12	0.40
548	0.00	0.12	-0.01	0.15
549	-0.06	0.10	0.06	0.41
550	0.01	0.13	0.09	0.38
551	--	--	b	--
552	-0.02	0.11	0.04	0.28
553	0.11	0.07	-0.01	0.32
554	-0.05	0.10	0.06	0.35
555	-0.03	0.08	0.08	0.36
556	-0.01	0.05	0.07	0.21
557	-0.02	0.20	-0.07	0.38
558	-0.06	0.09	e	--
559	0.04	0.12	0.02	0.32
560	--	--	b	--
MEAN	0.00	0.11	0.03	0.33
S.O.	0.047	0.059	0.061	0.073
N	16	16	15	15

--: Data Unavailable b: Scheduled Sacrifice e: Aborted/Sacrificed

^aSuccessive periods

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms) ^a

STUDY: 156

GROUP: 4-F

SEX: FEMALE

DOSE: 25 (mg base/kg/day)

ANIMAL #	DAY 7 ^b	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 16	DAY 17
561	--	--	--	--	--	--	--	--	--	--	--
562	--	--	--	--	--	--	--	--	--	--	--
563	0.04	-0.02	-0.06	0.05	-0.01	0.07	0.02	0.05	0.01	0.00	-0.02
564	--	--	--	--	--	--	--	--	--	--	--
565	0.01	0.03	-0.01	0.02	0.03	0.06	0.00	0.06	0.02	0.03	-0.03
566	0.05	0.03	0.03	0.01	0.03	-0.02	0.02	0.05	-0.03	0.01	0.00
567	-0.03	0.09	-0.15	0.06	0.03	0.05	0.04	-0.02	0.06	0.03	-0.11
568	0.01	0.07	-0.08	0.01	0.11	-0.10	0.14	-0.06	0.10	-0.04	0.08
569	-0.13	0.10	-0.02	0.06	0.02	0.02	0.06	0.02	0.05	-0.01	-0.05
570	-0.01	-0.03	0.04	0.02	0.04	d	d	d	d	d	d
571	0.00	0.04	0.01	0.00	0.01	0.03	0.12	-0.01	0.02	0.00	-0.02
572	-0.04	0.03	-0.04	0.07	0.00	0.01	0.01	0.04	0.02	-0.01	0.02
573	-0.02	-0.04	0.00	0.03	-0.04	0.07	0.06	-0.01	0.05	0.00	0.06
574	-0.04	-0.01	-0.13	0.08	-0.02	0.04	-0.04	0.03	0.00	0.03	0.01
575	-0.03	0.10	-0.11	0.03	0.07	0.04	0.03	0.04	0.00	0.09	0.01
576	0.01	0.01	-0.03	0.02	0.05	-0.03	0.03	0.04	-0.01	0.03	-0.07
577	--	--	--	--	--	--	--	--	--	--	--
578	0.06	-0.01	0.01	0.04	0.00	-0.02	0.03	0.05	-0.06	0.07	0.01
579	0.04	0.01	-0.06	-0.01	0.00	0.00	0.09	0.10	0.06	0.04	0.07
580	0.02	-0.02	-0.02	0.00	0.01	0.03	0.00	-0.04	-0.02	0.01	-0.08
MEAN	0.00	0.02	-0.04	0.03	0.02	0.02	0.04	0.02	0.02	0.02	-0.01
S.D.	0.046	0.046	0.056	0.027	0.036	0.045	0.047	0.043	0.041	0.033	0.055
N	16	16	16	16	16	15	15	15	15	15	15

--: Data Unavailable

d: Sacrificed Moribund

^aSuccessive periods

^bBaseline is day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 156

GROUP: 4-F
 DOSE: 25 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	DAY 18	DAY 24	DAY 29	TOTAL GAIN
561	--	--	b	--
562	--	--	b	--
563	0.00	0.09	0.10	0.32
564	--	--	b	--
565	-0.03	0.00	-0.62	-0.43
566	0.00	0.05	0.14	0.37
567	0.00	0.18	0.09	0.32
568	-0.05	0.16	0.06	0.41
569	0.08	0.15	-0.02	0.33
570	d	d	d	--
571	0.01	0.11	-0.01	0.31
572	-0.03	0.09	0.05	0.22
573	-0.01	0.04	0.01	0.20
574	-0.03	0.09	0.11	0.12
575	0.00	e	e	--
576	-0.10	c	c	--
577	--	--	b	--
578	0.07	0.09	0.11	0.45
579	-0.01	-0.16	-0.03	0.14
580	-0.13	-0.25	e	--

MEAN	-0.02	0.05	0.00	0.23
S.D.	0.054	0.124	0.203	0.232
N	15	13	12	12

--: Data Unavailable b: Scheduled Sacrifice c: Animal Found Dead d: Sacrificed Moribund e: Aborted/Sacrificed

^aSuccessive periods

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 156

GROUP: 5-F
DOSE: 300 (mg/kg/day)^c

SEX: FEMALE

ANIMAL #	DAY 7 ^b	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 16	DAY 17
581	-0.03	0.04	-0.03	-0.02	0.01	0.00	0.07	0.05	0.00	0.04	0.01
582	-0.08	0.02	0.00	-0.02	0.00	0.00	0.04	0.03	0.06	-0.05	0.00
583	0.04	0.00	-0.03	0.02	-0.05	0.09	-0.02	0.04	0.06	0.03	-0.02
584	-0.05	0.03	-0.01	0.02	-0.06	0.04	0.00	0.06	0.06	-0.06	-0.04
585	--	--	-0.10	-0.16	0.11	-0.01	0.10	0.05	0.02	0.04	0.02
586	0.06	-0.01	0.03	-0.02	0.07	0.00	0.05	0.06	-0.01	0.02	0.02
587	0.10	0.01	0.06	-0.01	0.04	0.01	0.03	-0.01	0.02	0.03	-0.02
588	0.05	0.12	0.00	-0.03	-0.02	0.03	0.03	0.01	-0.01	0.00	-0.03
589	0.04	0.03	0.02	-0.01	0.03	0.03	-0.03	0.07	0.04	0.01	0.01
590	0.02	0.09	-0.03	0.05	-0.06	0.03	0.04	0.05	0.01	0.08	-0.01
591	0.03	0.00	0.01	-0.01	0.02	-0.02	0.06	0.04	0.08	-0.01	-0.01
592	-0.05	0.08	-0.01	0.00	-0.02	-0.01	0.04	0.07	0.04	-0.02	0.02
593	--	--	--	--	--	--	--	--	--	--	--
594	-0.02	0.06	-0.01	0.02	0.07	-0.06	0.02	0.04	0.00	-0.01	0.01
595	0.12	-0.08	-0.06	0.01	0.05	0.09	0.13	0.02	0.04	0.01	0.02
596	--	--	--	--	--	--	--	--	--	--	--
597	0.04	-0.01	0.03	-0.01	-0.03	0.02	0.04	0.01	0.04	0.00	0.00
598	0.03	0.01	0.00	0.03	0.01	0.00	-0.01	0.03	0.03	0.04	-0.03
599	0.08	0.00	0.03	-0.01	0.00	0.00	0.03	0.04	-0.03	0.02	-0.04
600	-0.07	0.07	0.05	-0.03	-0.01	-0.02	0.04	0.03	-0.01	-0.02	0.04
MEAN	0.02	0.03	0.00	-0.01	0.01	0.01	0.04	0.04	0.02	0.01	0.00
S.D.	0.059	0.047	0.039	0.043	0.047	0.037	0.039	0.021	0.031	0.034	0.023
N	17	17	18	18	18	18	18	18	18	18	18

--: Data Unavailable

^aSuccessive periods

^bBaseline is day 6

^cRetinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms) ^a

STUDY: 156

GROUP: 5-F
 DOSE: 300 (mg/kg/day) ^c

SEX: FEMALE

ANIMAL #	DAY 18	DAY 24	DAY 29	TOTAL GAIN
581	-0.01	0.08	0.14	0.35
582	-0.01	0.13	0.07	0.19
583	0.00	0.12	0.05	0.33
584	-0.02	0.02	-0.02	-0.03
585	-0.01	0.06	0.12	0.24
586	-0.04	0.19	0.06	0.48
587	0.02	0.06	0.10	0.44
588	0.04	0.17	0.05	0.41
589	-0.02	0.11	-0.08	0.25
590	-0.14	0.10	0.16	0.39
591	0.02	0.06	0.03	0.30
592	0.04	0.06	0.10	0.34
593	--	--	b	--
594	0.01	0.01	0.03	0.17
595	0.00	0.05	0.11	0.51
596	--	--	b	--
597	0.03	0.06	0.08	0.30
598	0.02	0.09	0.02	0.27
599	0.00	0.07	0.00	0.19
600	0.00	0.08	0.11	0.26

MEAN	0.00	0.08	0.06	0.30
S.D.	0.040	0.047	0.060	0.128
N	18	18	18	18

--: Data Unavailable b: Scheduled Sacrifice

^aSuccessive periods

^cRetinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 156A

GROUP: 1-F

SEX: FEMALE

DOSE: 0 (mg base/kg/day)

ANIMAL #	DAY 0	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
601	--	--	--	--	--	--	--	--	--	--	--	--
602	4.23	4.11	4.07	4.00	4.02	3.97	3.95	3.94	3.99	4.07	4.10	4.05
603	3.77	3.83	3.62	3.66	3.75	3.77	3.73	3.73	3.75	3.78	3.84	3.89
604	3.12	3.05	2.96	2.93	2.93	2.95	2.95	2.96	2.99	2.96	3.00	3.03
605	3.72	3.31	3.26	3.25	3.26	3.26	3.22	3.26	3.28	3.34	3.37	3.41
606	3.57	3.43	3.38	3.35	3.37	3.43	3.46	3.44	3.48	3.52	3.53	3.56
607	3.76	3.61	3.54	3.53	3.53	3.53	3.53	3.53	3.51	3.54	3.53	3.57
608	3.42	3.21	3.17	3.19	3.17	3.15	3.15	3.15	3.17	3.23	3.26	3.27
609	3.76	3.68	3.47	3.55	3.49	3.56	3.62	3.77	3.64	3.72	3.73	3.87
610	3.54	3.53	3.30	3.48	3.37	3.39	3.40	3.42	3.44	3.43	3.49	3.55
611	4.28	3.99	4.03	4.03	3.99	4.01	4.00	4.01	4.05	4.17	4.17	4.23
612	4.00	3.02	3.03	2.99	3.06	3.05	3.02	3.02	3.08	3.10	3.01	3.20
613	3.66	3.76	3.65	3.59	3.71	3.64	3.54	3.68	3.77	3.80	3.83	3.86
614	3.77	3.42	3.30	3.38	3.40	3.38	3.43	3.40	3.44	3.44	3.47	3.52
615	4.28	3.98	3.99	3.96	4.03	4.02	3.99	3.99	3.99	4.07	4.02	4.16
616	4.27	4.33	4.21	4.15	4.14	4.18	4.22	4.20	4.23	4.31	4.35	4.35
617	4.00	3.71	3.72	3.74	3.74	3.74	3.72	3.72	3.80	3.86	3.89	3.91
618	3.72	3.48	3.46	3.45	3.48	3.50	3.51	3.53	3.54	3.54	3.62	3.64
619	3.94	3.66	3.64	3.64	3.64	3.67	3.66	3.64	3.69	3.71	3.73	3.74
620	3.48	3.31	3.26	3.31	3.28	3.27	3.29	3.31	3.31	3.33	3.37	3.38
MEAN	3.80	3.60	3.53	3.54	3.55	3.55	3.55	3.56	3.59	3.63	3.65	3.69
S.D.	0.319	0.352	0.355	0.339	0.344	0.343	0.342	0.341	0.341	0.367	0.370	0.360
N	19	19	19	19	19	19	19	19	19	19	19	19

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 156A

GROUP: 1-F

SEX: FEMALE

DOSE: 0 (mg base/kg/day)

ANIMAL # DAY 16 DAY 17 DAY 18 DAY 24 DAY 29

601	--	--	--	--	b
602	4.07	4.03	4.12	4.13	4.26
603	3.85	3.86	3.92	3.94	3.97
604	2.96	3.01	3.02	3.08	3.10
605	3.39	3.38	3.36	3.46	3.53
606	3.60	3.60	3.60	3.70	3.77
607	3.57	3.59	3.59	3.63	3.69
608	3.27	3.25	3.26	3.37	3.41
609	3.79	3.87	3.84	3.89	3.98
610	3.54	3.54	3.51	3.56	3.66
611	4.26	4.22	4.23	4.24	4.38
612	3.21	3.18	3.20	3.21	3.20
613	3.88	3.84	3.82	3.87	3.99
614	3.51	3.53	3.53	3.61	3.72
615	4.16	4.19	4.19	4.18	4.24
616	4.44	4.44	4.52	4.44	4.50
617	4.03	4.03	4.07	4.04	4.10
618	3.67	3.73	3.77	3.87	3.95
619	3.73	3.72	3.71	3.78	3.80
620	3.37	3.36	3.38	3.41	3.43

MEAN	3.70	3.70	3.72	3.76	3.83
S.D.	0.384	0.380	0.394	0.363	0.386
N	19	19	19	19	19

--: Data Unavailable

b: Scheduled Sacrifice

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 156A

GROUP: 2-F

SEX: FEMALE

DOSE: 25/16^a (mg base/kg/day)

ANIMAL #	DAY 0	DAY 5	DAY 6	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15
621	3.35	3.22	3.16	3.16	3.12	3.12	3.15	3.16	3.17	3.16	3.10	3.10
622	3.64	3.61	3.45	3.48	3.40	3.39	3.45	3.48	3.41	3.39	3.36	3.27
623	3.43	3.56	3.42	3.37	3.32	3.37	3.39	3.39	3.45	3.36	3.27	3.22
624	3.79	3.83	3.56	3.50	3.47	3.42	3.35	3.30	3.13	c	c	c
625	3.80	3.83	3.74	3.77	3.78	3.69	3.56	d	d	d	d	d
626	3.75	3.70	3.60	3.61	3.53	3.59	3.56	3.60	3.62	3.58	3.74	3.72
627	3.27	3.07	3.13	3.04	3.07	3.06	3.07	3.07	3.10	3.15	3.13	3.18
628	--	--	--	--	--	--	--	--	--	--	--	--
629	3.51	3.53	3.29	3.33	3.32	3.35	3.26	3.20	3.18	3.11	3.04	2.99
630	3.37	3.27	3.26	3.23	3.21	3.18	3.26	3.19	3.26	3.23	3.17	3.15
631	3.98	3.66	3.64	3.62	3.63	3.61	3.61	3.64	3.64	3.59	3.54	3.46
632	3.80	3.78	3.59	3.57	3.61	3.62	3.63	3.63	3.71	3.59	3.71	3.82
633	3.77	3.55	3.56	3.56	3.57	3.57	3.54	3.55	3.59	3.55	3.53	3.51
634	3.78	3.74	3.75	3.77	3.72	3.65	3.71	3.73	3.74	3.80	3.79	3.83
635	3.90	3.63	3.61	3.56	3.62	3.56	3.62	3.59	3.61	3.67	3.78	3.80
636	3.41	3.20	3.18	3.19	3.19	3.19	3.20	3.22	3.24	3.30	3.34	3.33
637	3.41	3.01	3.06	3.07	3.07	3.12	3.08	3.02	2.99	2.96	2.89	2.84
638	3.70	3.33	3.37	3.37	3.37	3.45	3.44	3.47	3.51	3.52	3.57	3.56
639	4.16	4.28	4.33	4.34	4.20	4.31	4.33	4.29	4.25	4.28	4.16	4.04
640	4.16	4.05	3.94	3.96	3.90	3.88	3.90	3.88	3.91	3.95	3.93	3.99
MEAN	3.68	3.57	3.51	3.50	3.48	3.48	3.48	3.47	3.47	3.48	3.47	3.46
S.D.	0.266	0.329	0.310	0.320	0.299	0.302	0.304	0.317	0.323	0.333	0.351	0.362
N	19	19	19	19	19	19	19	18	18	17	17	17

--: Data Unavailable

c: Animal Found Dead

d: Sacrificed Moribund

^aThe high dose was reduced from 25 mg base/kg/day to 16 mg base/kg/day on GD15 - GD16 (the range of days reflects study stagger-start over 2 days)

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 156A

GROUP: 2-F
 DOSE: 25/16^a (mg base/kg/day)

SEX: FEMALE

ANIMAL #	DAY 16	DAY 17	DAY 18	DAY 24	DAY 29
621	3.11	3.06	3.16	3.30	3.38
622	3.24	3.24	3.16	e	e
623	3.12	3.11	3.07	3.37	3.47
624	c	c	c	c	c
625	d	d	d	d	d
626	3.71	3.70	3.70	3.85	3.90
627	3.19	3.16	3.19	3.36	3.44
628	--	--	--	--	b
629	2.97	2.90	2.88	3.02	3.11
630	3.10	3.04	3.04	3.00	e
631	3.42	3.38	3.35	3.01	2.99
632	3.76	3.84	3.90	4.02	4.21
633	3.46	3.39	3.32	3.65	3.69
634	3.91	3.89	3.82	3.94	3.99
635	3.70	3.69	3.69	3.81	3.78
636	3.35	3.35	3.38	3.43	3.49
637	2.78	2.76	2.79	c	c
638	3.58	3.56	3.62	3.67	3.83
639	3.93	d	d	d	d
640	4.04	3.95	4.04	4.22	4.28
MEAN	3.43	3.38	3.38	3.55	3.66
S.D.	0.369	0.365	0.374	0.395	0.392
N	17	16	16	14	13

--: Data Unavailable b: Scheduled Sacrifice c: Animal Found Dead d: Sacrificed Moribund e: Aborted/Sacrificed

^aThe high dose was reduced from 25 mg base/kg/day to 16 mg base/kg/day on GD15 - GD16 (the range of days reflects study stagger-start over 2 days)

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)

STUDY: 156A

GROUP: 1-F
 DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OAY 7	OAY 8	DAY 9	OAY 10	OAY 11	OAY 12	OAY 13	DAY 14	OAY 15	DAY 16	OAY 17
601	--	--	--	--	--	--	--	--	--	--	--
602	-0.07	0.02	-0.05	-0.02	-0.01	0.05	0.08	0.03	-0.05	0.02	-0.04
603	0.04	0.09	0.02	-0.04	0.00	0.02	0.03	0.06	0.05	-0.04	0.01
604	-0.03	0.00	0.02	0.00	0.01	0.03	-0.03	0.04	0.03	-0.07	0.05
605	-0.01	0.01	0.00	-0.04	0.04	0.02	0.06	0.03	0.04	-0.02	-0.01
606	-0.03	0.02	0.06	0.03	-0.02	0.04	0.04	0.01	0.03	0.04	0.00
607	-0.01	0.00	0.00	0.00	0.00	-0.02	0.03	-0.01	0.04	0.00	0.02
608	0.02	-0.02	-0.02	0.00	0.00	0.02	0.06	0.03	0.01	0.00	-0.02
609	0.08	-0.06	0.07	0.06	0.15	-0.13	0.08	0.01	0.14	-0.08	0.08
610	0.18	-0.11	0.02	0.01	0.02	0.02	-0.01	0.06	0.06	-0.01	0.00
611	0.00	-0.04	0.02	-0.01	0.01	0.04	0.12	0.00	0.06	0.03	-0.04
612	-0.04	0.07	-0.01	-0.03	0.00	0.06	0.02	-0.09	0.19	0.01	-0.03
613	-0.06	0.12	-0.07	-0.10	0.14	0.09	0.03	0.03	0.03	0.02	-0.04
614	0.08	0.02	-0.02	0.05	-0.03	0.04	0.00	0.03	0.05	-0.01	0.02
615	-0.03	0.07	-0.01	-0.03	0.00	0.00	0.08	-0.05	0.14	0.00	0.03
616	-0.06	-0.01	0.04	0.04	-0.02	0.03	0.08	0.04	0.00	0.09	0.00
617	0.02	0.00	0.00	-0.02	0.00	0.08	0.06	0.03	0.02	0.12	0.00
618	-0.01	0.03	0.02	0.01	0.02	0.01	0.00	0.08	0.02	0.03	0.06
619	0.00	0.00	0.03	-0.01	-0.02	0.05	0.02	0.02	0.01	-0.01	-0.01
620	0.05	-0.03	-0.01	0.02	0.02	0.00	0.02	0.04	0.01	-0.01	-0.01
MEAN	0.01	0.01	0.01	0.00	0.02	0.02	0.04	0.02	0.05	0.01	0.00
S.O.	0.061	0.053	0.034	0.037	0.048	0.046	0.038	0.039	0.056	0.047	0.034
N	19	19	19	19	19	19	19	19	19	19	19

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)

STUDY: 156A

GROUP: 1-F
 DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	DAY 18	DAY 24	DAY 29	TOTAL GAIN
601	--	--	b	--
602	0.09	0.01	0.13	0.19
603	0.06	0.02	0.03	0.35
604	0.01	0.06	0.02	0.14
605	-0.02	0.10	0.07	0.27
606	0.00	0.10	0.07	0.39
607	0.00	0.04	0.06	0.15
608	0.01	0.11	0.04	0.24
609	-0.03	0.05	0.09	0.51
610	-0.03	0.05	0.10	0.36
611	0.01	0.01	0.14	0.35
612	0.02	0.01	-0.01	0.17
613	-0.02	0.05	0.12	0.34
614	0.00	0.08	0.11	0.42
615	0.00	-0.01	0.06	0.25
616	0.08	-0.08	0.06	0.29
617	0.04	-0.03	0.06	0.38
618	0.04	0.10	0.08	0.49
619	-0.01	0.07	0.02	0.16
620	0.02	0.03	0.02	0.17
MEAN	0.01	0.04	0.07	0.30
S.D.	0.034	0.049	0.041	0.115
N	19	19	19	19

--: Data Unavailable

b: Scheduled Sacrifice

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)

STUDY: 156A

GROUP: 2-F

SEX: FEMALE

DOSE: 25/16^a (mg base/kg/day)

ANIMAL #	DAY 7	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 16	DAY 17
621	0.00	-0.04	0.00	0.03	0.01	0.01	-0.01	-0.06	0.00	0.01	-0.05
622	0.03	-0.08	-0.01	0.06	0.03	-0.07	-0.02	-0.03	-0.09	-0.03	0.00
623	-0.05	-0.05	0.05	0.02	0.00	0.06	-0.09	-0.09	-0.05	-0.10	-0.01
624	-0.06	-0.03	-0.05	-0.07	-0.05	-0.17	c	c	c	c	c
625	0.03	0.01	-0.09	-0.13	d	d	d	d	d	d	d
626	0.01	-0.08	0.06	-0.03	0.04	0.02	-0.04	0.16	-0.02	-0.01	-0.01
627	-0.09	0.03	-0.01	0.01	0.00	0.03	0.05	-0.02	0.05	0.01	-0.03
628	--	--	--	--	--	--	--	--	--	--	--
629	0.04	-0.01	0.03	-0.09	-0.06	-0.02	-0.07	-0.07	-0.05	-0.02	-0.07
630	-0.03	-0.02	-0.03	0.08	-0.07	0.07	-0.03	-0.06	-0.02	-0.05	-0.06
631	-0.02	0.01	-0.02	0.00	0.03	0.00	-0.05	-0.05	-0.08	-0.04	-0.04
632	-0.02	0.04	0.01	0.01	0.00	0.08	-0.12	0.12	0.11	-0.06	0.08
633	0.00	0.01	0.00	-0.03	0.01	0.04	-0.04	-0.02	-0.02	-0.05	-0.07
634	0.02	-0.05	-0.07	0.06	0.02	0.01	0.06	-0.01	0.04	0.08	-0.02
635	-0.05	0.06	-0.06	0.06	-0.03	0.02	0.06	0.11	0.02	-0.10	-0.01
636	0.01	0.00	0.00	0.01	0.02	0.02	0.06	0.04	-0.01	0.02	0.00
637	0.01	0.00	0.05	-0.04	-0.06	-0.03	-0.03	-0.07	-0.05	-0.06	-0.02
638	0.00	0.00	0.08	-0.01	0.03	0.04	0.01	0.05	-0.01	0.02	-0.02
639	0.01	-0.14	0.11	0.02	-0.04	-0.04	0.03	-0.12	-0.12	-0.11	d
640	0.02	-0.06	-0.02	0.02	-0.02	0.03	0.04	-0.02	0.06	0.05	-0.09
MEAN	-0.01	-0.02	0.00	0.00	-0.01	0.01	-0.01	-0.01	-0.01	-0.03	-0.03
S.D.	0.035	0.048	0.052	0.054	0.036	0.058	0.055	0.079	0.058	0.054	0.039
N	19	19	19	19	18	18	17	17	17	17	16

--: Data Unavailable c: Animal Found Dead d: Sacrificed Moribund

^aThe high dose was reduced from 25 mg base/kg/day to 16 mg base/kg/day on GD15 - GD16 (the range of days reflects study stagger-start over 2 days)

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)

STUDY: 156A

GROUP: 2-F
 DOSE: 25/16^a (mg base/kg/day)

SEX: FEMALE

ANIMAL #	DAY 18	DAY 24	DAY 29	TOTAL GAIN
621	0.10	0.14	0.08	0.22
622	-0.08	e	e	--
623	-0.04	0.30	0.10	0.05
624	c	c	c	--
625	d	d	d	--
626	0.00	0.15	0.05	0.30
627	0.03	0.17	0.08	0.31
628	--	--	b	--
629	-0.02	0.14	0.09	-0.18
630	0.00	-0.04	e	--
631	-0.03	-0.34	-0.02	-0.65
632	0.06	0.12	0.19	0.62
633	-0.07	0.33	0.04	0.13
634	-0.07	0.12	0.05	0.24
635	0.00	0.12	-0.03	0.17
636	0.03	0.05	0.06	0.31
637	0.03	c	c	--
638	0.06	0.05	0.16	0.46
639	d	d	d	--
640	0.09	0.18	0.06	0.34
MEAN	0.01	0.11	0.07	0.18
S.D.	0.056	0.159	0.061	0.315
N	16	14	13	13

--: Data Unavailable b: Scheduled Sacrifice c: Animal Found Dead d: Sacrificed Moribund e: Aborted/Sacrificed

^aThe high dose was reduced from 25 mg base/kg/day to 16 mg base/kg/day on GD15 - GD16 (the range of days reflects study stagger-start over 2 days)

DRAFT

APPENDIX 4

Individual Maternal Food Consumption Data

Initial Study: 4-2 through 4-6
Retest: 4.1-1 through 4.1-2

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 156

GROUP: 1-F
 DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	DAY 8	DAY 10	DAY 12	DAY 15	DAY 18	DAY 24	DAY 29
501	130	130	130	130	130	130	130
502	--	--	--	--	--	--	--
503	130	130	130	130	130	130	130
504	130	130	130	130	130	130	130
505	130	130	130	130	130	130	130
506	130	130	130	130	130	130	130
507	130	130	130	130	130	130	130
508	130	130	130	130	130	130	130
509	130	130	130	130	130	130	130
510	130	130	130	130	130	130	130
511	130	130	130	130	130	130	130
512	130	130	130	130	130	130	130
513	--	--	--	--	--	--	--
514	130	130	130	130	130	130	130
515	130	130	130	130	130	130	130
516	130	130	130	130	130	130	130
517	130	130	130	130	130	130	130
518	130	130	130	130	130	130	130
519	130	130	130	130	130	130	130
520	130	130	130	130	130	130	130
MEAN	130	130	130	130	130	130	130
S.D.	0.0	0.0	0.0	0.0	0.0	0.0	0.0
N	18	18	18	18	18	18	18

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 156

GROUP: 2-F

SEX: FEMALE

DOSE: 2 (mg base/kg/day)

ANIMAL #	DAY 8	DAY 10	DAY 12	DAY 15	DAY 18	DAY 24	DAY 29
521	130	130	130	130	130	130	130
522	130	130	130	130	130	130	130
523	130	130	130	130	130	130	130
524	--	--	--	--	--	--	--
525	--	--	--	--	--	--	--
526	130	130	130	130	130	130	130
527	130	130	75	130	130	130	85
528	--	--	--	--	--	--	--
529	130	130	130	130	130	130	130
530	130	130	130	130	130	130	130
531	130	130	130	130	130	130	130
532	130	130	130	130	130	130	130
533	130	130	130	130	130	130	130
534	130	130	130	130	130	130	130
535	130	130	130	130	130	130	130
536	130	130	130	130	130	130	130
537	--	--	--	--	--	--	--
538	130	130	130	130	130	130	130
539	--	--	--	--	--	--	--
540	130	130	130	130	130	130	130
MEAN	130	130	126	130	130	130	127
S.D.	0.0	0.0	14.2	0.0	0.0	0.0	11.6
N	15	15	15	15	15	15	15

---: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 156

GROUP: 3-F
 DOSE: 7 (mg base/kg/day)

SEX: FEMALE

ANIMAL # DAY 8 DAY 10 DAY 12 DAY 15 DAY 18 DAY 24 DAY 29

541	--	--	--	--	--	--	--
542	--	--	--	--	--	--	--
543	130	130	130	130	130	130	130
544	130	130	130	109	130	130	130
545	230	130	130	130	130	130	130
546	130	130	130	130	130	130	130
547	130	130	130	130	130	130	130
548	130	130	130	130	130	130	130
549	130	130	130	130	130	130	130
550	130	130	130	130	130	130	130
551	--	--	--	--	--	--	--
552	130	130	130	130	130	130	130
553	130	130	130	130	130	130	130
554	130	130	130	130	130	130	130
555	130	130	130	130	130	130	130
556	130	130	130	130	130	130	130
557	130	130	130	130	130	130	130
558	130	130	130	130	130	130	e
559	130	130	130	130	130	130	130
560	--	--	--	--	--	--	--

MEAN	136	130	130	129	130	130	130
S.D.	25.0	0.0	0.0	5.3	0.0	0.0	0.0
N	16	16	16	16	16	16	15

--: Data Unavailable e: Aborted/Sacrificed

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 156

GROUP: 4-F

SEX: FEMALE

DOSE: 25 (mg base/kg/day)

ANIMAL # DAY 8 DAY 10 DAY 12 DAY 15 DAY 18 DAY 24 DAY 29

561	--	--	--	--	--	--	--
562	--	--	--	--	--	--	--
563	130	130	130	130	130	130	130
564	--	--	--	--	--	--	--
565	130	130	130	130	120	130	10
566	130	130	130	130	130	130	130
567	130	130	130	78	124	116	130
568	130	130	130	130	130	130	130
569	130	130	130	130	130	130	130
570	130	130	--	d	d	d	d
571	130	130	130	130	130	130	130
572	130	130	130	130	130	89	91
573	130	130	130	130	130	130	130
574	130	130	130	130	130	130	130
575	130	130	130	130	130	e	e
576	130	130	130	130	1	c	c
577	--	--	--	--	--	--	--
578	130	130	130	130	130	130	130
579	130	130	130	127	75	130	125
580	130	130	130	1	1	47	e

MEAN 130 130 130 118 108 119 116

S.D. 0.0 0.0 0.0 34.9 45.7 24.7 35.3

N 16 16 15 15 15 13 12

--: Data Unavailable c: Animal Found Dead d: Sacrificed Moribund e: Aborted/Sacrificed

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 156A

GROUP: 1-F
 DOSE: 0 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	DAY 8	DAY 10	DAY 12	DAY 15	DAY 18	DAY 24	DAY 29
601	--	--	--	--	--	--	--
602	130	130	130	130	130	130	130
603	130	130	130	130	130	130	130
604	130	130	130	106	105	130	91
605	130	80	111	109	130	117	130
606	130	130	130	130	130	130	130
607	130	130	130	130	130	130	130
608	130	130	130	130	130	130	130
609	130	130	130	130	130	130	130
610	130	130	130	119	130	130	130
611	130	130	130	130	130	130	130
612 ^a	130	130	130	130	130	130	130
613	130	130	130	130	130	130	130
614 ^a	130	130	130	130	130	130	130
615	130	130	130	130	130	130	130
616 ^a	130	130	130	130	130	130	130
617	130	130	130	130	130	130	130
618 ^a	130	130	130	130	130	130	130
619 ^a	130	130	130	130	130	130	130
620	130	130	130	130	130	130	130
MEAN	130	127	129	127	129	129	128
S.D.	0.0	11.5	4.4	7.4	5.7	3.0	8.9
N	19	19	19	19	19	19	19

--: Data Unavailable

^aFood consumption determined on GD 8/9 and included in Day 8 mean

DEVELOPMENTAL TOXICITY (SEGMENT II)
 STUDY OF WR238605 SUCCINATE IN RABBITS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 156A

GROUP: 2-F
 DOSE: 25/16^a (mg base/kg/day)

SEX: FEMALE

ANIMAL #	DAY 8	DAY 10	DAY 12	DAY 15	DAY 18	DAY 24	DAY 29
621	130	130	106	37	83	85	130
622	130	130	111	4	2	e	e
623	114	130	126	0	3	130	130
624	130	93	0	c	c	c	c
625	130	39	d	d	d	d	d
626	130	130	130	130	130	130	130
627	130	130	130	130	119	121	130
628	--	--	--	--	--	--	--
629	130	15	0	103	0	130	130
630	130	130	130	2	3	1	e
631	130	130	130	2	6	102	0
632 ^a	130	130	130	130	130	130	130
633 ^a	130	130	130	0	6	130	130
634 ^a	130	130	130	110	78	130	130
635 ^a	130	130	130	130	130	130	130
636 ^a	130	130	130	130	130	130	130
637 ^a	130	130	18	0	0	c	c
638	130	130	130	130	130	130	130
639	130	130	130	11	d	d	d
640 ^a	130	130	130	130	130	130	130
MEAN	129	117	107	69	68	115	120
S.D.	3.7	33.1	47.0	61.6	61.0	35.5	36.1
N	19	19	18	17	16	14	13

--: Data Unavailable c: Animal Found Dead d: Sacrificed Moribund e: Aborted/Sacrificed

^a Food consumption determined on GD 8/9 and included in Day 8 mean

DRAFT

APPENDIX 5
Teratology Report



TERATOLOGY REPORT

FOR

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY
OF WR238605 SUCCINATE IN RABBITS

UIC/TRL STUDY NUMBER: 156

PREPARED FOR

TOXICOLOGY RESEARCH LABORATORY (TRL)
UNIVERSITY OF ILLINOIS AT CHICAGO (UIC)
DEPARTMENT OF PHARMACOLOGY
1940 W. TAYLOR ST.
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Teratology Report

Developmental Toxicity (Segment II)
Study of WR238605 Succinate in Rabbits

QUALITY ASSURANCE STATEMENT

This teratology project has been inspected and audited by the PAI Quality Assurance Unit (QAU) as required by the Good Laboratory Practice (GLP) regulations promulgated by the U.S. Food and Drug Administration. Results of these activities indicate that the portions of the study performed by PAI conformed with GLP regulations and applicable Standard Operating Procedures. The teratology narrative report is an accurate reflection of the recorded data. The following table is a record of the inspections/audits performed and reported by the QAU.

<u>Date of Inspection</u>	<u>Phase Inspected</u>	<u>Date Findings Reported to Management/ Study Pathologist</u>
10/3-4/95	Individual Animal Data (Raw Data)	10/04/95
10/4-11/95	Individual Animal Data (Data Entry)	10/11/95
10/5-8/95	Summary Table Review	10/09/95
10/10-11/95	Draft Teratology Report	10/11/95
10/24/95	Second Draft Teratology Report	10/24/95
11/07/95	Third Draft Teratology Report	11/07/95

Sharon E. Abel
Quality Assurance Auditor

November 7, 1995

Date

Developmental Toxicity (Segment II) Study of WR238605 Succinate in Rabbits

II. MATERIALS AND METHODS

A. Introduction

The study was conducted in two phases. The initial phase consisted of a vehicle control group, a positive control group and three WR238605 Succinate-treated groups (at dosage levels of 2, 7 and 25 mg base/kg/day). The second phase was conducted to retest the high dose level (25/16 mg base/kg/day) of the initial phase and consisted of a vehicle control group and a WR238605 Succinate-treated group. The initial phase will be identified and reported using study number 156 and the second phase will be reported using study number 156A. The data for study number 156 will be presented in tables 1-7 and appendicies A-D. The data for study number 156A will be presented in tables 1A-7A and appendicies AA-DD.

B. Cesarean Section

On gestation day 29, all surviving rabbits were euthanized in a random order by intravenous injection of sodium pentobarbital. The abdominal and thoracic cavities were opened by a ventral midline incision and the uterus and ovaries were removed from the body. A gross necropsy was then performed and abnormalities were recorded. Gross findings did not indicate the necessity of retaining any tissue samples containing gross lesions for possible histopathological examination. Following the gross necropsy examination, the carcass of each dam was discarded.

The uterus was examined and weighed. For gravid females, the number of corpora lutea on each ovary was recorded and the ovaries were discarded after evaluation. The uterus was opened and the development of the fetuses was classified using the following criteria:

- Viable fetus: a term fetus which responds to stimuli.
- Nonviable fetus: a term fetus which did not respond to stimuli *in utero* or was not breathing.
- Early resorption: an implantation for which it was not grossly evident that organogenesis had occurred.
- Late resorption: an implantation for which it was grossly evident that organogenesis had occurred. A fetus with autolysis was considered a late resorption.

The number and location of fetuses, early resorption(s), late resorption(s) and their uterine position were documented using the following procedure. All implantation sites were numbered in consecutive fashion per uterine horn beginning with the left distal horn and proceeding to the cervix and then similarly for the right uterine horn beginning with

the distal end and proceeding to the cervix. Uteri with no evidence of pregnancy were placed in 10% aqueous ammonium sulfide solution for detection of possible implantation sites.

C. Fetal Evaluation

1. External Examination

A detailed examination of each fetus was conducted to include the eyes, palate, head shape, extremities and general body integument. The fetuses were then weighed.

2. Visceral Examination

Each fetus was euthanized by intraperitoneal injection of a 40% sodium pentobarbital solution (approximately 0.4 ml/fetus) and then dissected. The abdominal, thoracic and cranial cavities were opened and the internal organs were examined as described by Staples (1974). During the examination, the fetal sex was determined. The fetuses were then individually tagged.

3. Skeletal Examination

Following the visceral examination, the fetuses were eviscerated, skinned and retained in 95% ethyl alcohol for skeletal examination. The fetuses from groups 1-3 and 5 of the initial phase and groups 1 and 2 of the second phase were macerated in 2% potassium hydroxide, stained with Alizarin Red S and cleared with 25% glycerin (Dawson, 1926). The fetuses were then examined for skeletal formation and ossification. The fetuses from group 4 of the initial phase were not scheduled for skeletal staining or examination, however, fetuses 1-3 from dam 569 were inadvertently processed as previously described but were not examined.

D. Statistical Analyses

The incidences or the means and standard deviations of the maternal and fetal observations were calculated. Gravid uterus weights and fetal body weights were analyzed by one-way analysis of variance (ANOVA). If a significant F ratio was obtained ($p \leq 0.05$), Dunnett's test was used for pair-wise comparisons of each treated group to the vehicle control group.

The numbers of early and late resorptions, nonviable fetuses, viable fetuses, total implantation sites and corpora lutea and the percent preimplantation loss, post-implantation loss and total loss/litter were compared across groups using the Kruskal-Wallis nonparametric ANOVA test. If a significant effect occurred ($p \leq 0.05$), the Wilcoxon (Mann-Whitney U) test was used for pair-wise comparisons of each treated group to the vehicle control group.

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Study No. 156

Statistical analyses were performed comparing the treated groups to the respective vehicle control group for each study phase.

Calculations were as follows:

$$\text{Pre-implantation loss \%} = \frac{\#Corpora\ lutea - \#Implants}{\#Corpora\ Lutea} \times 100$$

$$\text{Post-implantation loss \%} = \frac{\#Implants - \#Viable\ fetuses}{\#Implants} \times 100$$

$$\text{Total loss/litter \%} = \frac{\#Corpora\ lutea - \#Viable\ fetuses}{\#Corpora\ Lutea} \times 100$$

Male to female fetal sex ratios were compared using the Chi-square test. The incidences of malformations and variations were compared using the Fisher's exact test with the litter as the experimental unit. The total number of litters with external, visceral and skeletal malformations as well as the total number of litters with malformations and variations were also statistically compared. The percent of fetuses and litters with malformations and variations were calculated and reported, however, these data were not statistically analyzed.

Statistical analyses of the cesarean section and fetal morphological examination data were performed using an IBM™ compatible computer with SAS computer programs (SAS/STAT User's Guide, 1989).

III. RESULTS

A. Survival and Pregnancy

Tables 1 and 1A (Summary Data)

In the initial phase, one female in the 7 mg base/kg/day group aborted on gestation day 25. In the 25 mg base/kg/day group, one female died, one female was euthanized due to back trauma, two females aborted on gestation day 23-25 and one female prematurely delivered prior to scheduled Cesarean section on day 29. In the 25/16 mg base/kg/day group of the second study phase, four females died or were euthanized moribund, two females aborted on gestation day 23-24 and one female aborted, however, the day of abortion could not be determined.

The pregnancy rate of the initial phase was 90% in the vehicle control, 75% in the 2 mg base/kg/day group, and 80% in the 7 and 25 mg base/kg/day and positive control groups. In second phase, the pregnancy rate was 95% for the vehicle control and the 25/16 mg base/kg/day groups.

B. Maternal Gross Necropsy

Tables 2 and 2A (Summary Data)
Appendices A and AA (Individual Data)

No treatment-related changes were observed in either study phase.

C. Cesarean Section Data

Tables 3 and 3A (Summary Data)
Appendices B, BB, C and CC (Individual Data)

There were no statistically significant or biologically meaningful differences between the vehicle control and the WR238605 Succinate-treated groups of either study phase in the cesarean section parameters measured, including the numbers of corpora lutea, implantation sites, viable and nonviable fetuses, early and late resorptions, pre-implantation loss, post-implantation loss, total loss/litter, fetal sex ratios, and gravid uterus and fetal weights. Treatment-related differences noted in the positive control group included a statistically significant increase in the number of early resorptions and a corresponding nonstatistically significant decrease in the mean number of viable fetuses, and nonstatistically significant increases in the percent post-implantation loss, the percent total loss/litter. In addition, the slightly reduced gravid uterus weight in the positive control group was attributable to the reduced number of viable fetuses in the group.

D. Fetal Morphological Observations

Tables 4-7 and 4A-7A (Summary Data)
Appendices D and DD (Individual Data)

No apparent treatment-related malformations or developmental variations were observed in the 2, 7 and 25 mg base/kg/day levels of the initial phase or in the 25/16 mg/kg/day level of the second phase. An incidental but statistically significant decrease in the number of litters with variations occurred in the 25 mg base/kg/day group. In the positive control group, statistical increases were observed in the number of litters with external, visceral, and skeletal malformations. The external malformations primarily involved structures of the head including the mouth, jaws, palate, pinnae and tail. In addition, a significant increase in the occurrence of additional structures in the facial

region was noted. The visceral malformations primarily included heart/great vessel and kidney/ureter anomalies. Skeletal malformations included skull, caudal vertebrae and hyoid anomalies. The incidences of two developmental variations (major blood vessels variations and distended ureters) were also increased in the positive control group compared to the vehicle control group.

IV. DISCUSSION AND CONCLUSIONS

This study was conducted to evaluate the embryo/fetal toxicity and the teratogenic potential of WR238605 Succinate in rabbits.

Treatment-related mortality and abortion occurred in the 25 mg base/kg/day group of the initial phase and in the 25/16 mg base/kg/day group of the second phase. The occurrence of one abortion in the 7 mg base/kg/day group was not considered sufficient to indicate a treatment-related effect. Overall pregnancy and maternal gross necropsy findings were not affected by treatment with WR238605 Succinate. Cesarean section data were comparable between the vehicle control and the 2, 7 and 25 mg base/kg/day groups of the initial phase and the vehicle control and 25/16 mg base kg/day groups of the second phase. Similarly, no biologically meaningful differences were noted in the fetal morphological examination data from the 2, 7, 25 and 25/16 mg base/kg/day WR238605 Succinate-treated groups.

The use of Vitamin A (Retinol Palmitate) as a positive control agent was effective in producing a teratogenic response. A dose level of 300 mg/kg/day, administered on gestation days 9 and 10 resulted in increased post-implantation loss and percent total loss/litter as characterized by an increase in early resorptions and a decrease in viable fetuses. A decrease in gravid uterus weights associated with a lower number of surviving fetuses was also observed. The incidences of external, visceral and skeletal malformations were significantly increased. Salient findings were primarily related to the structures of the head (including the skull and hyoid), kidneys and ureters, and vertebral column (including the tail).

In conclusion, maternal toxicity was produced in the 25 and 25/16 mg base/kg/day groups. No evidence of embryo/fetal toxicity or teratogenicity was produced in either study phase at dose levels of 2, 7, 25 and 25/16 mg base/kg/day. Results of the positive control group demonstrated that the procedures utilized in the conduct of this study were sufficiently sensitive to identify potential developmental toxicants.

Michael D. Mercieca, B.S.
Teratologist

Date _____

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V. REFERENCES

Staples, R.E. (1974). Detection of visceral alterations in mammalian fetuses. *Teratol.* 9,A-37.

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

SAS Institute Inc., SAS/STAT User's Guide, Version 6, Fourth Edition, Volume 2
Cary, NC:SAS Institute Inc., 1989. 846 pp.

TABLE 1

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

SUMMARY OF PREGNANCY STATUS

GROUP: DOSE LEVEL (MG BASE/KG/DAY):	1		2		3		4		5	
	No.	%	No.	%	No.	%	No.	%	No.	%
FEMALES ON STUDY	20		20		20		20		20	
FOUND DEAD/EUTHANIZED	0	0.0	0	0.0	0	0.0	2	10.0	0	0.0
PREMATURE DELIVERY/ABORTION	0	0.0	0	0.0	1	5.0	3	15.0	0	0.0
EXAMINED AT CESAREAN SECTION	20	100.0	20	100.0	19	95.0	15	75.0	20	100.0
NONGRAVID	2	10.0	5	25.0	4	21.1	4	26.7	2	20.0
GRAVID	18	90.0	15	75.0	15	78.9	11	73.3	18	80.0
WITH TOTAL RESORPTIONS	0	0.0	0	0.0	0	0.0	0	0.0	1	5.6
WITH LIVE FETUSES	18	100.0	15	100.0	15	100.0	11	100.0	17	94.4
TOTAL GRAVID FEMALES	18	90.0	15	75.0	16	80.0	16	80.0	18	90.0

* RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10).

TABLE 1A

UIC/TRL STUDY NO.: 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

SUMMARY OF PREGNANCY STATUS

GROUP: DOSE LEVEL (MG BASE/KG/DAY):	1		2	
	No.	%	No.	%
	20		20	
	0	0.0	4	20.0
	0	0.0	3	15.0
	20	100.0	13	100.0
	1	5.0	1	7.7
	19	95.0	12	92.3
	0	0.0	0	0.0
	19	100.0	12	100.0
	19	95.0	19	95.0

* DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 25 MG BASE/KG/DAY TO 16 MG BASE/KG/DAY ON GESTATION DAYS 15 OR 16 (THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 2 DAYS).

TABLE 2

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

SUMMARY OF GROSS NECROPSY OBSERVATIONS

	GROUP:				
	1	2	3	4	5
DOSE LEVEL (MG BASE/KG/DAY):	0	2	7	25	300 MG/KG/DAY ^a
NUMBER OF FEMALES EXAMINED AT THE SCHEDULED GESTATION DAY 29 CESAREAN SECTION	20	20	19 ^b	15 ^b	20
NO ABNORMALITIES DETECTED	20	19	17	15	20
NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE	2	5	4	4	2
GRAVID - AMMONIUM SULFIDE TEST POSITIVE	0	0	0	0	0
CORPORA LUTEA					
- HEMORRHAGIC	0	1	2	0	0

^a RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10).

^b DOES NOT INCLUDE FEMALES WHICH DIED EARLY (SEE APPENDIX A FOR INDIVIDUAL FINDINGS).

TABLE 2A

UIC/TRL STUDY NO.: 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 SUMMARY OF GROSS NECROPSY OBSERVATIONS

	GROUP:	
	1	2
DOSE LEVEL (MG BASE/KG/DAY):	0	25/16 ^a
NUMBER OF FEMALES EXAMINED AT THE SCHEDULED GESTATION DAY 29 CESAREAN SECTION	20	13 ^b
NO ABNORMALITIES DETECTED	19	13
NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE	1	1
GRAVID - AMMONIUM SULFIDE TEST POSITIVE	0	0
OVIDUCT - CYST	1	0

^a DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 25 MG BASE/KG/DAY TO 16 MG BASE/KG/DAY ON GESTATION DAYS 15 OR 16 (THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 2 DAYS).

^b DOES NOT INCLUDE FEMALES WHICH DIED EARLY (SEE APPENDIX A FOR INDIVIDUAL FINDINGS).

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 TABLE 3
 SUMMARY OF CESAREAN SECTION DATA

	GROUP: DOSE LEVEL (MG BASE/KG/DAY):				
	1 0	2 2	3 7	4 25	5 300
	MG/KG/DAY*				
NUMBER OF GRAVID FEMALES	18	15	15	11	18
NUMBER OF CORPORA LUTEA	MEAN 8.8 S.D. 1.6	9.1 1.8	8.6 ^b 0.8	9.3 ^b 2.4	8.1 ^b 1.7
NUMBER OF IMPLANTATIONS	MEAN 8.2 S.D. 1.7	8.2 2.5	7.9 1.1	8.5 1.6	7.3 2.1
PERCENT PRE-IMPLANTATION LOSS	MEAN 6.5 S.D. 7.1	10.9 17.3	7.9 ^b 12.8	5.9 ^b 8.6	8.9 ^b 18.7
NUMBER OF VIABLE FETUSES	MEAN 7.8 S.D. 1.8	8.1 2.5	7.4 1.2	7.8 1.6	5.7 2.7
NUMBER OF NONVIABLE FETUSES	MEAN 0.0 S.D. 0.0	0.0 0.0	0.0 0.0	0.0 0.0	0.0 0.0
NUMBER OF EARLY RESORPTIONS	MEAN 0.3 S.D. 0.6	0.1 0.4	0.4 0.7	0.4 0.5	1.4* 0.5
NUMBER OF LATE RESORPTIONS	MEAN 0.1 S.D. 0.3	0.0 0.0	0.1 0.3	0.3 0.5	0.1 0.5
PERCENT POST-IMPLANTATION LOSS	MEAN 6.0 S.D. 8.2	1.7 4.5	6.1 10.1	7.5 6.1	22.9 30.9
PERCENT TOTAL LOSS/LITTER	MEAN 11.8 S.D. 12.5	12.5 17.2	13.8 15.4	12.3 9.7	28.8 30.3

* RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10).

^b DOES NOT INCLUDE ONE FEMALE EACH IN GROUPS 3 AND 5 AND TWO FEMALES IN GROUP 4 FOR WHICH CORPORA LUTEA WERE NOT RECORDED.

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05

TABLE 3 (CONT.)

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 SUMMARY OF CESAREAN SECTION DATA

GROUP: DOSE LEVEL (MG BASE/KG/DAY):	1		2		3		4		5	
	0	0	2	2	7	7	25	25	300	300
SEX: MALES / FEMALES	3.9	3.9	4.5	3.5	3.9	3.5	3.8	4.0	2.8	2.9
	1.8	1.8	1.8	1.7	1.8	2.1	1.5	1.5	1.8	2.0
FETAL WEIGHT (g) (LITTER) ^b	38.91	38.91	35.72	35.72	37.01	37.01	35.92	35.92	40.35	40.35
	5.24	5.24	4.53	4.53	4.44	4.44	4.79	4.79	4.51	4.51
(MALES) ^b	39.02	39.02	35.84	35.84	36.72	36.72	36.23	36.23	41.92	41.92
	5.97	5.97	4.19	4.19	4.34	4.34	3.79	3.79	5.62	5.62
(FEMALES) ^b	38.74	38.74	35.47	35.47	37.60	37.60	36.44	36.44	39.10	39.10
	5.76	5.76	5.71	5.71	6.70	6.70	5.97	5.97	4.53	4.53
GRAVID UTERUS WEIGHT (g)	419.87	419.87	390.14	390.14	384.83	384.83	413.08	413.08	345.68 ^c	345.68 ^c
	93.59	93.59	98.68	98.68	64.81	64.81	113.41	113.41	98.58	98.58

^a RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10).

^b VALUE FOR EACH GROUP REPRESENTS THE MEAN OF THE TOTAL OF THE LITTER MEANS.

^c DOES NOT INCLUDE ONE FEMALE FOR WHICH THE GRAVID UTERUS WEIGHT WAS NOT RECORDED. NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 3A

UIC/TRL STUDY NO.: 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
SUMMARY OF CESAREAN SECTION DATA

	GROUP:	
	1	2
DOSE LEVEL (MG BASE/KG/DAY):	0	25/16*
NUMBER OF GRAVID FEMALES	19	12
NUMBER OF CORPORA LUTEA	MEAN 9.8	10.3
	S.D. 2.0	1.7
NUMBER OF IMPLANTATIONS	MEAN 8.7	9.9
	S.D. 2.6	1.6
PERCENT PRE-IMPLANTATION LOSS	MEAN 11.5	3.8
	S.D. 18.9	6.0
NUMBER OF VIABLE FETUSES	MEAN 8.1	9.5
	S.D. 2.5	1.7
NUMBER OF NONVIABLE FETUSES	MEAN 0.0	0.0
	S.D. 0.0	0.0
NUMBER OF EARLY RESORPTIONS	MEAN 0.2	0.4
	S.D. 0.4	0.8
NUMBER OF LATE RESORPTIONS	MEAN 0.4	0.0
	S.D. 0.7	0.0
PERCENT POST-IMPLANTATION LOSS	MEAN 6.3	4.2
	S.D. 7.3	7.8
PERCENT TOTAL LOSS/LITTER	MEAN 17.2	7.8
	S.D. 19.0	10.1

* DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 25 MG BASE/KG/DAY TO 16 MG BASE/KG/DAY ON GESTATION DAYS 15 OR 16 (THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 2 DAYS).
NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 3A (CONT.)

UIC/TRL STUDY NO.: 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

SUMMARY OF CESAREAN SECTION DATA

GROUP: DOSE LEVEL (MG BASE/KG/DAY):	1		2	
	0	0	25/16 ^a	25/16 ^a
SEX: MALES / FEMALES	MEAN S.D.	4.3 3.8 1.9 1.7	3.9 5.6 1.4 1.7	
FETAL WEIGHT (g) (LITTER) ^b	MEAN S.D.	38.97 4.89	35.37 4.61	
(MALES) ^b	MEAN S.D.	39.42 6.24	35.80 4.89	
(FEMALES) ^b	MEAN S.D.	38.49 4.91	35.00 4.51	
GRAVID UTERUS WEIGHT (g)	MEAN S.D.	448.58 111.11	477.93 80.05	

^a DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 25 MG BASE/KG/DAY TO 16 MG BASE/KG/DAY ON GESTATION DAYS 15 OR 16.
(THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 2 DAYS).

^b VALUE FOR EACH GROUP REPRESENTS THE MEAN OF THE TOTAL OF THE LITTER MEANS.
NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 4

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS

- ABSOLUTE -

GROUP:	FETUSES					LITTERS				
	1	2	3	4	5	1	2	3	4	5
DOSE LEVEL (MG BASE/KG/DAY):	0	2	7	25	300	0	2	7	25	300
NUMBER EXAMINED EXTERNALLY	140	121	111	86	103	18	15	15	11	17
MICROCEPHALY	0	0	0	0	18	0	0	0	0	7*
CLEFT PALATE	0	0	0	0	13	0	0	0	0	6*
MACROSTOMIA	0	0	0	0	9	0	0	0	0	5*
FACE - FACIAL BLEB(S)	0	0	0	0	39	0	0	0	0	10*
MANDIBLE - MICROGNATHIA	0	0	0	0	12	0	0	0	0	5*
MAXILLAE - MICROGNATHIA	0	0	0	0	15	0	0	0	0	5*
PINNA ANOMALY	0	0	0	0	33	0	0	0	0	8*
TAIL ANOMALY	0	0	0	0	30	0	0	0	0	12*
ANAL ATRESIA	0	0	0	0	8	0	0	0	0	5*
SMALL ANAL OPENING	0	0	0	0	1	0	0	0	0	1
TONGUE/MANDIBLE ANOMALY	0	0	0	0	3	0	0	0	0	3
MOUTH - FACIAL BLEB(S)	0	0	0	0	1	0	0	0	0	1
NECK - BLEB(S)	0	0	0	0	16	0	0	0	0	6*
MICROSTOMIA	0	0	0	0	6	0	0	0	0	4*
NUMBER EXAMINED VISCERALLY	138 ^b	121	108 ^b	86	102 ^b	18	15	15	11	17
HEART AND/OR GREAT VESSEL ANOMALY	0	0	0	0	2	0	0	0	0	2
KIDNEY AND/OR URETER ANOMALY	0	0	0	0	15	0	0	0	0	8*
LUNGS - SMALL IN SIZE	0	1	0	0	0	0	1	0	0	0

^a RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10).

^b DOES NOT INCLUDE TWO FETUSES FROM GROUP 1, THREE FETUSES FROM GROUP 3 AND ONE FETUS FROM GROUP 5 FOR WHICH VISCERAL OBSERVATIONS WERE NOT RECORDED.
SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P \leq 0.05$.

TABLE 4 (CONT.)

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS

- ABSOLUTE -

GROUP:	FETUSES										LITTERS				
	1	2	3	4	5	18	15	15	15	17	1	2	3	4	5
DOSE LEVEL (MG BASE/KG/DAY):	0	2	7	25	300	0 ^b	103	0 ^b	103	18	15	15	15	0 ^b	17
NUMBER EXAMINED SKELETALLY	140	121	111	0 ^b	103	18	103	0 ^b	103	18	15	15	15	0 ^b	17
VERTEBRAL ANOMALY WITH ASSOCIATED RIB ANOMALY	0	0	1	1	1	0	1	0	1	0	0	1	0	0	1
VERTEBRAE ANOMALY	2	1	3	2	2	1	2	1	2	1	1	3	0	1	2
SKULL ANOMALY	0	0	0	41	41	0	41	0	41	0	0	0	0	0	10*
CAUDAL VERTEBRAE ANOMALY	0	0	0	22	22	0	22	0	22	0	0	0	0	0	8*
FUSED STERNEBRAE	0	2	0	1	1	0	1	0	1	0	2	0	0	0	1
VERTEBRAL CENTRA - EXTRA SITE OF OSSIFICATION	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0
STERNEBRA (E) - EXTRA SITE OF OSSIFICATION	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0
HYOID ANOMALY	0	0	0	50	50	0	50	0	50	0	0	0	0	0	11*
STERNEBRA (E) MALALIGNED AND FUSED	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
TOTAL MALFORMATIONS	0	0	0	0	52	0	52	0	52	0	0	0	0	0	13*
NUMBER WITH EXTERNAL MALFORMATIONS	0	1	0	0	16	0	16	0	16	0	1	0	0	0	9*
NUMBER WITH VISCERAL MALFORMATIONS	3	5	6	b	71	3	71	2	71	2	4	5	b	5	15*
TOTAL WITH MALFORMATIONS	3	6	6	0	75	3	75	2	75	2	5	5	0	0	16*

* RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10).

b SKELETAL EXAMINATIONS OF GROUP 4 FETUSES WERE NOT PERFORMED SIGNIFICANTLY DIFFERENT FROM CONTROL; * = P<0.05.

TABLE 4A

UIC/TRL STUDY NO.: 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS

- ABSOLUTE -

GROUP:	FETUSES	LITTERS
DOSE LEVEL (MG BASE/KG/DAY):	1 2	1 2
	0 25/16°	0 25/16°
NUMBER EXAMINED EXTERNALLY	154 114	19 12
NO EXTERNAL MALFORMATIONS OBSERVED		
NUMBER EXAMINED VISCERALLY	154 113 ^b	19 12
KIDNEY AND/OR URETER ANOMALY	1 0	1 0
IRIS BOMBE'	1 0	1 0
NUMBER EXAMINED SKELETALLY	154 114	19 12
VERTEBRAL ANOMALY WITH ASSOCIATED RIB ANOMALY	2 0	2 0
FUSED RIBS	0 1	0 1
VERTEBRAL CENTRA - EXTRA SITE OF OSSIFICATION	0 1	0 1
STERNEBRA (E) MALALIGNED - SEVERE	0 1	0 1
TOTAL MALFORMATIONS		
NUMBER WITH EXTERNAL MALFORMATIONS	0 0	0 0
NUMBER WITH VISCERAL MALFORMATIONS	2 0	2 0
NUMBER WITH SKELETAL MALFORMATIONS	2 3	2 2
TOTAL WITH MALFORMATIONS	4 3	4 2

* DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 25 MG BASE/KG/DAY TO 16 MG BASE/KG/DAY ON GESTATION DAYS 15 OR 16 (THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 2 DAYS)

^b DOES NOT INCLUDE ONE FETUS FROM GROUP 2 FOR WHICH VISCERAL OBSERVATIONS WERE NOT RECORDED. NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 5

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 SUMMARY OF FETAL OBSERVATIONS - VARIATIONS

- ABSOLUTE -

GROUP:	DOSE LEVEL (MG BASE/KG/DAY):							FETUSES		LITTERS			
	0	2	7	25	4	5	300	0	2	2	3	4	5
NUMBER EXAMINED EXTERNALLY	140	121	111	86	103	15	15	18	15	15	11	11	17
NO EXTERNAL VARIATIONS OBSERVED													
NUMBER EXAMINED VISCERALLY	138 ^b	121	108 ^b	86	102 ^b	18	15	15	15	11	11	17	17
MAJOR BLOOD VESSEL VARIATION	2	6	8	6	14	2	3	2	3	4	5	10*	
THYMUS VARIATION	0	0	0	0	2	0	0	0	0	0	0	0	1
GALL BLADDER VARIATION	3	0	0	1	11	2	0	2	0	0	1	1	5
SPLEEN - SMALL IN SIZE	1	0	1	2	5	1	0	1	0	1	1	1	5
HYDRONEPHROSIS	0	0	0	0	5	0	0	0	0	0	0	0	3
RETROCAVAL URETER	0	1	0	2	4	0	1	0	1	0	1	1	3
IRIS - HEMORRHAGIC RING	1	0	0	0	0	1	0	1	0	0	0	0	0
DISTENDED URETER	0	0	0	0	6	0	0	0	0	0	0	0	4*
URINARY BLADDER - DISTENDED	0	0	0	0	2	0	0	0	0	0	0	0	2
LIVER - ENLARGED	1	0	0	0	0	1	0	1	0	0	0	0	0

* RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10).

^b DOES NOT INCLUDE TWO FETUSES FROM GROUP 1, THREE FETUSES FROM GROUP 3 AND ONE FETUS FROM GROUP 5 FOR WHICH VISCERAL OBSERVATIONS WERE NOT RECORDED.
 SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05.

TABLE 5 (CONT.)

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

SUMMARY OF FETAL OBSERVATIONS - VARIATIONS

- ABSOLUTE -

GROUP:	FETUSES					LITTERS				
	1	2	3	4	5	1	2	3	4	5
DOSE LEVEL (MG BASE/KG/DAY):	0	2	7	25	300	0	2	7	25	300
					MG/KG/DAY*					MG/KG/DAY*
NUMBER EXAMINED SKELETALLY	140	121	111	0 ^b	103	18	15	15	0 ^b	17
HYOID BODY UNOSSIFIED	1	5	1		0	1	1	1		0
HYOID ARCH(ES) UNOSSIFIED	0	0	0		1	0	0	0		1
7TH CERVICAL RIBS	2	0	0		5	2	0	0		3
13TH FULL RIBS	67	39	41		46	17	14	12		13
13TH RUDIMENTARY RIBS	33	21	27		16	13	11	12		12
HYOID ARCH(ES) BENT	5	5	6		5	4	4	6		5
STERNEBRA (E) #5 - #6 UNOSSIFIED	32	22	16		12	11	10	9		7
STERNEBRA (E) MALALIGNED										
(SLIGHT-MODERATE)										
25 PRESACRAL VERTEBRAE	28	5	11		18	10	4	6		13
27 PRESACRAL VERTEBRAE	1	0	0		0	1	0	0		0
TALUS UNOSSIFIED	18	16	27		40	8	9	10		15
ACCESSORY SKULL BONES	2	3	0		0	1	1	0		0
	1	0	0		0	1	0	0		0
TOTAL FETUSES/LITTERS WITH VARIATIONS	114	84	86	8	92	18	15	15	5*	17

* RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10).

^b SKELETAL EXAMINATIONS OF GROUP 4 FETUSES WERE NOT PERFORMED SIGNIFICANTLY DIFFERENT FROM CONTROL; * = P<0.05.

TABLE 5A

UIC/TRL STUDY NO.: 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 SUMMARY OF FETAL OBSERVATIONS - VARIATIONS

- ABSOLUTE -

GROUP:	FETUSES		LITTERS	
	1	2	1	2
DOSE LEVEL (MG BASE/KG/DAY):	0	25/16 ^a	0	25/16 ^a
NUMBER EXAMINED EXTERNALLY	154	114	19	12
NO EXTERNAL VARIATIONS OBSERVED				
NUMBER EXAMINED VISCERALLY	154	113 ^b	19	12
MAJOR BLOOD VESSEL VARIATION	12	8	6	4
GALL BLADDER VARIATION	6	4	3	4
SPLEEN - SMALL IN SIZE	5	9	2	3
HYDRONEPHROSIS	3	3	3	2
IRIS - HEMORRHAGIC RING	1	0	1	0
RETROCAVAL URETER	0	1	0	1
NUMBER EXAMINED SKELETALLY	154	114	19	12
HYOID BODY UNOSSIFIED	1	1	1	1
13TH FULL RIBS	72	58	19	11
13TH RUDIMENTARY RIBS	27	13	12	9
12TH RUDIMENTARY RIBS	1	0	1	0
HYOID ARCH(ES) BENT	3	10	3	4
STERNEBRA(E) #5 - #6 UNOSSIFIED	32	20	12	9
STERNEBRA(E) MALALIGNED (SLIGHT-MODERATE)	8	3	6	3
25 PRESACRAL VERTEBRAE	1	0	1	0
27 PRESACRAL VERTEBRAE	29	19	9	7
TALUS UNOSSIFIED	1	0	1	0
TOTAL FETUSES/LITTERS WITH VARIATIONS	119	89	19	12

^aDUE TO MORTALITY, THE HIGH DOSE WAS DECREASED FROM 25 MG BASE/KG/DAY TO 16 MG BASE/KG/DAY ON GESTATION DAYS 15 OR 16 (THE RANGE OF DAYS REFLECTS STUDY STAGGER START OVER 2 DAYS).

^b DOES NOT INCLUDE ONE FETUS FROM GROUP 2 FOR WHICH VISCERAL OBSERVATIONS WERE NOT RECORDED. NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 6

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS

- PERCENT -

GROUP:	FETUSES					LITTERS				
	1	2	3	4	5	0	2	3	4	5
DOSE LEVEL (MG BASE/KG/DAY):	0	2	7	25	300	0	2	7	25	300
NUMBER EXAMINED EXTERNALLY	140	121	111	86	103	18	15	15	11	17
MICROCEPHALY	0.0	0.0	0.0	0.0	17.5	0.0	0.0	0.0	0.0	41.2
CLEFT PALATE	0.0	0.0	0.0	0.0	12.6	0.0	0.0	0.0	0.0	35.3
MACROSTOMIA	0.0	0.0	0.0	0.0	8.7	0.0	0.0	0.0	0.0	29.4
FACE - FACIAL BLEB(S)	0.0	0.0	0.0	0.0	37.9	0.0	0.0	0.0	0.0	58.8
MANDIBLE - MICROGNATHIA	0.0	0.0	0.0	0.0	11.7	0.0	0.0	0.0	0.0	29.4
MAXILLAE - MICROGNATHIA	0.0	0.0	0.0	0.0	14.6	0.0	0.0	0.0	0.0	29.4
PINNA ANOMALY	0.0	0.0	0.0	0.0	32.0	0.0	0.0	0.0	0.0	47.1
TAIL ANOMALY	0.0	0.0	0.0	0.0	29.1	0.0	0.0	0.0	0.0	70.6
ANAL ATRESIA	0.0	0.0	0.0	0.0	7.8	0.0	0.0	0.0	0.0	29.4
SMALL ANAL OPENING	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0	5.9
TONGUE/MANDIBLE ANOMALY	0.0	0.0	0.0	0.0	2.9	0.0	0.0	0.0	0.0	17.6
MOUTH - FACIAL BLEB(S)	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0	5.9
NECK - BLEB(S)	0.0	0.0	0.0	0.0	15.5	0.0	0.0	0.0	0.0	35.3
MICROSTOMIA	0.0	0.0	0.0	0.0	5.8	0.0	0.0	0.0	0.0	23.5
NUMBER EXAMINED VISCERALLY	138 ^b	121	108 ^b	86	102 ^b	18	15	15	11	17
HEART AND/OR GREAT VESSEL ANOMALY	0.0	0.0	0.0	0.0	2.0	0.0	0.0	0.0	0.0	11.8
KIDNEY AND/OR URETER ANOMALY	0.0	0.0	0.0	0.0	14.7	0.0	0.0	0.0	0.0	47.1
LUNGS - SMALL IN SIZE	0.0	0.8	0.0	0.0	0.0	0.0	6.7	0.0	0.0	0.0

^a RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10).

^b DOES NOT INCLUDE TWO FETUSES FROM GROUP 1, THREE FETUSES FROM GROUP 3 AND ONE FETUS FROM GROUP 5 FOR WHICH VISCERAL OBSERVATIONS WERE NOT RECORDED.

TABLE 6 (CONT.)

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS

- PERCENT -

GROUP:	FETUSES				LITTERS					
	1	2	3	4	5	1	2	3	4	5
DOSE LEVEL (MG BASE/KG/DAY):	0	2	7	25	103	0	2	7	25	300 MG/KG/DAY*
NUMBER EXAMINED SKELETALLY	140	121	111	0 ^b	103	18	15	15	0 ^b	17
VERTEBRAL ANOMALY WITH ASSOCIATED RIB ANOMALY	0.0	0.0	0.9		1.0	0.0	0.0	6.7		5.9
VERTEBRAE ANOMALY	1.4	0.8	2.7		1.9	5.6	6.7	20.0		11.8
SKULL ANOMALY	0.0	0.0	0.0		39.8	0.0	0.0	0.0		58.8
CAUDAL VERTEBRAE ANOMALY	0.0	0.0	0.0		21.4	0.0	0.0	0.0		47.1
FUSED STERNEBRAE	0.0	1.7	0.0		1.0	0.0	13.3	0.0		5.9
VERTEBRAL CENTRA - EXTRA SITE OF OSSIFICATION	0.0	0.8	0.0		0.0	0.0	6.7	0.0		0.0
STERNEBRA (E) - EXTRA SITE OF OSSIFICATION	0.0	0.0	0.9		0.0	0.0	0.0	6.7		0.0
HYOID ANOMALY	0.0	0.0	0.0		48.5	0.0	0.0	0.0		64.7
STERNEBRA (E) MALALIGNED AND FUSED	0.7	0.8	0.9		1.0	5.6	6.7	6.7		5.9
TOTAL MALFORMATIONS	2.1	5.0	5.4	0.0	72.8	11.1	33.3	33.3	0.0	94.1
NUMBER WITH EXTERNAL MALFORMATIONS	0.0	0.0	0.0	0.0	50.5	0.0	0.0	0.0	0.0	76.5
NUMBER WITH VISCERAL MALFORMATIONS	0.0	0.8	0.0	0.0	15.5	0.0	6.7	0.0	0.0	52.9
NUMBER WITH SKELETAL MALFORMATIONS	2.1	4.1	5.4	b	68.9	11.1	26.7	33.3	b	88.2
TOTAL WITH MALFORMATIONS	2.1	5.0	5.4	0.0	72.8	11.1	33.3	33.3	0.0	94.1

* RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10).

b SKELETAL EXAMINATIONS OF GROUP 4 FETUSES WERE NOT PERFORMED

TABLE 6A

UIC/TRL STUDY NO.: 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS

- PERCENT -

GROUP:	FETUSES		LITTERS	
	1	2	1	2
DOSE LEVEL (MG BASE/KG/DAY):	0	25/16*	0	25/16*
NUMBER EXAMINED EXTERNALLY	154	114	19	12
NO EXTERNAL MALFORMATIONS OBSERVED				
NUMBER EXAMINED VISCERALLY	154	113 ^b	19	12
KIDNEY AND/OR URETER ANOMALY	0.6	0.0	5.3	0.0
IRIS BOMBE'	0.6	0.0	5.3	0.0
NUMBER EXAMINED SKELETALLY	154	114	19	12
VERTEBRAL ANOMALY WITH ASSOCIATED RIB ANOMALY	1.3	0.0	10.5	0.0
FUSED RIBS	0.0	0.9	0.0	8.3
VERTEBRAL CENTRA - EXTRA SITE OF OSSIFICATION	0.0	0.9	0.0	8.3
STERNEBRA (E) MALALIGNED - SEVERE	0.0	0.9	0.0	8.3
TOTAL MALFORMATIONS				
NUMBER WITH EXTERNAL MALFORMATIONS	0.0	0.0	0.0	0.0
NUMBER WITH VISCERAL MALFORMATIONS	1.3	0.0	10.5	0.0
NUMBER WITH SKELETAL MALFORMATIONS	1.3	2.6	10.5	16.7
TOTAL WITH MALFORMATIONS	2.6	2.6	21.1	16.7

* DUE TO MORTALITY, THE HIGH DOSE WAS REDUCED FROM 25 MG BASE/KG/DAY TO 16 MG BASE/KG/DAY ON GESTATION DAYS 15 OR 16 (THE RANGE OF DAYS REFLECTS STUDY STAGGER-START OVER 2 DAYS)

^b DOES NOT INCLUDE ONE FETUS EACH FROM GROUP 2 FOR WHICH VISCERAL OBSERVATIONS WERE NOT RECORDED.

TABLE 7

UIC/TRI STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 SUMMARY OF FETAL OBSERVATIONS - VARIATIONS

- PERCENT -

GROUP:	FETUSES					LITTERS				
	1	2	3	4	5	1	2	3	4	5
DOSE LEVEL (MG BASE/KG/DAY):	0	2	7	25	300	0.0	2	7	25	300
NUMBER EXAMINED EXTERNALLY	140	121	111	86	103	18	15	15	11	17
NO EXTERNAL VARIATIONS OBSERVED										
NUMBER EXAMINED VISCERALLY	138 ^b	121	108 ^b	86	102 ^b	18	15	15	11	17
MAJOR BLOOD VESSEL VARIATION	1.4	5.0	7.4	7.0	13.7	11.1	20.0	26.7	45.5	58.8
THYMUS VARIATION	0.0	0.0	0.0	0.0	2.0	0.0	0.0	0.0	0.0	5.9
GALL BLADDER VARIATION	2.2	0.0	0.0	1.2	10.8	11.1	0.0	0.0	9.1	29.4
SPLEEN - SMALL IN SIZE	0.7	0.0	0.9	2.3	4.9	5.6	0.0	6.7	9.1	29.4
HYDRONEPHROSIS	0.0	0.0	0.0	0.0	4.9	0.0	0.0	0.0	0.0	17.6
RETROCAVAL URETER	0.0	0.8	0.0	2.3	3.9	0.0	6.7	0.0	9.1	17.6
IRIS - HEMORRHAGIC RING	0.7	0.0	0.0	0.0	0.0	5.6	0.0	0.0	0.0	0.0
DISTENDED URETER	0.0	0.0	0.0	0.0	5.9	0.0	0.0	0.0	0.0	23.5
URINARY BLADDER - DISTENDED	0.0	0.0	0.0	0.0	2.0	0.0	0.0	0.0	0.0	11.8
LIVER - ENLARGED	0.7	0.0	0.0	0.0	0.0	5.6	0.0	0.0	0.0	0.0

^a RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10).

^b DOES NOT INCLUDE TWO FETUSES FROM GROUP 1, THREE FETUSES FROM GROUP 3 AND ONE FETUS FROM GROUP 5 FOR WHICH VISCERAL OBSERVATIONS WERE NOT RECORDED.

TABLE 7 (CONT.)

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

SUMMARY OF FETAL OBSERVATIONS - VARIATIONS

- PERCENT -

GROUP:	FETUSES					LITTERS				
	1	2	3	4	5	1	2	3	4	5
DOSE LEVEL (MG BASE/KG/DAY):	0	2	7	25	300	0	2	7	25	300
	0	2	7	25	300	0	2	7	25	300
NUMBER EXAMINED SKELETALLY	140	121	111	0 ^b	103	18	15	15	0 ^b	17
HYOID BODY UNOSSIFIED	0.7	4.1	0.9		0.0	5.6	6.7	6.7		0.0
HYOID ARCH(ES) UNOSSIFIED	0.0	0.0	0.0		1.0	0.0	0.0	0.0		5.9
STERNEBRA(E) #1-#4 UNOSSIFIED	0.0	0.0	0.0		1.0	0.0	0.0	0.0		5.9
7TH CERVICAL RIBS	1.4	0.0	0.0		4.9	11.1	0.0	0.0		17.6
13TH FULL RIBS	47.9	32.2	36.9		44.7	94.4	93.3	80.0		76.5
13TH RUDIMENTARY RIBS	23.6	17.4	24.3		15.5	72.2	73.3	80.0		70.6
HYOID ARCH(ES) BENT	3.6	4.1	5.4		4.9	22.2	26.7	40.0		29.4
STERNEBRA(E) #5 - #6 UNOSSIFIED	22.9	18.2	14.4		11.7	61.1	66.7	60.0		41.2
STERNEBRA(E) MALALIGNED										
(SLIGHT-MODERATE)										
25 PRESACRAL VERTEBRAE	20.0	4.1	9.9		17.5	55.6	26.7	40.0		76.5
27 PRESACRAL VERTEBRAE	0.7	0.0	0.0		0.0	5.6	0.0	0.0		0.0
TALUS UNOSSIFIED	12.9	13.2	24.3		38.8	44.8	60.0	66.7		88.2
ACCESSORY SKULL BONES	1.4	2.5	0.0		0.0	5.6	6.7	0.0		0.0
	0.7	0.0	0.0		0.0	5.6	0.0	0.0		0.0
TOTAL FETUSES/LITTERS WITH VARIATIONS	81.4	69.4	77.5	9.3	89.3	100.0	100.0	100.0	45.5	100.0

* RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10).

^b SKELETAL EXAMINATIONS OF GROUP 4 FETUSES WERE NOT PERFORMED

TABLE 7A

UIC/TRL STUDY NO.: 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
SUMMARY OF FETAL OBSERVATIONS - VARIATIONS

- PERCENT -

	FETUSES		LITTERS	
	1	2	1	2
GROUP:	0	25/16 ^a	0	25/16 ^a
DOSE LEVEL (MG BASE/KG/DAY):	0	25/16 ^a	0	25/16 ^a
NUMBER EXAMINED EXTERNALLY	154	114	19	12
NO EXTERNAL VARIATIONS OBSERVED				
NUMBER EXAMINED VISCERALLY	154	113 ^b	19	12
MAJOR BLOOD VESSEL VARIATION	7.8	7.0	31.6	33.3
GALL BLADDER VARIATION	3.9	3.5	15.8	33.3
SPLEEN - SMALL IN SIZE	3.2	7.9	10.5	25.0
HYDRONEPHROSIS	1.9	2.6	15.8	16.7
IRIS - HEMORRHAGIC RING	0.6	0.0	5.3	0.0
RETROCAVAL URETER	0.0	0.9	0.0	8.3
NUMBER EXAMINED SKELETALLY	154	114	19	12
HYOID BODY UNOSSIFIED	0.6	0.9	5.3	8.3
13TH FULL RIBS	46.8	50.9	100.0	91.7
13TH RUDIMENTARY RIBS	17.5	11.4	63.2	75.0
12TH RUDIMENTARY RIBS	0.6	0.0	5.3	0.0
HYOID ARCH(ES) BENT	1.9	8.8	15.8	33.3
STERNEBRA (E) #5 - #6 UNOSSIFIED	20.8	17.5	63.2	75.0
STERNEBRA (E) MALALIGNED (SLIGHT-MODERATE)	5.2	2.6	31.6	25.0
25 PRESACRAL VERTEBRAE	0.6	0.0	5.3	0.0
27 PRESACRAL VERTEBRAE	18.8	16.7	47.4	58.3
TALUS UNOSSIFIED	0.6	0.0	5.3	0.0
TOTAL FETUSES/LITTERS WITH VARIATIONS	77.3	78.1	100.0	100.0

*DUE TO MORTALITY, THE HIGH DOSE WAS DECREASED FROM 25 MG BASE/KG/DAY TO 16 MG BASE/KG/DAY ON GESTATION DAYS 15 OR 16 (THE RANGE OF DAYS REFLECTS STUDY STAGGER START OVER 2 DAYS).

^b DOES NOT INCLUDE ONE FETUS EACH FROM GROUP 2 FOR WHICH VISCERAL OBSERVATIONS WERE NOT RECORDED.

APPENDIX A

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

DAM#	ORGAN	OBSERVATION
501		NO ABNORMALITIES DETECTED
502		NO ABNORMALITIES DETECTED
503		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
504		NO ABNORMALITIES DETECTED
505		NO ABNORMALITIES DETECTED
506		NO ABNORMALITIES DETECTED
507		NO ABNORMALITIES DETECTED
508		NO ABNORMALITIES DETECTED
509		NO ABNORMALITIES DETECTED
510		NO ABNORMALITIES DETECTED
511		NO ABNORMALITIES DETECTED
512		NO ABNORMALITIES DETECTED
513		NO ABNORMALITIES DETECTED
514		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
515		NO ABNORMALITIES DETECTED
516		NO ABNORMALITIES DETECTED
517		NO ABNORMALITIES DETECTED
518		NO ABNORMALITIES DETECTED
519		NO ABNORMALITIES DETECTED
520		NO ABNORMALITIES DETECTED

APPENDIX A

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 2: 2 MG BASE/KG/DAY

DAM#	ORGAN	OBSERVATION
521		NO ABNORMALITIES DETECTED
522		NO ABNORMALITIES DETECTED
523		NO ABNORMALITIES DETECTED
524*		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
525	CORPORA LUTEA	HEMORRHAGIC
		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
526		NO ABNORMALITIES DETECTED
527		NO ABNORMALITIES DETECTED
528		NO ABNORMALITIES DETECTED
		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
529		NO ABNORMALITIES DETECTED
530		NO ABNORMALITIES DETECTED
531		NO ABNORMALITIES DETECTED
532		NO ABNORMALITIES DETECTED
533		NO ABNORMALITIES DETECTED
534		NO ABNORMALITIES DETECTED
535		NO ABNORMALITIES DETECTED
536		NO ABNORMALITIES DETECTED
537		NO ABNORMALITIES DETECTED
		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
538		NO ABNORMALITIES DETECTED
539		NO ABNORMALITIES DETECTED
		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
540		NO ABNORMALITIES DETECTED

*Necropsy observation for Dam 524 was not recorded.

APPENDIX A

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

DAM#	ORGAN	OBSERVATION
541		NO ABNORMALITIES DETECTED
542	CORPORA LUTEA	NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE HEMORRHAGIC
543		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
544		NO ABNORMALITIES DETECTED
545		NO ABNORMALITIES DETECTED
546		NO ABNORMALITIES DETECTED
547		NO ABNORMALITIES DETECTED
548		NO ABNORMALITIES DETECTED
549		NO ABNORMALITIES DETECTED
550		NO ABNORMALITIES DETECTED
551	CORPORA LUTEA	HEMORRHAGIC, BILATERAL
551		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
552		NO ABNORMALITIES DETECTED
553		NO ABNORMALITIES DETECTED
554		NO ABNORMALITIES DETECTED
555		NO ABNORMALITIES DETECTED
556		NO ABNORMALITIES DETECTED
557		NO ABNORMALITIES DETECTED
558		ABORTED - GESTATION DAY 25
		ONE NORMAL FEMALE FETUS WAS ABORTED AND FOUND DEAD ALONG WITH THE PLACENTA; NO ABNORMALITIES DETECTED; CORPORA LUTEA: 3, LEFT; 4, RIGHT; UTERINE IMPLANTATIONS: 1 IMPLANTATION SITE (REMNANTS OF FRESH PLACENTA) AND 1 NORMAL, FEMALE, NON-VIABLE FETUS, LEFT; 1 IMPLANTATION SITE (REMNANTS OF FRESH PLACENTA), 1 EARLY RESORPTION, 1 NORMAL, FEMALE, NON-VIABLE FETUS AND 1 MALE NON-VIABLE FETUS WITH BILATERAL, TESTICULAR HEMORRHAGE; RIGHT
559		NO ABNORMALITIES DETECTED
560		NO ABNORMALITIES DETECTED
		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE

APPENDIX A

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 4: 25 MG BASE/KG/DAY

DAM#	ORGAN	OBSERVATION
561		NO ABNORMALITIES DETECTED
562		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
563		NO ABNORMALITIES DETECTED
564		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
565		NO ABNORMALITIES DETECTED
		NO ABNORMALITIES DETECTED
		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
		PREMATURE DELIVERY - GESTATION DAY 29
		1 LATE RESORPTION (CROWN-RUMP LENGTH: 6.2 CM) AND 9 NORMAL FETUSES DELIVERED (ONE WITH A PARTIALLY CANNIBALIZED TAIL); CORPORA LUTEA NOT RECORDED; IMPLANTATIONS; 5 FORMER IMPLANTATION SITES, LEFT; 5 FORMER IMPLANTATION SITES, RIGHT; NO ABNORMALITIES DETECTED
566		NO ABNORMALITIES DETECTED
567		NO ABNORMALITIES DETECTED
568		NO ABNORMALITIES DETECTED
569		NO ABNORMALITIES DETECTED
570		SACRIFIED MORIBUND - GESTATION DAY 12
		APPARENT BROKEN BACK; CORPORA LUTEA: 6, LEFT; 1, RIGHT; UTERINE IMPLANTATIONS: 5 LATE RESORPTIONS, LEFT; 1 LATE RESORPTIONS, RIGHT
571		NO ABNORMALITIES DETECTED
572		NO ABNORMALITIES DETECTED
573		NO ABNORMALITIES DETECTED
574		NO ABNORMALITIES DETECTED
575		ABORTED - GESTATION DAY 23
		ONE ABORTED DEAD PUP FOUND UNDERNEATH CAGE; PALE LIVER WITH FATTY INFILTRATION; CORPORA LUTEA: 5, LEFT; 5, RIGHT; UTERINE IMPLANTATIONS: 2 NORMAL, VIABLE FETUSES AND 1 NONVIABLE FETUS, LEFT; 2 NORMAL, VIABLE FETUSES, ONE VIABLE FETUS WITH EXTENSIVE SUBCUTANEOUS HEMATOMA AT FOREHEAD, SPINAL CORD AND LEFT LOWER LIMB, AND 1 NONVIABLE FETUS AND 1 PLACENTA, RIGHT FOUND DEAD - GESTATION DAY 19
576		ANIMAL SPASTIC IN THE FORELIMBS, WITH LOCKED JAW AND BLOOD (FRESH) AROUND MOUTH, ACCUMULATED FLUID IN THE ABDOMEN, RUPTURE STOMACH (P.M.), COLLAPSED LUNGS WITH HEMATOMA; CORPORA LUTEA: 5, LEFT; 2, RIGHT; UTERINE IMPLANTATIONS: 5 LATE RESORPTIONS, LEFT; 2 LATE RESORPTIONS, RIGHT
577		NO ABNORMALITIES DETECTED
		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
578		NO ABNORMALITIES DETECTED
579		NO ABNORMALITIES DETECTED
580		ABORTED - GESTATION DAY 25
		ONE SKULL FOUND UNDERNEATH CAGE; NO ABNORMALITIES DETECTED; CORPORA LUTEA: 3, LEFT; 5, RIGHT; UTERINE IMPLANTATIONS: 3 IMPLANTATION SITES (WITH REMNANTS OF FRESH PLACENTA), LEFT; 4 IMPLANTATION SITES (WITH REMNANTS OF FRESH PLACENTA), AND 1 EARLY RESORPTION, RIGHT

APPENDIX A

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

DAM#	ORGAN	OBSERVATION
581		NO ABNORMALITIES DETECTED
582		NO ABNORMALITIES DETECTED
583		NO ABNORMALITIES DETECTED
584		NO ABNORMALITIES DETECTED
585		NO ABNORMALITIES DETECTED
586		NO ABNORMALITIES DETECTED
587		NO ABNORMALITIES DETECTED
588		NO ABNORMALITIES DETECTED
589		NO ABNORMALITIES DETECTED
590		NO ABNORMALITIES DETECTED
591		NO ABNORMALITIES DETECTED
592		NO ABNORMALITIES DETECTED
593		NO ABNORMALITIES DETECTED
		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
594		NO ABNORMALITIES DETECTED
595		NO ABNORMALITIES DETECTED
596		NO ABNORMALITIES DETECTED
		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
597		NO ABNORMALITIES DETECTED
598		NO ABNORMALITIES DETECTED
599		NO ABNORMALITIES DETECTED
600		NO ABNORMALITIES DETECTED

APPENDIX AA

UIC/TRL STUDY NO.: 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

DAM#	ORGAN	OBSERVATION
601		NO ABNORMALITIES DETECTED
602		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
603		NO ABNORMALITIES DETECTED
604		NO ABNORMALITIES DETECTED
605		NO ABNORMALITIES DETECTED
606		NO ABNORMALITIES DETECTED
607		NO ABNORMALITIES DETECTED
608		NO ABNORMALITIES DETECTED
609		NO ABNORMALITIES DETECTED
610	OVIDUCT	CYST, 3, 1mm, 3mm and 4mm IN DIAMETER
611		NO ABNORMALITIES DETECTED
612		NO ABNORMALITIES DETECTED
613		NO ABNORMALITIES DETECTED
614		NO ABNORMALITIES DETECTED
615		NO ABNORMALITIES DETECTED
616		NO ABNORMALITIES DETECTED
617		NO ABNORMALITIES DETECTED
618		NO ABNORMALITIES DETECTED
619		NO ABNORMALITIES DETECTED
620		NO ABNORMALITIES DETECTED

APPENDIX AA

UIC/TRL STUDY NO.: 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 2: 25/16 MG BASE/KG/DAY*

DAM#	ORGAN	OBSERVATION
621		NO ABNORMALITIES DETECTED
622		ABORTED - GESTATION DAY 23 STOMACH FULL OF FOOD, INTESTINES EMPTY. TWO NORMAL ABORTED FETUSES FOUND. CORPORA LUTEA: 5, LEFT; 3, RIGHT; IMPLANTATION SITES: 4 NORMAL VIABLE FETUSES AND 1 FORMER IMPLANTATION SITE, LEFT; 1 NORMAL VIABLE FETUS AND 1 FORMER IMPLANTATION SITE, RIGHT NO ABNORMALITIES DETECTED
623		FOUND DEAD - GESTATION DAY 13
624		TISSUES AUTOLYZED; LUNG: RAISED AREAS (SOME WHITISH) FROM 2-10 MM IN SIZE OVER RIGHT LOBES, GREENISH-BROWN AREAS DIFFUSELY DISTRIBUTED OVER ALL LOBES; CONGESTION PRESENT THROUGH LUNG; GASTRO-INTESTINAL TRACT BLOATED; CORPORA LUTEA: 2, LEFT; 8, RIGHT; IMPLANTATION SITES: 2 LEFT; 8, RIGHT (IMPLANTATION SITES CONSISTED OF AUTOLYZED, NONDISCERNABLE TISSUE) SACRIFICED MORIBUND - GESTATION DAY 10 PALE LIVER; CORPORA LUTEA: 6, LEFT; 5, RIGHT; IMPLANTATION SITES: 6 LEFT; 5, RIGHT (IMPLANTATION SITES CONSISTED OF NONDISCERNABLE TISSUE)
625		NO ABNORMALITIES DETECTED
626		NO ABNORMALITIES DETECTED
627		NO ABNORMALITIES DETECTED
628		NO ABNORMALITIES DETECTED
629		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
630		NO ABNORMALITIES DETECTED ABORTED - GESTATION DAY 24 FULL STOMACH, EMPTY INTESTINALE TRACT; TWO PIECES OF FETAL TISSUE FOUND IN CAGE; CORPORA LUTEA: 5, LEFT; 3, RIGHT; IMPLANTATION SITES: 5, LEFT; 3, RIGHT (NO FETUSES PRESENT AT IMPLANTATION SITES)
631		PREMATURE DELIVERY - GESTATION DAY 29 NO ABNORMALITIES DETECTED; CORPORA LUTEA: 4, LEFT; 6, RIGHT; IMPLANTATION SITES: 3 FORMER IMPLANTATION SITES, LEFT; 6 FORMER IMPLANTATION SITES, RIGHT NO ABNORMALITIES DETECTED
632		NO ABNORMALITIES DETECTED
633		NO ABNORMALITIES DETECTED
634 ^b		NO ABNORMALITIES DETECTED
635		NO ABNORMALITIES DETECTED
636		NO ABNORMALITIES DETECTED

*DUE TO MORTALITY, THE HIGH DOSE WAS DECREASED FROM 25 MG BASE/KG/DAY TO 16 MG BASE/KG/DAY ON GESTATION DAYS 15 OR 16 (THE RANGE OF DAYS REFLECTS STUDY STAGGER START OVER 2 DAYS).

^bNECROPSY OBSERVATION FOR DAM 634 WAS NOT RECORDED.

APPENDIX AA

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 2: 25/16 MG BASE/KG/DAY* (CONT.)

DAM#	ORGAN	OBSERVATION
637		FOUND DEAD - GESTATION DAY 22 PALE LIVER; LUNGS PALE WITH MULTIPLE RED FOCI; KIDNEYS MOTTLED; STOMACH FULL OF FOOD; NO FOOD IN INTESTINAL TRACT; CORPORA LUTEA: 4, LEFT; 6, RIGHT; IMPLANTATION SITES: 4 EARLY RESORPTIONS, LEFT; 5 EARLY RESORPTIONS, RIGHT (IMPLANTATION SITES CONSISTED OF NONDISCERNABLE TISSUE)
638		NO ABNORMALITIES DETECTED
639		MORIBUND SACRIFICE - GESTATION DAY 17
		NORMAL; CORPORA LUTEA: 3, LEFT; 4, RIGHT; IMPLANTATION SITES: 2 EARLY RESORPTIONS, LEFT; 4 EARLY RESORPTIONS, RIGHT
640		NO ABNORMALITIES DETECTED

*DUE TO MORTALITY, THE HIGH DOSE WAS DECREASED FROM 25 MG BASE/KG/DAY TO 16 MG BASE/KG/DAY ON GESTATION DAYS 15 OR 16
(THE RANGE OF DAYS REFLECTS STUDY STAGGER START OVER 2 DAYS).

APPENDIX B

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL CESAREAN SECTION DATA

GROUP 2: 2 MG BASE/KG/DAY

DAM#	CORPORA LUTEA		TOTAL IMPLANTATIONS		SEX		VIABLE FETUSES		NONVIABLE FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS	
	LEFT	RIGHT	LEFT	RIGHT	M	F	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT
	TOTAL	TOTAL	TOTAL	TOTAL	TOTAL	TOTAL	TOTAL	TOTAL	TOTAL	TOTAL	TOTAL	TOTAL	TOTAL	TOTAL
521	5	5	10	5	3	4	4	8	0	0	1	0	0	0
522	5	5	10	6	4	5	10	0	0	0	0	0	0	
523	3	3	6	1	1	2	0	2	0	0	0	0	0	
524	NONGRAVID													
525	NONGRAVID													
526	4	5	9	3	5	4	4	8	0	0	0	0	0	0
527	4	5	9	7	1	3	5	8	0	0	0	0	0	0
528	NONGRAVID													
529	8	5	13	7	6	8	5	13	0	0	0	0	0	0
530	5	6	11	6	5	5	6	11	0	0	0	0	0	0
531	5	4	9	3	5	4	4	8	0	0	0	0	0	0
532	3	4	7	4	2	3	4	7	0	0	0	0	0	0
533	4	5	9	3	5	3	4	7	0	0	0	0	0	0
534	4	5	9	6	1	3	4	7	0	0	0	0	0	0
535	2	5	7	5	2	2	5	7	0	0	0	0	0	0
536	6	5	11	6	5	6	4	10	0	0	0	0	0	0
537	NONGRAVID													
538	3	6	9	5	4	3	6	9	0	0	0	0	0	0
539	NONGRAVID													
540	3	4	7	3	3	2	4	6	0	0	1	0	0	0
TOTAL	136	123	259	68	52	121	0	0	0	0	2	0	0	0
MEAN	9.1	8.2	8.6	4.5	3.5	8.1	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0
S.D.	1.8	2.5	2.1	1.8	1.7	2.5	0.0	0.0	0.0	0.4	0.4	0.0	0.0	0.0
N	15	15	15	15	15	15	15	15	15	15	15	15	15	15

NOTE: THE SEX OF FETUS 3 FROM DAM 532 WAS NOT RECORDED

APPENDIX B

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL CESAREAN SECTION DATA

GROUP 3: 7 MG BASE/KG/DAY

DAM#	CORPORA LUTEA		IMPLANTATIONS		SEX		VIABLE FETUSES		NONVIABLE FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS	
	LEFT	RIGHT	LEFT	RIGHT	M	F	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT
541	NONGRAVID													
542	NONGRAVID													
543	4	5	9	4	3	6	4	5	9	0	0	0	0	0
544	3	5	8	3	3	4	3	4	7	0	0	0	0	0
545	6	4	10	5	5	1	5	1	6	0	0	0	0	0
546	6	3	9	6	1	8	6	3	9	0	0	0	0	0
547	3	7	10	3	6	2	2	6	8	0	0	1	2	0
548	3	5	8	2	3	1	1	3	4	0	0	1	2	0
549	4	4	8	4	4	3	3	4	7	0	0	1	0	0
550	3	5	8	3	4	4	3	5	8	0	0	0	0	0
551	NONGRAVID													
552	4	5	9	3	3	4	3	4	7	0	0	0	0	0
553	3	5	8	3	6	2	3	5	8	0	0	0	0	0
554	4	4	8	4	5	3	4	4	8	0	0	0	0	0
555	7	2	9	7	7	1	7	1	8	0	0	0	0	0
556	6	a	a	6	5	3	6	2	8	0	0	0	0	0
557	5	3	8	5	1	6	4	3	7	0	0	1	0	0
558	ABORTED - GESTATION DAY 25													
559	5	3	8	5	2	5	4	3	7	0	0	0	0	1
560	NONGRAVID													
TOTAL	120		118	58	53		111		0		6		1	
MEAN	8.6		7.9	3.9	3.5		7.4		0.0		0.4		0.1	
S.D.	0.8		1.1	1.8	2.1		1.2		0.0		0.7		0.3	
N	14		15	15	15		15		15		15		15	

a = CORPORA LUTEA NOT RECORDED; NOT INCLUDED IN CALCULATIONS

APPENDIX B

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL CESAREAN SECTION DATA

GROUP 4: 25 MG BASE/KG/DAY

DAM#	CORPORA LUTEA		TOTAL IMPLANTATIONS		SEX		VIABLE FETUSES		NONVIABLE FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS		
	LEFT	RIGHT	LEFT	RIGHT	M	F	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	
561	NONGRAVID														
562	NONGRAVID														
563	4	8	4	4	8	3	4	3	4	7	0	0	1	0	0
564	NONGRAVID														
565	PREMATURE DELIVERY - GESTATION DAY 29														
566	4	5	4	5	9	4	5	4	5	9	0	0	0	0	0
567	7	12	7	4	11	6	4	6	4	10	0	0	0	1	0
568	a	a	3	4	7	3	3	2	4	6	0	0	1	0	0
569	2	3	5	2	3	5	4	1	2	5	0	0	0	0	0
570	EUTHANIZED - GESTATION DAY 12														
571	5	6	11	3	6	9	2	6	3	8	0	0	1	1	0
572	6	2	8	6	2	8	6	2	6	8	0	0	0	0	0
573	2	6	8	2	6	8	2	5	2	7	0	0	1	1	0
574	5	8	13	2	8	10	6	4	2	10	0	0	0	0	0
575	ABORTED - GESTATION DAY 23														
576	FOUND DEAD - GESTATION DAY 19														
577	NONGRAVID														
578	2	6	8	2	6	8	3	4	2	7	0	0	0	0	1
579	6	5	11	5	5	10	3	6	4	9	0	0	0	0	1
580	ABORTED - GESTATION DAY 25														
TOTAL	93	93	93	42	44	86	0	4	3	0	0	0	0	0	3
MEAN	9.3	9.3	8.5	3.8	4.0	7.8	0.0	0.4	0.3	0.0	0.0	0.0	0.5	0.5	0.3
S.D.	2.4	2.4	1.6	1.5	1.5	1.6	0.0	0.5	0.5	0.0	0.0	0.0	0.5	0.5	0.3
N	10	10	11	11	11	11	11	11	11	11	11	11	11	11	11

a = CORPORA LUTEA NOT RECORDED; NOT INCLUDED IN CALCULATIONS

APPENDIX B

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL CESAREAN SECTION DATA

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

DAM#	CORPORA LUTEA		TOTAL IMPLANTATIONS		SEX		VIABLE FETUSES		NONVIABLE FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS	
	LEFT	RIGHT	LEFT	RIGHT	M	F	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT
581	4	3	7	4	4	3	4	3	0	0	0	0	0	0
582	3	5	8	4	4	3	3	4	0	0	0	1	0	0
583	5	3	8	7	2	4	5	1	0	0	0	1	0	0
584	3	0	3	3	0	0	0	0	0	0	3	0	0	0
585	5	5	10	4	5	3	4	4	0	0	0	0	0	0
586	4	4	8	4	1	4	1	4	0	0	1	0	2	0
587	5	5	10	5	3	7	5	5	0	0	0	0	0	0
588	2	5	7	5	2	5	2	5	0	0	0	0	0	0
589	4	5	9	4	2	1	0	3	0	0	4	2	0	0
590	5	5	10	5	1	2	2	1	0	0	2	4	0	0
591	3	6	9	6	6	2	3	5	0	0	0	1	0	0
592	4	4	8	4	5	2	4	3	0	0	0	1	0	0
593	NONGRAVID													
594	1	a	a	1	5	2	0	2	0	0	1	3	4	0
595	3	5	8	3	5	1	7	3	0	0	0	0	0	0
596	NONGRAVID													
597	3	4	7	4	3	3	2	4	0	0	1	0	0	0
598	3	7	10	7	6	3	3	6	0	0	0	1	0	0
599	3	4	7	4	2	2	0	4	0	0	0	0	0	0
600	6	3	9	3	1	2	0	3	0	0	0	0	0	0
TOTAL	138		131	50	53		103		0		26		2	
MEAN	8.1		7.3	2.8	2.9		5.7		0.0		1.4		0.1	
S.D.	1.7		2.1	1.8	2.0		2.7		0.0		2.0		0.5	
N	17		18	18	18		18		18		18		18	

a = CORPORA LUTEA NOT RECORDED; NOT INCLUDED IN CALCULATIONS

APPENDIX BB

UIC/TRL STUDY NO.: 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL CESAREAN SECTION DATA

GROUP 1: 0 MG/KG/DAY

DAM#	CORPORA LUTEA		IMPLANTATIONS		SEX		VIABLE FETUSES		NONVIABLE FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS	
	LEFT	RIGHT	LEFT	RIGHT	M	F	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT
601	5	7	7	12	5	5	5	10	0	0	0	0	0	2
602	3	6	5	8	5	3	5	8	0	0	0	0	0	0
603	3	5	5	8	7	1	3	8	0	0	0	0	0	0
604	5	4	4	8	1	6	4	7	0	0	0	1	0	0
605	4	5	4	8	3	4	3	7	0	0	0	1	0	0
606	4	6	1	3	1	2	1	3	0	0	0	1	0	0
607	4	4	4	7	2	5	3	7	0	0	0	0	0	0
608	3	8	3	11	6	3	3	9	0	0	0	0	0	0
609	3	4	3	6	2	3	2	5	0	0	0	1	0	2
610	7	7	7	14	8	6	7	14	0	0	0	0	0	0
611	1	8	1	6	4	1	1	5	0	0	0	1	0	0
612	6	7	4	7	5	2	3	7	0	0	0	0	0	0
613	7	1	7	8	4	4	4	8	0	0	0	0	0	0
614	4	4	4	8	3	5	4	8	0	0	0	0	0	0
615	5	6	6	11	6	5	5	11	0	0	0	0	0	0
616	8	3	3	10	5	4	6	9	0	0	0	0	0	1
617	5	7	7	12	6	5	5	11	0	0	0	0	0	1
618	6	5	5	11	4	6	6	10	0	0	0	0	0	1
619	3	4	4	7	5	2	3	7	0	0	0	0	0	0
620	3	4	3	7	5	2	3	7	0	0	0	0	0	0
TOTAL	187	187	165	82	72	154	0	4	0	0	7	0.4	0.7	19
MEAN	9.8	9.8	8.7	4.3	3.8	8.1	0.0	0.2	0.0	0.4	0.7	0.4	0.7	19
S.D.	2.0	2.0	2.6	1.9	1.7	2.5	0.0	0.4	0.0	0.4	0.7	0.4	0.7	19
N	19	19	19	19	19	19	19	19	19	19	19	19	19	19

APPENDIX BB

UIC/TRL STUDY NO.: 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL CESAREAN SECTION DATA

GROUP 2: 25/16 MG BASE/KG/DAY*

DAM#	CORPORA LUTEA		TOTAL IMPLANTATIONS		SEX		VIABLE FETUSES		NONVIABLE FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS	
	LEFT	RIGHT	LEFT	RIGHT	M	F	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT
621	5	10	5	10	4	6	5	5	0	0	0	0	0	0
622	ABORTED - GESTATION DAY 23		8	5	5	6	5	11	0	0	2	0	0	0
623	FOUND DEAD - GESTATION DAY 13		5	13	5	6	6	11	0	0	2	0	0	0
624	SACRIFICED MORIBUND - GESTATION DAY 10		5	3	8	4	5	3	8	0	0	0	0	0
626	4	9	5	3	8	4	4	5	3	8	0	0	0	0
627	2	9	7	2	9	3	6	7	2	9	0	0	0	0
628	NONGRAVID													
629	3	9	6	3	9	4	3	5	2	7	0	1	2	0
630	ABORTED - GESTATION DAY 24													
631	PREMATURE DELIVERY - GESTATION DAY 29													
632	4	9	4	4	8	4	3	4	3	7	0	0	1	0
633	5	10	5	5	10	1	9	5	5	10	0	0	0	0
634	6	7	13	6	7	13	7	6	7	13	0	0	0	0
635	7	5	12	6	4	10	3	7	6	4	10	0	0	0
636	3	6	9	3	6	9	4	5	3	6	9	0	0	0
637	FOUND DEAD - GESTATION DAY 22													
638	4	10	6	4	10	4	6	6	4	10	0	0	0	0
639	SACRIFICED MORIBUND - GESTATION DAY 17													
640	6	4	10	6	4	10	6	6	4	10	0	0	0	0
TOTAL	124		119	47	67			114		0		5		0
MEAN	10.3		9.9	3.9	5.6			9.5		0.0		0.4		0.0
S.D.	1.7		1.6	1.4	1.7			1.7		0.0		0.8		0.0
N	12		12	12	12			12		12		12		12

*DUE TO MORTALITY, THE HIGH DOSE WAS DECREASED FROM 25 MG BASE/KG/DAY TO 16 MG BASE/KG/DAY ON GESTATION DAYS 15 OR 16 (THE RANGE OF DAYS REFLECTS STUDY STAGGER START OVER 2 DAYS).

APPENDIX C

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 1: 0 MG BASE/KG/DAY

DAM #	GRAVID UTERUS WEIGHT	MEAN FETAL WEIGHT	INDIVIDUAL FETAL WEIGHT																
			1	2	3	4	5	6	7	8	9	10	11	12	13	14			
501	477.24	38.00	40.94F	39.83M	34.63F	35.93M	33.19F	40.01F	35.66F	43.13F	38.71M								
503	400.71	41.46	48.46F	30.54M	34.77M	44.84F	44.84F	45.20F	41.57F										
504	338.18	33.90	E	39.82M	32.29M	43.49F	41.90M	E	30.06F	24.42M	25.32F								
505	397.92	35.87	35.64M	35.52M	35.56M	36.74F	38.59M	37.35M	33.00M	34.55M									
506	521.52	36.93	38.57F	38.41F	35.50F	26.86M	36.87M	39.35F	41.53M	39.23M	31.92F	41.05M							
507	484.30	38.71	45.54F	40.59F	42.21F	45.12M	42.57F	E	37.63M	38.31F	28.06M	28.35M							
508	676.07	43.25	43.99F	41.12F	44.11M	45.05M	42.60F	40.78F	39.81F	47.56F	45.33F	45.03F							
509	446.42	40.88	45.47M	37.41F	40.10F	45.23M	42.22M	41.78M	36.67F	38.14F									
510	475.64	31.79	37.13M	L	32.36F	35.27M	40.14F	31.04M	31.89M	25.55F	25.75M	26.92F	31.89M						
511	442.14	39.28	42.23M	40.01M	39.38F	37.81F	42.82F	38.46M	34.21M	39.31M									
512	292.69	42.19	43.93M	E	48.10F	44.89M	35.61M	38.40F											
514	326.87	30.04	38.35M	27.37F	32.38M	36.04M	34.41M	24.11M	21.37M	26.31M									
515	372.24	36.22	39.76F	38.70M	35.02F	37.26M	L	39.51M	35.15M	28.17F									
516	307.44	43.45	43.76F	46.03F	40.02M	43.41F	E	44.01F											
517	453.40	35.22	37.94F	33.85M	33.64F	35.73M	33.82M	35.76M	37.30F	36.12M	32.84F								
518	377.98	39.54	34.40F	45.01M	42.64F	38.21F	37.70F	39.69M	39.10F										
519	448.32	40.09	46.56F	40.61F	49.91M	45.95M	36.40F	34.43M	29.78F	37.04M									
520	318.65	53.55	E	57.22M	48.91F	59.05F	49.02F												

MEAN 419.87 38.91
S.D. 93.59 5.24
N 18 18

E=EARLY RESORPTION L=LATE RESORPTION
M=MALE F=FEMALE

APPENDIX C

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 2: 2 MG BASE/KG/DAY

DAM #	GRAVID UTERUS WEIGHT	MEAN FETAL WEIGHT	INDIVIDUAL FETAL WEIGHT														
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	
521	411.86	37.32	E	40.81M	31.53F	34.22M	35.12M	42.91F	40.40M	38.87M	34.73F						
522	440.76	32.15	31.01M	32.19M	30.05M	30.97F	31.71M	34.60M	30.76F	33.80F	29.88M	36.52F					
523	139.75	48.46	49.69F	47.22M													
526	399.67	36.73	40.06F	35.60M	27.66F	35.82M	42.08F	38.71F	35.76F	38.13M							
527	458.29	40.00	43.16F	39.30M	36.73M	42.92M	41.37M	40.20M	38.89M	37.44M							
529	537.83	29.86	37.86M	34.28F	34.95M	21.66F	21.25F	20.65F	22.15M	25.27F	37.93M	36.16M	29.81F	30.96M	35.29M		
530	513.14	33.16	47.78F	37.14F	25.55M	19.21F	33.59F	42.70M	36.14M	30.55M	31.11F	28.65M	32.29M				
531	343.75	30.85	34.62F	31.03F	29.52F	27.20M	35.90M	32.79F	27.15F	28.56M							
532	376.88	36.69	37.05F	33.97M	35.21U	38.05F	37.61M	39.36M	35.56M								
533	337.88	36.90	40.34F	39.87F	34.17M	42.51F	32.26F	36.17M	32.97F								
534	310.05	32.67	36.88M	32.70M	31.11M	37.85M	31.48F	28.33M	30.31M								
535	347.88	37.42	41.25M	36.96M	43.21M	40.69F	38.54M	27.40F	33.91M								
536	466.73	32.38	38.47F	30.45F	31.45M	29.77F	27.13F	26.00M	39.23M	34.87M	33.68F	32.77M					
538	453.57	35.11	38.52M	28.71F	32.83F	40.23M	35.79M	31.09F	39.04M	33.51F	36.28M						
540	314.11	36.16	40.76F	37.19M	E	38.33F	36.40F	31.46M	32.79M								

MEAN 390.14 35.72
S.D. 98.68 4.53
N 15 15

E=EARLY RESORPTION L=LATE RESORPTION
M=MALE F=FEMALE U=UNDETERMINED (THE SEX FOR DAM 532 FETUS 3 WAS NOT RECORDED)

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 APPENDIX C
 INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 3: 7 MG BASE/KG/DAY

DAM #	GRAVID UTERUS WEIGHT	MEAN FETAL WEIGHT	INDIVIDUAL FETAL WEIGHT														
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	
543	388.56	31.80	36.28M	32.92F	30.79F	34.76F	34.60F	34.11F	24.55F	29.01M	29.14M						
544	333.70	34.32	34.49F	35.17M	34.19F	34.68M	36.51F	31.43F	33.75M								
545	337.47	40.53	52.10F	41.29M	35.86M	36.82M	34.53M	42.55M									
546	433.60	34.81	36.96F	34.71F	31.88F	27.12F	29.10F	35.80M	40.85F	39.68F	37.18F						
547	442.04	39.43	E	32.46M	45.54M	39.76F	40.45M	39.96M	44.06F	E	36.20M	37.00M					
548	257.14	43.82	E	36.65M	47.25F	E	45.35M	46.01M									
549	419.54	42.10	45.05F	E	45.02M	42.02M	42.66M	40.96F	38.08M	40.90F							
550	446.22	38.14	40.78M	41.24M	37.14F	39.33M	39.45F	33.27M	33.42F	40.45F							
552	367.32	37.53	40.96F	37.87M	34.81M	39.08F	37.98F	35.20M	36.78F								
553	356.13	31.40	32.33F	31.98M	30.33M	38.87M	30.73M	33.37M	26.61M	27.01F							
554	348.95	31.42	34.14M	24.37F	26.87F	30.24M	35.77M	32.50M	31.39F	36.05M							
555	437.66	39.53	48.39M	35.81M	40.14M	39.84M	35.24M	37.57M	35.55F	43.67M							
556	507.34	43.00	34.51F	41.15M	48.93F	40.12M	37.52M	47.72M	50.98M	43.03F							
557	302.91	30.72	E	36.67F	30.67F	27.85F	28.54M	32.43F	28.16F	30.69F							
559	393.82	36.64	38.88F	30.34F	34.65M	L	38.23F	39.92F	38.99F	35.47M							

MEAN 384.83 37.01
 S.D. 64.81 4.44
 N 15 15

E=EARLY RESORPTION L=LATE RESORPTION
 M=MALE F=FEMALE

APPENDIX C

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 4: 25 MG BASE/KG/DAY

DAM #	GRAVID UTERUS WEIGHT	MEAN FETAL WEIGHT	INDIVIDUAL FETAL WEIGHT															
			1	2	3	4	5	6	7	8	9	10	11	12	13	14		
563	396.69	41.38	45.13M	39.08F	E	39.77F	43.08F	41.55F	40.91M	40.13M								
566	407.31	31.49	33.64F	29.02M	30.38F	32.57F	30.89F	34.47M	32.96F	29.62M	29.90M							
567	601.05	41.62	42.80F	42.20F	39.57F	39.03M	L	34.60M	40.37M	40.23M	41.99M	45.54M						
568	276.78	32.18	34.53M	E	30.92F	30.87F	36.97M	30.88F	28.92M									
569	291.06	39.51	42.34M	39.32M	43.53F	38.12M	34.25M											
571	318.26	27.10	34.29M	28.08F	27.78F	27.83F	29.50M	28.77F	E	19.44F	21.09F							
572	414.48	36.39	37.07M	35.41M	37.42M	30.69M	33.86M	37.84M	37.18F	41.61F								
573	305.16	30.76	33.15F	32.67F	34.06F	35.34M	25.93F	E	30.79M									
574	523.69	37.78	42.58F	39.59M	45.75F	41.39M	43.17M	36.80M	34.97M	30.41M	31.40F	31.75F						
578	434.55	38.80	45.74F	42.90F	41.82M	35.70M	36.04F	25.82F	L	43.57M								
579	574.90	38.09	L	42.54F	37.15F	33.03M	35.72M	43.84F	39.27F	38.94F	36.17M	36.19F						

MEAN 413.08 35.92
S.D. 113.41 4.79
N 11 11

E=EARLY RESORPTION L=LATE RESORPTION
M=MALE F=FEMALE

APPENDIX C

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

DAM #	GRAVID UTERUS WEIGHT	MEAN FETAL WEIGHT	INDIVIDUAL FETAL WEIGHT															
			1	2	3	4	5	6	7	8	9	10	11	12	13	14		
581	423.53	41.09	42.48M	37.16M	38.48M	46.61F	48.28F	38.72M	35.88F									
582	366.89	37.61	38.69M	40.75M	33.95F	44.38M	37.97F	31.75M	E	35.81F								
583	309.75	33.77	35.77M	41.12F	32.72F	29.12F	28.00M	E	35.86F									
584	^a		E	E	E													
585	412.23	37.96	43.74F	39.62M	33.14M	29.70F	45.74M	44.38M	32.51F	34.85M								
586	334.55	40.12	L	E	L	37.92F	46.12M	41.57F	37.25F	37.72F								
587	524.20	37.25	43.49M	36.88F	36.99F	30.45M	37.45F	38.05F	36.60F	36.43F	37.55F	38.62M						
588	395.37	39.13	40.74F	37.09F	45.15M	35.82F	40.58M	37.52F	36.99F									
589	246.26	45.90	E	E	E	E	43.21F	47.25M	E	47.23M								
590	235.18	45.17	E	48.20F	E	42.45F	E	44.85M	E	E								
591	376.21	32.54	37.77M	35.83M	35.70F	27.91M	E	34.94M	26.09M	29.33M	32.72F							
592	400.35	41.85	46.09M	43.54M	34.98F	37.98M	41.46M	E	42.07F	46.81M								
594	153.43	42.97	E	E	E	42.80M												
595	418.58	38.02	42.46F	30.03F	35.21F	45.90M	40.21F	37.35F	36.05F	36.93F								
597	345.85	42.01	46.01M	40.13F	E	44.27M	41.14F	40.68F	39.83M									
598	467.55	36.93	42.88M	39.11M	41.47M	40.49M	34.94F	36.31F	E	37.80M	25.53F	33.82M						
599	247.17	42.90	45.18F	41.59M	41.37F	43.46M												
600	219.41	50.71	45.06F	51.69F	55.38M													

MEAN 345.68 40.35
S.D. 98.58 4.51
N 17 17

E=EARLY RESORPTION L=LATE RESORPTION
M=MALE F=FEMALE

a= UTERUS WEIGHT FOR DAM 584 NOT RECORDED

APPENDIX CC

UIC/TRL STUDY NO.: 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 1: 0 MG BASE/KG/DAY

DAM #	GRAVID UTERUS WEIGHT	MEAN FETAL WEIGHT	INDIVIDUAL FETAL WEIGHT													
			1	2	3	4	5	6	7	8	9	10	11	12	13	14
602	456.13	29.57	32.11M	29.55F	25.63M	31.46M	31.62F	30.41F	32.41M	29.81M	23.58F	L	29.11F	L		
603	356.09	32.36	40.32M	27.81M	33.89F	38.60M	33.46F	31.55M	27.70M	25.51F						
604	462.32	43.27	44.71M	43.91M	44.29M	43.73M	43.91M	41.37F	36.95M	47.31M						
605	415.01	41.67	44.77F	39.85F	44.80F	41.00F	E	47.39F	40.03F	33.85M						
606	432.35	41.79	44.68F	41.03M	34.35F	37.71M	47.28F	43.33F	44.12M	E						
607	229.13	48.69	47.06F	42.71F	56.30M											
608	457.04	42.84	41.77F	44.87M	36.43F	46.15M	43.73F	41.95F	45.00F							
609	475.79	35.34	45.85F	37.30M	38.76M	44.29F	30.64F	35.32M	34.97M	L	L	22.19M	28.74M			
610	313.55	42.59	42.90M	44.54F	41.27F	E	42.99M	41.25F								
611	699.33	36.70	42.29M	40.67F	39.27M	28.89M	31.62M	30.67M	25.79F	45.58M	33.62F	40.23M	40.90F	38.16F	40.65F	35.43M
612	368.53	47.82	52.16M	E	47.75F	50.48M	44.33M	44.39M								
613	377.03	36.26	37.95M	E	35.47F	42.82F	40.19M	35.84M	31.38M							
614	407.58	38.67	43.42M	44.55M	42.08M	36.45M	29.30F	31.75F	39.68F	42.12F						
615	427.27	37.50	36.74F	36.87M	32.65F	40.58F	38.92M	38.14M	38.03F	38.10F						
616	597.82	38.36	42.58M	41.15M	34.00F	37.01F	38.54M	42.18M	36.79M	31.94F	38.48F	38.68F	40.61M			
617	541.66	38.33	41.03F	40.35M	37.08F	30.77F	31.51M	L	37.43M	44.80M	42.61M	39.43F				
618	620.23	35.43	48.77M	37.01F	30.45M	30.79M	34.27F	40.72M	43.50M	39.08M	L	28.64F	32.02F	24.44F		
619	505.58	34.17	31.34M	30.45M	30.83F	41.79F	29.21M	29.26F	41.69F	33.07F	39.29M	34.80F				
620	380.59	39.11	43.81M	38.84M	36.03M	41.01F	38.90M	37.70F	37.50M							

MEAN 448.58 38.97
 S.D. 111.11 4.89
 N 19 19

E=EARLY RESORPTION L=LATE RESORPTION
 M=MALE F=FEMALE

APPENDIX CC

UIC/TRL STUDY NO.: 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 2: 25/16 MG BASE/KG/DAY*

DAM #	GRAVID UTERUS		INDIVIDUAL FETAL WEIGHT													
	WEIGHT	MEAN FETAL WEIGHT	1	2	3	4	5	6	7	8	9	10	11	12	13	14
621	517.91	35.30	42.70F	34.39M	36.27M	33.66F	37.15F	42.40F	29.29M	27.89F	34.81F	34.40M				
623	518.18	33.42	31.92F	34.45M	E	35.46F	37.40F	E	26.85M	34.33M	33.10M	36.51F	33.30M	31.53F	32.79F	
626	458.56	42.20	46.01F	42.21M	42.09F	40.39F	38.52M	46.02M	43.73M	38.64F						
627	484.80	35.86	42.24F	34.88M	32.74F	24.17F	35.24F	34.27M	35.64M	40.95F	42.63F					
629	293.65	26.39	32.53M	22.74F	28.91F	E	21.40M	23.70F	32.84M	E	22.58M					
632	439.10	43.28	44.86M	37.67M	41.74F	40.01F	E	49.51M	42.53F	46.62M						
633	448.06	31.27	34.93M	33.55F	30.86F	30.23F	32.54F	27.48F	32.23F	31.30F	28.75F	30.87F	35.50F	32.41F	36.67F	
634	643.40	35.42	41.05M	35.73M	36.60F	31.43M	29.90F	30.80F	40.53M	36.77M	35.57M	37.56M	32.94F			
635	452.24	32.97	39.23F	33.01F	28.91M	25.09M	29.70F	28.57F	39.62F	39.09M	33.52F	32.94F				
636	491.39	38.55	44.42F	41.93F	37.34M	39.52F	47.42M	39.85M	30.07F	34.12F	32.28M					
638	523.61	36.67	45.87M	36.58F	35.76M	31.07M	31.14F	36.61F	41.40M	39.97F	32.28F	36.06F				
640	464.22	33.08	39.04M	35.76F	33.59F	30.22F	25.52F	27.67M	42.76F	33.84M	29.23F	33.13M				

MEAN 477.93 35.37
 S.D. 80.05 4.61
 N 12 12

E=EARLY RESORPTION L=LATE RESORPTION
 M=MALE F=FEMALE

*DUE TO MORTALITY, THE HIGH DOSE WAS DECREASED FROM 25 MG BASE/KG/DAY TO 16 MG BASE/KG/DAY ON GESTATION DAYS 12-15 (THE RANGE OF DAYS REFLECTS STUDY STAGGER START OVER 2 DAYS).

APPENDIX D

UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 501		Unique Fetal Id.: 3
Fetal Position: Left 03		
STERNUM	(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION	
Fetal Position: Left 04		Unique Fetal Id.: 4
STERNUM	(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position: Right 01		Unique Fetal Id.: 6
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY	
Fetal Position: Right 02		Unique Fetal Id.: 7
STERNUM	(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position: Right 03		Unique Fetal Id.: 8
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL	
STERNUM	(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Animal: 503		Unique Fetal Id.: 2
Fetal Position: Left 02		
VERTEBRAL COLUMN	(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
SKULL	(SKELETAL) HYOID ARCH(ES), BENT - VARIATION; LEFT SLIGHT, RIGHT MODERATE	
Fetal Position: Right 01		Unique Fetal Id.: 4
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT	
Fetal Position: Right 02		Unique Fetal Id.: 5
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT (NO ARTICULATING HEAD)	
SKULL (SKELETAL)	SKULL, ACCESSORY SKULL BONES - VARIATION; BETWEEN PARIETALS	

APPENDIX D

UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 504		Unique Fetal Id.: 4
Fetal Position: Right 01		
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 02		Unique Fetal Id.: 5
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 04		Unique Fetal Id.: 7
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD)	
Fetal Position: Right 05		Unique Fetal Id.: 8
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY	
STERNUM	(SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT	
Fetal Position: Right 06		Unique Fetal Id.: 9
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT	
STERNUM	(SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 3 AND 4, SLIGHT	
Fetal Position: Left 01		Unique Fetal Id.: 1
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	

APPENDIX D

UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 505 (CONT.)	Unique Fetal Id.: 2
Fetal Position: Left 02	
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD)	
Fetal Position: Left 04	Unique Fetal Id.: 4
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY	
Fetal Position: Right 01	Unique Fetal Id.: 5
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 02	Unique Fetal Id.: 6
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 03	Unique Fetal Id.: 7
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 04	Unique Fetal Id.: 8
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	

APPENDIX D

UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 506	Unique Fetal Id.: 1
Fetal Position: Left 01	
STERNUM	
(SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 25 PRESACRAL VERTEBRAE - VARIATION	
VERTEBRAE, ANOMALY - MALFORMATION; CERVICAL ARCHES 1-2	
FUSED, BILATERAL; RIGHT CERVICAL ARCH 3 ABSENT; CERVICAL	
CENTRUM 1 MALFORMED, CERVICAL CENTRUM 3 FORMED ON RIGHT	
SIDE ONLY, 7TH CERVICAL RIBS, STERNEBRA 1 MALFORMED	
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, ANOMALY - MALFORMATION; 6 CERVICAL VERTEBRAE	
SKULL	
(SKELETAL) HYOID ARCH(ES), BENT - VARIATION; LEFT, SLIGHT	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL	
STERNUM	
(SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;	
4 AND 5, SLIGHT	
Fetal Position: Left 04	Unique Fetal Id.: 4
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY	
STERNUM	
(SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;	
4, SLIGHT	
STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	

APPENDIX D

UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 506 (CONT.)	Unique Fetal Id.: 5
Fetal Position: Left 05	
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT	
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT	
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 01	Unique Fetal Id.: 6
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT (NO ARTICULATING HEAD)	
STERNUM	
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 02	Unique Fetal Id.: 7
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT	
Fetal Position: Right 03	Unique Fetal Id.: 8
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
Fetal Position: Right 04	Unique Fetal Id.: 9
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 05	Unique Fetal Id.: 10
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL	

APPENDIX D

UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 507	Unique Fetal Id.: 1
Fetal Position: Left 01	
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY	
EYES	
(VISCERAL) AROUND IRIS, HEMORRHAGIC RING - VARIATION; LEFT	
ABDOMEN	
(VISCERAL) GALL BLADDER, VARIATION - VARIATION; DISTENDED	
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT	
STERNUM	
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position: Right 01	Unique Fetal Id.: 4
STERNUM	
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
ABDOMEN	
(VISCERAL) LIVER, ENLARGED - VARIATION	
Fetal Position: Right 02	Unique Fetal Id.: 5
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT	
STERNUM	
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 507 (CONT.) Unique Fetal Id.: 9
Fetal Position: Right 06
STERNUM
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

ABDOMEN
(VISCERAL) SPLEEN, SMALL IN SIZE - VARIATION

Fetal Position: Right 07 Unique Fetal Id.: 10
STERNUM
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Animal: 508
Fetal Position: Left 01 Unique Fetal Id.: 1
RIBS
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT

Fetal Position: Left 02 Unique Fetal Id.: 2
STERNUM
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Left 03 Unique Fetal Id.: 3
RIBS
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT

Fetal Position: Left 04 Unique Fetal Id.: 4
RIBS
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 05 Unique Fetal Id.: 5
RIBS
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Left 06 Unique Fetal Id.: 6
RIBS
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 508 (CONT.)
 Fetal Position: Left 07 Unique Fetal Id.: 7
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 01 Unique Fetal Id.: 8
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; LEFT

STERNUM
 (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY
 Fetal Position: Right 03 Unique Fetal Id.: 10
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Animal: 509
 Fetal Position: Left 01 Unique Fetal Id.: 1
 RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

Fetal Position: Left 02 Unique Fetal Id.: 2
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

STERNUM
 (SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
 4,5 SLIGHT

Fetal Position: Left 03 Unique Fetal Id.: 3
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

STERNUM
 (SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
 4,5 SLIGHT

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 509 (CONT.)	Unique Fetal Id.: 4
Fetal Position: Right 01	
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT	
Fetal Position: Right 02	Unique Fetal Id.: 5
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 03	Unique Fetal Id.: 6
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT	
Fetal Position: Right 04	Unique Fetal Id.: 7
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT	
Fetal Position: Right 05 *	Unique Fetal Id.: 8
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Animal: 510	
Fetal Position: Left 02	
LATE RESORPTION: CROWN-RUMP LENGTH: 30 mm	
Fetal Position: Left 03 *	Unique Fetal Id.: 3
Comment: VISCERAL OBSERVATION NOT RECORDED	
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT	

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 510 (CONT.)	Unique Fetal Id.: 4
Fetal Position: Left 04	
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
7TH CERVICAL RIB, PRESENT - VARIATION; BILATERAL	
Fetal Position: Right 01	Unique Fetal Id.: 5
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY	
Fetal Position: Right 03	Unique Fetal Id.: 7
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 04	Unique Fetal Id.: 8
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT, NO ARTICULATING HEAD	
Fetal Position: Right 06	Unique Fetal Id.: 10
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT, NO ARTICULATING HEAD	
Fetal Position: Right 07	Unique Fetal Id.: 11
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL; RIGHT, NO ARTICULATING HEAD	
Animal: 511	
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 511 (CONT.) Unique Fetal Id.: 4
 Fetal Position: Left 04
 THORACIC CAVITY
 (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL; LEFT, NO
 ARTICULATING HEAD

Fetal Position: Right 02 Unique Fetal Id.: 6
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY WITH NO
 ARTICULATING HEAD; RIGHT, FULL

SKULL
 (SKELETAL) HYOID ARCH(ES), BENT - VARIATION; LEFT, MODERATE

Fetal Position: Right 04 Unique Fetal Id.: 8
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY; RIGHT, FULL

Animal: 512 Unique Fetal Id.: 1
 Fetal Position: Left 01
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

STERNUM
 (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY

Fetal Position: Right 01 Unique Fetal Id.: 3
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 02 Unique Fetal Id.: 4
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 512 (CONT.) Unique Fetal Id.: 5
 Fetal Position: Right 03
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 04 Unique Fetal Id.: 6
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Animal: 514 Unique Fetal Id.: 1
 Fetal Position: Left 01
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 02 Unique Fetal Id.: 2
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

STERNUM
 (SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 01 Unique Fetal Id.: 3
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

STERNUM
 (SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT
 VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 514 (CONT.)	Unique Fetal Id.: 4
Fetal Position: Right 02	
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT	
Fetal Position: Right 03	Unique Fetal Id.: 5
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT	
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, 4 AND 5, SLIGHT	
Fetal Position: Right 04	Unique Fetal Id.: 6
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
SKULL	
(SKELETAL) HYOID BODY, UNOSSIFIED - VARIATION	
Fetal Position: Right 05	Unique Fetal Id.: 7
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
HINDLIMBS	
(SKELETAL) TALUS, UNOSSIFIED - VARIATION; BILATERAL	
Fetal Position: Right 06	Unique Fetal Id.: 8
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-4, SLIGHT	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
HINDLIMBS	
(SKELETAL) TALUS, UNOSSIFIED - VARIATION; BILATERAL	

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 515	Unique Fetal Id.: 1
Fetal Position: Left 01	
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY WITH NO ARTICULATING HEAD	
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT	
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL(LEFT NO ARTICULATING HEAD)	
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED AND FUSED - MALFORMATION; 2-4, MALALIGNED SLIGHT-MODERATE; 5, MALALIGNED SEVERE; 4 AND 5 FUSED	
Fetal Position: Left 03	Unique Fetal Id.: 3
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Fetal Position: Left 04	Unique Fetal Id.: 4
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT	
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT	
Fetal Position: Right 01	
LATE RESORPTION: CROWN-RUMP LENGTH: 34 mm	
Fetal Position: Right 02	Unique Fetal Id.: 6
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-4, SLIGHT	

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 516	Unique Fetal Id.: 1
Fetal Position: Left 01	
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY	
STERNUM	
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
SKULL	
(SKELETAL) HYOID ARCH(ES), BENT - VARIATION; LEFT, MODERATE	
Fetal Position: Right 01	Unique Fetal Id.: 3
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY	
Fetal Position: Right 02	Unique Fetal Id.: 4
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY	
STERNUM	
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY	
SKULL	
(SKELETAL) HYOID ARCH(ES), BENT - VARIATION; LEFT, MODERATE	
Fetal Position: Right 04	Unique Fetal Id.: 6
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 517		Unique Fetal Id.: 1
Fetal Position: Left 01		
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY	
STERNUM	(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT	
STERNUM	(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT	
Fetal Position: Left 04		Unique Fetal Id.: 4
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY	
Fetal Position: Left 05		Unique Fetal Id.: 5
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT	
STERNUM	(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT	
Fetal Position: Right 01		Unique Fetal Id.: 6
STERNUM	(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Fetal Position: Right 02		Unique Fetal Id.: 7
STERNUM	(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT	

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 517 (CONT.)	Unique Fetal Id.: 8
Fetal Position: Right 03	
STERNUM	
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Fetal Position: Right 04	Unique Fetal Id.: 9
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, SLIGHT; 4, MODERATE	
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Animal: 518	
Fetal Position: Left 01	Unique Fetal Id.: 1
THORACIC CAVITY	
(VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHEOCEPHALIC TRUNK	
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY	
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 6, SLIGHT	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL, LEFT WITH NO ARTICULATING HEAD	
ABDOMEN	
(VISCERAL) GALL BLADDER, VARIATION - VARIATION; SMALL	

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 518 (CONT.)	Unique Fetal Id.: 4
Fetal Position: Left 04	
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
Fetal Position: Right 01	Unique Fetal Id.: 5
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT	
STERNUM	
(SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3, 4 AND 6, SLIGHT	
STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
ABDOMEN	
(VISCERAL) GALL BLADDER, VARIATION - VARIATION; SMALL	
Fetal Position: Right 02	Unique Fetal Id.: 6
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY; RIGHT, FULL	
STERNUM	
(SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT	
STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Fetal Position: Right 03	Unique Fetal Id.: 7
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
STERNUM	
(SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Animal: 519	
Fetal Position: Left 01	Unique Fetal Id.: 1
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
Fetal Position: Right 01	Unique Fetal Id.: 3
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 519 (CONT.)	Unique Fetal Id.: 5
Fetal Position: Right 03	
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
STERNUM	(SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 6, SLIGHT STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
Fetal Position: Right 04	Unique Fetal Id.: 6
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL 7TH CERVICAL RIB, PRESENT - VARIATION; LEFT
Fetal Position: Right 05	Unique Fetal Id.: 7
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL
Animal: 520	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN	(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
Fetal Position: Left 04	Unique Fetal Id.: 4
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN	(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
Fetal Position: Left 05	Unique Fetal Id.: 5
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 2 MG BASE/KG/DAY

Animal: 521	Unique Fetal Id.: 2
Fetal Position: Left 02	
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT, WITH NO ARTICULATING HEAD	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY; RIGHT, FULL	
Fetal Position: Left 05	Unique Fetal Id.: 5
THORACIC CAVITY	
(VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK	
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 01	Unique Fetal Id.: 6
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 02	Unique Fetal Id.: 7
THORACIC CAVITY	
(VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK	
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 03	Unique Fetal Id.: 8
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT	
Fetal Position: Right 04	Unique Fetal Id.: 9
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 2 MG BASE/KG/DAY

Animal: 522	Unique Fetal Id.: 1
Fetal Position: Left 01	
THORACIC CAVITY (VISCERAL)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK; ACCESSORY LEFT SUBCLAVIAN
RIBS (SKELETAL)	RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN (SKELETAL)	VERTEBRAE, ANOMALY - MALFORMATION; CERVICAL CENTRUM 1 MALFORMED AND MISSHAPENED; CERVICAL CENTRUM 2 ABSENT; CERVICAL ARCHES 2, BILATERAL, SMALL IN SIZE, DORSAL ASPECT PRESENT ONLY
Fetal Position: Left 02	Unique Fetal Id.: 2
STERNUM (SKELETAL)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
Fetal Position: Left 03	Unique Fetal Id.: 3
THORACIC CAVITY (VISCERAL)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK
Fetal Position: Left 04	Unique Fetal Id.: 4
THORACIC CAVITY (VISCERAL)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; ACCESSORY LEFT SUBCLAVIAN
Fetal Position: Left 05	Unique Fetal Id.: 5
RIBS (SKELETAL)	RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY
Fetal Position: Right 01	Unique Fetal Id.: 6
RIBS (SKELETAL)	RIB 13, FULL - VARIATION; BILATERAL

APPENDIX D

UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 2 MG BASE/KG/DAY

Animal: 522 (CONT.) Unique Fetal Id.: 7
 Fetal Position: Right 02
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY
 VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 03 Unique Fetal Id.: 8
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; LEFT

SKULL (SKELETAL) HYOID ARCH(ES), BENT - VARIATION; LEFT, MODERATE
 Fetal Position: Right 04 Unique Fetal Id.: 9
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Animal: 523 Unique Fetal Id.: 2
 Fetal Position: Left 02
 RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

Animal: 526 Unique Fetal Id.: 2
 Fetal Position: Left 02
 RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

Fetal Position: Left 03 Unique Fetal Id.: 3
 STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 2 MG BASE/KG/DAY

Animal: 526 (CONT.)		
Fetal Position: Right 01		Unique Fetal Id.: 5
RIBS		
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY WITH NO ARTICULATING HEAD; RIGHT, FULL		
Fetal Position: Right 02		Unique Fetal Id.: 6
RIBS		
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL		
Fetal Position: Right 03		Unique Fetal Id.: 7
RIBS		
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL		
Fetal Position: Right 04		Unique Fetal Id.: 8
RIBS		
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT		
Animal: 527		
Fetal Position: Left 01		Unique Fetal Id.: 1
STERNUM		
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT		
Fetal Position: Left 02		Unique Fetal Id.: 2
SKULL		
(SKELETAL) HYOID ARCH(ES), BENT - VARIATION; RIGHT, SLIGHT		
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS		
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT, NO ARTICULATING HEAD		
Fetal Position: Right 02		Unique Fetal Id.: 5
RIBS		
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY		
Fetal Position: Right 03		Unique Fetal Id.: 6
VERTEBRAL COLUMN		
(SKELETAL) CENTRA, EXTRA SITE OF OSSIFICATION - MALFORMATION; CENTRUM 1		

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 2 MG BASE/KG/DAY

Animal: 527 (CONT.)	Unique Fetal Id.: 7
Fetal Position: Right 04	
STERNUM	
(SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Fetal Position: Right 05	Unique Fetal Id.: 8
SKULL	
(SKELETAL) HYOID ARCH(ES), BENT - VARIATION; LEFT, SLIGHT	
Animal: 529	
Fetal Position: Left 01	Unique Fetal Id.: 1
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 AND 6	
Fetal Position: Left 02	Unique Fetal Id.: 2
SKULL	
(SKELETAL) HYOID BODY, UNOSSIFIED - VARIATION	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY WITH NO ARTICULATING HEAD; RIGHT, FULL	
STERNUM	
(SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Fetal Position: Left 04	Unique Fetal Id.: 4
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
SKULL	
(SKELETAL) HYOID BODY, UNOSSIFIED - VARIATION	

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 2 MG BASE/KG/DAY

Animal: 529 (CONT.) Unique Fetal Id.: 5
Fetal Position: Left 05
STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

SKULL (SKELETAL) HYOID BODY, UNOSSIFIED - VARIATION

HINDLIMBS (SKELETAL) TALUS, UNOSSIFIED - VARIATION

Fetal Position: Left 06 Unique Fetal Id.: 6
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (SKELETAL) HYOID BODY, UNOSSIFIED - VARIATION

HINDLIMBS (SKELETAL) TALUS, UNOSSIFIED - VARIATION; BILATERAL

Fetal Position: Left 07 Unique Fetal Id.: 7
STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

SKULL (SKELETAL) HYOID BODY, UNOSSIFIED - VARIATION

HINDLIMBS (SKELETAL) TALUS, UNOSSIFIED - VARIATION; RIGHT

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 2 MG BASE/KG/DAY

Animal: 529 (CONT.)	Unique Fetal Id.: 9
Fetal Position: Right 01	
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY WITH NO ARTICULATING HEAD; RIGHT, FULL	
ABDOMEN	
(VISCERAL) URETER(S), RETROCAVAL - VARIATION; RIGHT	
Fetal Position: Right 02	Unique Fetal Id.: 10
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 03	Unique Fetal Id.: 11
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT, WITH NO ARTICULATING HEAD	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 04	Unique Fetal Id.: 12
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, WITH NO ARTICULATING HEAD	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 05	Unique Fetal Id.: 13
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 2 MG BASE/KG/DAY

Animal: 530
Fetal Position: Left 01 Unique Fetal Id.: 1
RIBS

(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT

Fetal Position: Left 03 Unique Fetal Id.: 3
SKULL

(SKELETAL) HYOID ARCH(ES), BENT - VARIATION; LEFT, MODERATE

Fetal Position: Left 04 Unique Fetal Id.: 4
RIBS

(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Left 05 Unique Fetal Id.: 5
RIBS

(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

Fetal Position: Right 02 Unique Fetal Id.: 7
RIBS

(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT

Fetal Position: Right 03 Unique Fetal Id.: 8
STERNUM

(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

Animal: 531

Fetal Position: Left 01 Unique Fetal Id.: 1
RIBS

(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

STERNUM

(SKELETAL) STERNEBRA(E), MALALIGNED AND FUSED - MALFORMATION; 2-5
MALALIGNED SLIGHT TO MODERATE; 3-5 FUSED
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY

VERTEBRAL COLUMN

(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 2 MG BASE/KG/DAY

Animal: 531 (CONT.)	Unique Fetal Id.: 3
Fetal Position: Left 03	
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;	
1-3, SLIGHT	
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Fetal Position: Left 04	Unique Fetal Id.: 4
STERNUM	
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Fetal Position: Right 02	Unique Fetal Id.: 6
STERNUM	
(SKELETAL) STERNEBRA(E), FUSED - MALFORMATION; 4 AND 5	
Fetal Position: Right 03	Unique Fetal Id.: 7
STERNUM	
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY	
Fetal Position: Right 04	Unique Fetal Id.: 8
STERNUM	
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY	
Animal: 532	
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	
(SKELETAL) RIB 13, RUDDIMENTARY - VARIATION; RIGHT	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 01	Unique Fetal Id.: 4
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 2 MG BASE/KG/DAY

Animal: 532 (CONT.) Unique Fetal Id.: 6
 Fetal Position: Right 03
 STERNUM
 (SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
 1-4, SLIGHT
 STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

Animal: 533 Unique Fetal Id.: 1
 Fetal Position: Left 01
 STERNUM
 (SKELETAL) STERNEBRA(E), FUSED - MALFORMATION; 3-5

Fetal Position: Left 02 Unique Fetal Id.: 2
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 03 Unique Fetal Id.: 3
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 01 Unique Fetal Id.: 4
 RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT

Fetal Position: Right 03 Unique Fetal Id.: 6
 STERNUM
 (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

Animal: 534 Unique Fetal Id.: 1
 Fetal Position: Left 01
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

STERNUM
 (SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 2 MG BASE/KG/DAY

Animal: 534 (CONT.)	Unique Fetal Id.: 2
Fetal Position: Left 02	
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 01	Unique Fetal Id.: 4
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY	
Fetal Position: Right 02	Unique Fetal Id.: 5
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT	
Fetal Position: Right 03	Unique Fetal Id.: 6
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT	
Fetal Position: Right 04	Unique Fetal Id.: 7
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Animal: 535	
Fetal Position: Left 01	Unique Fetal Id.: 1
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; RIGHT	
Fetal Position: Left 02	Unique Fetal Id.: 2
THORACIC CAVITY	
(VISCERAL) LUNGS, SMALL IN SIZE - MALFORMATION; ALL LOBES	
Fetal Position: Right 04	Unique Fetal Id.: 6
THORACIC CAVITY	
(VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 2 MG BASE/KG/DAY

Animal: 536
 Fetal Position: Left 01 Unique Fetal Id.: 1
 RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT

STERNUM
 (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
 Fetal Position: Left 02 Unique Fetal Id.: 2
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
 Fetal Position: Left 03 Unique Fetal Id.: 3
 RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

Fetal Position: Left 05 Unique Fetal Id.: 5
 RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT, WITH NO
 ARTICULATING HEAD
 Fetal Position: Right 01 Unique Fetal Id.: 7
 RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL; LEFT WITH NO
 ARTICULATING HEAD

Animal: 538
 Fetal Position: Left 02 Unique Fetal Id.: 2
 RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT, WITH NO
 ARTICULATING HEAD

Fetal Position: Left 03 Unique Fetal Id.: 3
 SKULL
 (SKELETAL) HYOID ARCH(ES), BENT - VARIATION; RIGHT, MODERATE

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 2 MG BASE/KG/DAY

Animal: 538 (CONT.)		Unique Fetal Id.: 4
Fetal Position: Right 01		
RIBS		
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY WITH NO ARTICULATING HEAD; RIGHT, FULL		
Fetal Position: Right 02		Unique Fetal Id.: 5
RIBS		
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY		
Fetal Position: Right 03		Unique Fetal Id.: 6
RIBS		
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT		
Fetal Position: Right 04		Unique Fetal Id.: 7
RIBS		
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT		
Animal: 540		
Fetal Position: Left 01		Unique Fetal Id.: 1
RIBS		
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL		
Fetal Position: Left 02		Unique Fetal Id.: 2
STERNUM		
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY		
Fetal Position: Right 01		Unique Fetal Id.: 4
RIBS		
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY		
VERTEBRAL COLUMN		
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position: Right 02		Unique Fetal Id.: 5
RIBS		
(SKELETAL) RIB 13, FULL - VARIATION		
Fetal Position: Right 03		Unique Fetal Id.: 6
STERNUM		
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY		

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 543
 Fetal Position: Right 02 Unique Fetal Id.: 6
 SKULL (SKELETAL) HYOID ARCH(ES), BENT - VARIATION; RIGHT, SLIGHT

Fetal Position: Right 03 Unique Fetal Id.: 7
 SKULL (SKELETAL) HYOID BODY, UNOSSIFIED - VARIATION

Fetal Position: Right 05 Unique Fetal Id.: 9
 STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

Animal: 544
 Fetal Position: Left 01 Unique Fetal Id.: 1
 STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

Fetal Position: Left 03 Unique Fetal Id.: 3
 STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

Fetal Position: Right 01 Unique Fetal Id.: 4
 RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT

Animal: 545
 Fetal Position: Left 01 Unique Fetal Id.: 1
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY WITH NO ARTICULATING HEAD; RIGHT, FULL

STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

Fetal Position: Left 02 Unique Fetal Id.: 2
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 545 (CONT.)
 Fetal Position: Left 03 Unique Fetal Id.: 3
 RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT, WITH NO
 ARTICULATING HEAD

Fetal Position: Left 04 Unique Fetal Id.: 4
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Left 05 Unique Fetal Id.: 5
 RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

Animal: 546
 Fetal Position: Left 01 Unique Fetal Id.: 1
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Left 02 Unique Fetal Id.: 2
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Left 03 Unique Fetal Id.: 3
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 04 Unique Fetal Id.: 4
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
 VERTEBRAE, ANOMALY - MALFORMATION; CERVICAL ARCHES 1 AND 2
 FUSED, BILATERAL

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 546 (CONT.) Unique Fetal Id.: 5
Fetal Position: Left 05
THORACIC CAVITY (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 06 Unique Fetal Id.: 6
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 01 Unique Fetal Id.: 7
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

STERNUM (SKELETAL) STERNEBRA (E), MALALIGNED AND FUSED - MALFORMATION; 1-4 MALALIGNED, SLIGHT TO MODERATE; 5 MALALIGNED, SEVERE; 2-4 FUSED

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 02 Unique Fetal Id.: 8
THORACIC CAVITY (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 546 (CONT.) Unique Fetal Id.: 9
 Fetal Position: Right 03 *
 Comments: VISCERAL OBSERVATION NOT RECORDED

RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Animal: 547 Unique Fetal Id.: 2
 Fetal Position: Left 02
 THORACIC CAVITY (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

STERNUM (SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
 Fetal Position: Right 01 Unique Fetal Id.: 4
 STERNUM (SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-4, SLIGHT TO MODERATE
 STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

Fetal Position: Right 02 Unique Fetal Id.: 5
 THORACIC CAVITY (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

SKULL (SKELETAL) HYOID ARCH(ES), BENT - VARIATION; RIGHT, SLIGHT
 Fetal Position: Right 03 Unique Fetal Id.: 6
 THORACIC CAVITY (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 547 (CONT.)

Fetal Position: Right 04

THORACIC CAVITY

(VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

Unique Fetal Id.: 7

RIBS

(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

STERNUM

(SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT

00

Fetal Position: Right 06

STERNUM

(SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT

Unique Fetal Id.: 9

Fetal Position: Right 07

RIBS

(SKELETAL) RIB 13, FULL - VARIATION; RIGHT

Unique Fetal Id.: 10

STERNUM

(SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 AND 6

VERTEBRAL COLUMN

(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Animal: 548

Fetal Position: Left 02

RIBS

(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Unique Fetal Id.: 2

STERNUM

(SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 548 (CONT.) Unique Fetal Id.: 3
Fetal Position: Right 01
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 03 Unique Fetal Id.: 5
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
A (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 04 Unique Fetal Id.: 6
RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT

STERNUM
(SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
3 AND 4, SLIGHT

Animal: 549 Unique Fetal Id.: 1
Fetal Position: Left 01
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 03 Unique Fetal Id.: 3
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 549 (CONT.)

Fetal Position: Left 04

THORACIC CAVITY

(VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM BRACHIOCEPHLIC TRUNK

Unique Fetal Id.: 4

RIBS

(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 01

RIBS

(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Unique Fetal Id.: 5

VERTEBRAL COLUMN

(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 02

RIBS

(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Unique Fetal Id.: 6

VERTEBRAL COLUMN

(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 03

RIBS

(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Unique Fetal Id.: 7

VERTEBRAL COLUMN

(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 04 *

RIBS

(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Unique Fetal Id.: 8

STERNUM

(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY

VERTEBRAL COLUMN

(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 550	Unique Fetal Id.: 1
Fetal Position: Left 01	
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY; RIGHT, FULL (BOTH WITH NO ARTICULATING HEAD)	
STERNUM	
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Fetal Position: Right 01	Unique Fetal Id.: 4
THORACIC CAVITY	
(VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK	
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL; RIGHT WITH NO ARTICULATING HEAD	
STERNUM	
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Fetal Position: Right 02	Unique Fetal Id.: 5
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 1-4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
SKULL	
(SKELETAL) HYOID ARCH(ES), BENT - VARIATION; BILATERAL, SLIGHT	

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 550 (CONT.)	Unique Fetal Id.: 6
Fetal Position: Right 03	
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
STERNUM	(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY
VERTEBRAL COLUMN	(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
	VERTEBRAE/RIBS, ANOMALY - MALFORMATION; INVOLVING THORACIC
	VERTEBRAE AND RIBS 5 THROUGH 7
Fetal Position: Right 04	Unique Fetal Id.: 7
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN	(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
Fetal Position: Right 05	Unique Fetal Id.: 8
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY
VERTEBRAL COLUMN	(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
Animal: 552	
Fetal Position: Left 01	Unique Fetal Id.: 1
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT
VERTEBRAL COLUMN	(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
	VERTEBRAE, ANOMALY - MALFORMATION; INVOLVING LUMBAR
	VERTEBRAE 4-6

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 552 (CONT.) Unique Fetal Id.: 4
 Fetal Position: Right 01
 RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL WITH NO ARTICULATING HEAD

Fetal Position: Right 02 Unique Fetal Id.: 5
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 03 Unique Fetal Id.: 6
 RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT

Fetal Position: Right 04 Unique Fetal Id.: 7
 RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT

Animal: 553 Unique Fetal Id.: 1
 Fetal Position: Left 01
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
 VERTEBRAE, ANOMALY - MALFORMATION; INVOLVING THORACIC VERTEBRAE 4 THROUGH 6

Fetal Position: Left 03 Unique Fetal Id.: 3
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 01 Unique Fetal Id.: 4
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY; RIGHT, FULL

STERNUM
 (SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 553 (CONT.)
 Fetal Position: Right 02 Unique Fetal Id.: 5

RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT, WITH NO
 ARTICULATING HEAD

Fetal Position: Right 03 Unique Fetal Id.: 6

RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT

Fetal Position: Right 04 Unique Fetal Id.: 7

RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT

Fetal Position: Right 05 Unique Fetal Id.: 8

RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

SKULL

(SKELETAL) HYOID ARCH(ES), BENT - VARIATION; LEFT, SLIGHT

Animal: 554

Fetal Position: Left 01 Unique Fetal Id.: 1

RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; LEFT

Fetal Position: Left 02 Unique Fetal Id.: 2

SKULL
 (SKELETAL) HYOID ARCH(ES), BENT - VARIATION; LEFT, SLIGHT

ABDOMEN

(VISCERAL) SPLEEN, SMALL IN SIZE - VARIATION

Fetal Position: Left 03 Unique Fetal Id.: 3

RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT

Fetal Position: Left 04 Unique Fetal Id.: 4

RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT, WITH NO
 ARTICULATING HEAD

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 554 (CONT.) Unique Fetal Id.: 5
Fetal Position: Right 01
VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 02 Unique Fetal Id.: 6
RIBS
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 03 Unique Fetal Id.: 7
RIBS
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT, WITH NO
ARTICULATING HEAD

Animal: 555 Unique Fetal Id.: 1
Fetal Position: Left 01
RIBS
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT

Fetal Position: Left 03 Unique Fetal Id.: 3
RIBS
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT

Fetal Position: Left 04 Unique Fetal Id.: 4
RIBS
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 05 Unique Fetal Id.: 5
RIBS
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 555 (CONT.)	Unique Fetal Id.: 6
Fetal Position: Left 06	
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY; RIGHT, FULL	
STERNUM	
(SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY	
Fetal Position: Left 07	Unique Fetal Id.: 7
STERNUM	
(SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY	
Fetal Position: Right 01	Unique Fetal Id.: 8
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Animal: 556	Unique Fetal Id.: 1
Fetal Position: Left 01	
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT, WITH NO ARTICULATING HEAD	
SKULL	
(SKELETAL) HYOID ARCH(ES), BENT - VARIATION; RIGHT, MODERATE	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Left 05	Unique Fetal Id.: 5
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT, WITH NO ARTICULATING HEAD	
Fetal Position: Right 02 *	Unique Fetal Id.: 8
Comments: VISCERAL OBSERVATIONS NOT RECORDED	
Animal: 557	Unique Fetal Id.: 2
Fetal Position: Left 02	
STERNUM	
(SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-4, SLIGHT	

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 557 (CONT.) Unique Fetal Id.: 3
 Fetal Position: Left 03
 STERNUM
 (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

Fetal Position: Left 04 Unique Fetal Id.: 4
 RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT, WITH NO ARTICULATING HEAD

Fetal Position: Left 05 Unique Fetal Id.: 5
 RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT

Fetal Position: Right 01 Unique Fetal Id.: 6
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 02 Unique Fetal Id.: 7
 RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT

Animal: 559 Unique Fetal Id.: 2
 Fetal Position: Left 02
 STERNUM
 (SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-4, SLIGHT STERNEBRA(E), EXTRA SITE OF OSSIFICATION - MALFORMATION; ANTERIOR TO STERNEBRA 1 STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

Fetal Position: Left 03 Unique Fetal Id.: 3
 RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

Fetal Position: Left 04
 LATE RESORPTION: CROWN-RUMP LENGTH: 49 mm

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 7 MG BASE/KG/DAY

Animal: 559 (CONT.)

Fetal Position: Left 05

STERNUM

(SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
2-4, SLIGHT

Unique Fetal Id.: 5

Fetal Position: Right 02

STERNUM

(SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
4-5, SLIGHT

Unique Fetal Id.: 7

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 25 MG BASE/KG/DAY

Animal: 563
 Fetal Position: Left 01 Unique Fetal Id.: 1
 THORACIC CAVITY
 (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 CAROTID ARISES FROM BRACHIOCEPHALIC ARTERY

Animal: 566
 Fetal Position: Right 01 Unique Fetal Id.: 5
 THORACIC CAVITY
 (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

Animal: 567
 Fetal Position: Left 05
 LATE RESORPTION: CROWN-RUMP LENGTH: 85 MM

Animal: 571
 Fetal Position: Left 02 Unique Fetal Id.: 2
 ABDOMEN
 (VISCERAL) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE
 SPLEEN, SMALL IN SIZE - VARIATION

Fetal Position: Right 05 Unique Fetal Id.: 8
 THORACIC CAVITY
 (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

Fetal Position: Right 06 Unique Fetal Id.: 9
 THORACIC CAVITY
 (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

ABDOMEN
 (VISCERAL) SPLEEN, SMALL IN SIZE - VARIATION

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 25 MG BASE/KG/DAY

Animal: 572 Unique Fetal Id.: 2
Fetal Position: Left 02
THORACIC CAVITY
(VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION;
ACCESSORY LEFT SUBCLAVIAN

ABDOMEN
(VISCERAL) URETER(S), RETROCAVAL - VARIATION

Fetal Position: Left 06 Unique Fetal Id.: 6
ABDOMEN
(VISCERAL) URETER(S), RETROCAVAL - VARIATION

Animal: 578
Fetal Position: Right 05
LATE RESORPTION: CROWN-RUMP LENGTH: 56 mm

Animal: 579
Fetal Position: Left 01
LATE RESORPTION: CROWN-RUMP LENGTH: 90 mm

Fetal Position: Left 04 Unique Fetal Id.: 4
THORACIC CAVITY
(VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal:	581	Unique Fetal Id.:	1
Fetal Position:	Left 01 *		
ANUS	(EXTERNAL) ANUS, ANAL ATRESIA - MALFORMATION		
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL		
VERTEBRAL COLUMN	(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
SKULL	(SKELETAL) SKULL, ANOMALY - MALFORMATION; MAXILLAE, JUGAL, SQUAMOSAL, MANDIBLE MALFORMED, BILATERAL HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES ABSENT/UNOSSIFIED		
TAIL	(EXTERNAL) TAIL, ANOMALY - MALFORMATION; SHORT		
ABDOMEN	(VISCERAL) KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SEVERE URETER(S), DISTENDED - VARIATION; BILATERAL, SEVERE		
HEAD	(EXTERNAL) MOUTH, PALATE, CLEFT PALATE - MALFORMATION FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL		
Comments:	SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: CLEFT PALATE; SHORT TAIL--CAUDAL VERTEBRAE 1-3 MALFORMED AND FUSED; REMAINING CAUDAL VERTEBRAE ABSENT		
Fetal Position:	Left 02 *	Unique Fetal Id.:	2
ANUS	(EXTERNAL) ANUS, ANAL ATRESIA - MALFORMATION		
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY; RIGHT, FULL		
STERNUM	(SKELETAL) STERNEBRA(S), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4-5, SLIGHT		

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 581

Fetal Position: Left 02 * Unique Fetal Id.: 2 (CONT.)

VERTEBRAL COLUMN

(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(SKELETAL) HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES
ABSENT

TAIL

(EXTERNAL) TAIL, ANOMALY - MALFORMATION; SHORT

ABDOMEN

(VISCERAL) KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, MODERATE
URETER(S), DISTENDED - VARIATION; BILATERAL, LEFT
SEVERE, RIGHT MODERATE

HEAD

(EXTERNAL) HEAD, MICROCEPHALY - MALFORMATION
PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL
IN SIZE AND MALPOSITIONED
MOUTH, PALATE, CLEFT PALATE - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Comments:

SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: CLEFT
PALATE; SHORT TAIL--SACRAL VERTEBRAE 3-4 MALFORMED, ALL CAUDAL
VERTEBRAE ABSENT; MICROCEPHALY--SKULL BONES MALFORMED AND/OR
FUSED.

Fetal Position: Left 03 * Unique Fetal Id.: 3

ANUS

(EXTERNAL) ANUS, ANAL ATRESIA - MALFORMATION

RIBS

(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

STERNUM

(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3-5, SLIGHT

SKULL

(SKELETAL) HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES ABSENT/UNOSSIFIED

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 581
Fetal Position: Left 03 * Unique Fetal Id.: 3 (CONT.)

TAIL (EXTERNAL) TAIL, ANOMALY - MALFORMATION; SHORT

HEAD (EXTERNAL) HEAD, MICROCEPHALY - MALFORMATION
PINNA (E), PINNA (E) ANOMALY - MALFORMATION; BILATERAL, SMALL
IN SIZE AND MALPOSITIONED
MOUTH, TONGUE/MANDIBLE ANOMALY - MALFORMATION; TONGUE
ATTACHED TO MANDIBLE
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS; MICROCEPHALY--
SKULL BONES MALFORMED AND/OR FUSED; SHORT TAIL--SACRAL
VERTEBRAE 2-4 MALFORMED/FUSED, ALL CAUDAL VERTEBRAE ABSENT

Fetal Position: Left 04 * Unique Fetal Id.: 4
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (SKELETAL) SKULL, ANOMALY - MALFORMATION; MAXILLAE, JUGAL, MALFORMED,
LEFT, SQUAMOSAL BILATERAL
HYOID, ANOMALY - MALFORMATION; ARCHES MALPOSITIONED

TAIL (EXTERNAL) TAIL, ANOMALY - MALFORMATION; ABSENT

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: TAIL ABSENT--
CAUDAL VERTEBRAE MALFORMED OR ABSENT

Fetal Position: Right 01 * Unique Fetal Id.: 5
STERNUM (SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 581
 Fetal Position: Right 01 * Unique Fetal Id.: 5 (CONT.)
 SKULL (SKELETAL) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED
 HYOID, ANOMALY - MALFORMATION; ARCHES MALPOSITIONED OR ABSENT

TAIL (EXTERNAL) TAIL, ANOMALY - MALFORMATION; ABSENT

HEAD (EXTERNAL) MOUTH, PALATE, CLEFT PALATE - MALFORMATION
 FACE, FACIAL BLEB(S) - MALFORMATION; LEFT

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: CLEFT PALATE; TAIL ABSENT--SACRAL VERTEBRAE 4 AND CAUDAL VERTEBRA 1 MALFORMED, ALL REMAINING CAUDAL VERTEBRAE ABSENT

Fetal Position: Right 02 Unique Fetal Id.: 6
 SKULL (SKELETAL) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED
 HYOID, ANOMALY - MALFORMATION; ARCHES UNOSSIFIED/ABSENT

HEAD (EXTERNAL) FACE, FACIAL BLEB(S) - MALFORMATION; LEFT

Fetal Position: Right 03 Unique Fetal Id.: 7
 SKULL (SKELETAL) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED
 HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES ABSENT/UNOSSIFIED

ABDOMEN (VISCERAL) KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; RIGHT KIDNEY SMALL, MALFORMED AND UNASCENDED

HEAD (EXTERNAL) FACE, FACIAL BLEB(S) - MALFORMATION; LEFT

APPENDIX D

UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 582	Unique Fetal Id.: 1
Fetal Position: Left 01	
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS (SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY	
STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
SKULL (SKELETAL) SKULL, ANOMALY - MALFORMATION; SKULL BONES FUSED	
Fetal Position: Left 03	Unique Fetal Id.: 3
THORACIC CAVITY (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK	
STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Fetal Position: Right 01	Unique Fetal Id.: 4
RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
SKULL (SKELETAL) HYOID ARCH(ES), BENT - VARIATION; BILATERAL, MODERATE TO SEVERE	

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 582 (CONT.) Unique Fetal Id.: 5
 Fetal Position: Right 02
 THORACIC CAVITY
 (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
 STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
 Fetal Position: Right 03 Unique Fetal Id.: 6
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; RIGHT, RUDIMENTARY; LEFT, FULL

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
 Fetal Position: Right 05 Unique Fetal Id.: 8
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; RIGHT, RUDIMENTARY; LEFT, FULL

SKULL (SKELETAL) SKULL, ANOMALY - MALFORMATION; SKULL BONES FUSED

Animal: 583 Unique Fetal Id.: 1
 Fetal Position: Left 01 *
 ANUS (EXTERNAL) ANUS, ANAL ATRESIA - MALFORMATION

RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
 VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 563
 Fetal Position: Left 01 Unique Fetal Id.: 1 (CONT.)
 SKULL (SKELETAL) HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES ABSENT/UNOSSIFIED

TAIL (EXTERNAL) TAIL, ANOMALY - MALFORMATION; SHORT, THREAD-LIKE

HEAD (EXTERNAL) HEAD, MICROCEPHALY - MALFORMATION
 MOUTH, TONGUE/MANDIBLE ANOMALY - MALFORMATION; MANDIBLE CLEFT
 MOUTH, PALATE, CLEFT PALATE - MALFORMATION
 FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: MICROCEPHALY AND MANDIBULAR CLEFT--SKULL BONES MALFORMED AND/OR FUSED; CLEFT PALATE; SHORT TAIL--CAUDAL VERTEBRAE 4 AND REMAINING ABSENT.

Fetal Position: Left 02 Unique Fetal Id.: 2
 RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (SKELETAL) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED
 HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES ABSENT/UNOSSIFIED

HEAD (EXTERNAL) PINNA (E), PINNA (E) ANOMALY - MALFORMATION; SMALL, BILATERAL FACE, FACIAL BLEB(S) - MALFORMATION; LEFT

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 583 (CONT.)	Unique Fetal Id.: 3
Fetal Position: Left 03 *	
THORACIC CAVITY	
(VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK	
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
SKULL	
(SKELETAL) HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES ABSENT/UNOSSIFIED	
TAIL	
(EXTERNAL) TAIL, ANOMALY - MALFORMATION; SHORT, BENT	
ABDOMEN	
(VISCERAL) KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; KIDNEY MALFORMED, UNASCENDED	
HEAD	
(EXTERNAL) HEAD, MICROCEPHALY - MALFORMATION	
PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE AND MALPOSITIONED	
MOUTH, PALATE, CLEFT PALATE - MALFORMATION	
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL	
Comments:	
SKELETAL CONFIRMATION OF EXTERNAL FINDINGS;	
MICROCEPHALY--SKULL BONES MALFORMED AND/OR FUSED; CLEFT PALATE; SHORT BENT TAIL--DISTAL CAUDAL VERTEBRAE MALFORMED, MALALIGNED AND/OR FUSED.	
Fetal Position: Left 04 *	Unique Fetal Id.: 4
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-5, SLIGHT	

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 583 (CONT.)
 Fetal Position: Left 04 * Unique Fetal Id.: 4 (CONT.)
 VERTEBRAL COLUMN

(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

TAIL

(EXTERNAL) TAIL, ANOMALY - MALFORMATION; SHORT

ABDOMEN

(VISCERAL) KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, SLIGHT

HEAD

(EXTERNAL) HEAD, MICROCEPHALY - MALFORMATION
 PINNA (E), PINNA (E) ANOMALY - MALFORMATION;
 SMALL, MALPOSITIONED, BILATERAL
 MOUTH, PALATE, CLEFT PALATE - MALFORMATION
 FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: MICROCEPHALY--
 SKULL BONES MALFORMED AND/OR FUSED; CLEFT PALATE; SHORT
 TAIL-- SACRAL VERTEBRAE 1-3 MALFORMED, SACRAL VERTEBRAE 4
 AND ALL CAUDAL VERTEBRAE ABSENT

Fetal Position: Left 05 * Unique Fetal Id.: 5

RIBS

(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(SKELETAL) HYOID, ANOMALY - MALFORMATION; BODY AND ARCHES ABSENT

TAIL

(EXTERNAL) TAIL, ANOMALY - MALFORMATION; SHORT, BENT

ABDOMEN

(VISCERAL) KIDNEY(S), HYDRONEPHROSIS - VARIATION; LEFT MODERATE
 URETER(S), DISTENDED - VARIATION; LEFT, SLIGHT
 KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION;
 RIGHT, SMALL AND MALFORMED, UNASCENDED

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 583 (CONT.)
Fetal Position: Left 05* Unique Fetal Id.: 5 (CONT.)

HEAD (EXTERNAL)
HEAD, MICROCEPHALY - MALFORMATION
PINNA (E), PINNA (E) ANOMALY - MALFORMATION;
SMALL, MALPOSITIONED, BILATERAL
MOUTH, MICROSTOMIA - MALFORMATION
JAW, MAXILLAE, MICROGNATHIA - MALFORMATION
JAW, MANDIBLE, MICROGNATHIA - MALFORMATION

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: MICROCEPHALY,
MANDIBULAR MICROGNATHIA, MICROGNATHIA (MAXILLAE), AND
MICROSTOMIA--SKULL BONES MALFORMED AND/OR FUSED; SHORT AND
BENT TAIL--MEDIAL AND DISTAL CAUDAL VERTEBRAE MALALIGNED
AND/OR FUSED

Fetal Position: Right 02 * Unique Fetal Id.: 7
STERNUM (SKELETAL) STERNEBRA (E), MALALIGNED AND FUSED - MALFORMATION; 3-5
MALALIGNED, SLIGHT; 4-5 FUSED

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

TAIL (EXTERNAL) TAIL, ANOMALY - MALFORMATION; SHORT

HEAD (EXTERNAL)
HEAD, MICROCEPHALY - MALFORMATION
PINNA (E), PINNA (E) ANOMALY - MALFORMATION;
SMALL, MALPOSITIONED, BILATERAL
MOUTH, FACIAL BLEB(S) - MALFORMATION; BILATERAL
MOUTH, PALATE, CLEFT PALATE - MALFORMATION

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS:
MICROCEPHALY--SKULL BONES MALFORMED AND FUSED; CLEFT
PALATE; SHORT TAIL--MEDIAL AND CAUDAL VERTEBRAE MALALIGNED
AND/OR FUSED.

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 585
Fetal Position: Left 01 * Unique Fetal Id.: 1
RIBS

(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

TAIL
(EXTERNAL) TAIL, ANOMALY - MALFORMATION; BENT

ABDOMEN
(VISCERAL) GALL BLADDER, VARIATION - VARIATION; SMALL

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: BENT TAIL--
CAUDAL VERTEBRA 10 MALALIGNED

Fetal Position: Left 02 Unique Fetal Id.: 2

THORACIC CAVITY
(VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS
(SKELETAL) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY; RIGHT, FULL
7TH CERVICAL RIB, PRESENT - VARIATION; RIGHT

Fetal Position: Left 03 Unique Fetal Id.: 3
RIBS

(SKELETAL) 7TH CERVICAL RIB, PRESENT - VARIATION; RIGHT

Fetal Position: Left 04 Unique Fetal Id.: 4
RIBS

(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT

VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 585 (CONT.) Unique Fetal Id.: 5
Fetal Position: Right 01

RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 02 Unique Fetal Id.: 6
THORACIC CAVITY (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
7TH CERVICAL RIB, PRESENT - VARIATION; BILATERAL

STERNUM (SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
2-5, SLIGHT

Fetal Position: Right 03 Unique Fetal Id.: 7
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 04 Unique Fetal Id.: 8
SKULL (SKELETAL) HYOID ARCH(ES), UNOSSIFIED - VARIATION; BILATERAL

Animal: 586
Fetal Position: Left 01
LATE RESORPTION: CROWN-RUMP LENGTH: 47 mm

Fetal Position: Left 03
LATE RESORPTION: CROWN-RUMP LENGTH: 23 mm

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 586 (CONT.) Unique Fetal Id.: 4
Fetal Position: Left 04

NECK (EXTERNAL) NECK, BLEB(S) - MALFORMATION; VENTRAL

RIBS (SKELETAL) 7TH CERVICAL RIB, PRESENT - VARIATION; BILATERAL

SKULL (SKELETAL) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED
HYOID, ANOMALY - MALFORMATION; ARCHES MALPOSITIONED OR ABSENT

ABDOMEN (VISCERAL) KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; LEFT
KIDNEY SMALL, MALFORMED, AND UNASCENDED

HEAD (EXTERNAL) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; RIGHT, SMALL
FACE, FACIAL BLEB(S) - MALFORMATION; LEFT

Fetal Position: Right 01 * Unique Fetal Id.: 5
NECK (EXTERNAL) NECK, BLEB(S) - MALFORMATION; VENTRAL

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (SKELETAL) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED
HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES UNOSSIFIED/ABSENT

TAIL (EXTERNAL) TAIL, ANOMALY - MALFORMATION; SHORT AND BENT

HEAD (EXTERNAL) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL AND
MALPOSITIONED
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: SHORT, BENT
TAIL-- CAUDAL VERTEBRAE MALFORMED AND/OR MALALIGNED/FUSED

APPENDIX D

UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 586 (CONT.)

Fetal Position: Right 02 *

Unique Fetal Id.: 6

ANUS

(EXTERNAL) ANUS, ANAL ATRESIA - MALFORMATION

NECK

(EXTERNAL) NECK, BLEB(S) - MALFORMATION; VENTRAL

VERTEBRAL COLUMN

(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(SKELETAL) HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES UNOSSFIFIED/ABSENT

TAIL

(EXTERNAL) TAIL, ANOMALY - MALFORMATION; ABSENT

HEAD

(EXTERNAL) HEAD, MICROCEPHALY - MALFORMATION
 PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL AND MALPOSITIONED
 MOUTH, MACROSTOMIA - MALFORMATION
 MOUTH, PALATE, CLEFT PALATE - MALFORMATION
 FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Comments:

SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: MICROCEPHALY, MACROSTOMIA, CLEFT PALATE--SKULL BONES MALFORMED AND/OR FUSED; TAIL ABSENT--SACRAL VERTEBRAE MALFORMED, CAUDAL VERTEBRAE ABSENT

Fetal Position: Right 03 *

Unique Fetal Id.: 7

NECK

(EXTERNAL) NECK, BLEB(S) - MALFORMATION; VENTRAL

VERTEBRAL COLUMN

(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(SKELETAL) HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, LEFT ARCH UNOSSFIFIED/ABSENT

APPENDIX D

UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 586 (CONT.)
Fetal Position: Right 03 * Unique Fetal Id.: 7 (CONT.)
TAIL (EXTERNAL) TAIL, ANOMALY - MALFORMATION; SHORT AND BENT

ABDOMEN (VISCERAL) URINARY BLADDER, DISTENDED - VARIATION
KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION;
KIDNEYS BILATERAL, MALFORMED, AND UNASCENDED

HEAD (EXTERNAL) HEAD, MICROCEPHALY - MALFORMATION
PINNA (E), PINNA (E) ANOMALY - MALFORMATION; SMALL AND
MALPOSITIONED
MOUTH, MACROSTOMIA - MALFORMATION
MOUTH, PALATE, CLEFT PALATE - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: MICROCEPHALY,
MACROSTOMIA, CLEFT PALATE--SKULL BONES MALFORMED AND/OR
FUSED; SHORT, BENT TAIL--SACRAL AND CAUDAL VERTEBRAE
MALFORMED, MALALIGNED AND/OR FUSED

Fetal Position: Right 04 Unique Fetal Id.: 8
VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE
MALFORMED, MALALIGNED AND/OR FUSED

SKULL (SKELETAL) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED
AND/OR FUSED
HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES
MALPOSITIONED OR UNOSSIFIED/ABSENT

ABDOMEN (VISCERAL) SPLEEN, SMALL IN SIZE - VARIATION

HEAD (EXTERNAL) PINNA (E), PINNA (E) ANOMALY - MALFORMATION; RIGHT, SMALL
FACE, FACIAL BLEB(S) - MALFORMATION

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 587	Unique Fetal Id.: 1
Fetal Position: Left 01	
STERNUM	
(SKELETAL) STERNBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4-5, SLIGHT	
VERTEBRAL COLUMN	
(SKELETAL) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALFORMED AND/OR MALALIGNED	
SKULL	
(SKELETAL) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED	
ABDOMEN	
(VISCERAL) KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; RIGHT KIDNEY AND URETER ABSENT	
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
SKULL	
(SKELETAL) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED	
HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES ABSENT/UNOSSIFIED	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; LEFT	
VERTEBRAL COLUMN	
(SKELETAL) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALFORMED AND/OR MALALIGNED	
SKULL	
(SKELETAL) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED	
HYOID ARCH(ES), BENT - VARIATION; RIGHT, SEVERE	

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 587 (CONT.)

Fetal Position: Left 04

RIBS

Unique Fetal Id.: 4

(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE
MALFORMED

SKULL

(SKELETAL) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED
AND/OR FUSED

HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, RIGHT ARCH
ABSENT/UNOSSIFIED

ABDOMEN

(VISCERAL) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE
SPLEEN, SMALL IN SIZE - VARIATION

HEAD

(EXTERNAL) FACE, FACIAL BLEB(S) - MALFORMATION

Fetal Position: Left 05

Unique Fetal Id.: 5

RIBS

(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 01

Unique Fetal Id.: 6

SKULL

(SKELETAL) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED
AND/OR FUSED

ABDOMEN

(VISCERAL) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE

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UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 587 (CONT.) Unique Fetal Id.: 7
Fetal Position: Right 02
RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT

STERNUM
(SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
2-4, SLIGHT
STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

VERTEBRAL COLUMN
(SKELETAL) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; DISTAL CAUDAL
VERTEBRAE MALALIGNED

SKULL
(SKELETAL) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED
AND/OR FUSED
HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES
MALPOSITIONED

HEAD
(EXTERNAL) FACE, FACIAL BLEB(S) - MALFORMATION

Fetal Position: Right 03 Unique Fetal Id.: 8
RIBS (SKELETAL) RIB 13, FULL - VARIATION; RIGHT, RUDIMENTARY; LEFT, FULL

SKULL
(SKELETAL) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED
AND/OR FUSED, LEFT

APPENDIX D

UIC/TRL STUDY NO. 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 587 (CONT.)

Fetal Position: Right 04
RIBS

Unique Fetal Id.: 9

(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT

VERTEBRAL COLUMN

(SKELETAL) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; DISTAL VERTEBRAE
MALALIGNED

SKULL

(SKELETAL) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED
AND/OR FUSED
HYOID, ANOMALY - MALFORMATION; LEFT ARCH MALPOSITIONED,
RIGHT ARCH ABSENT/UNOSSIFIED

HEAD

(EXTERNAL) FACE, FACIAL BLEB(S) - MALFORMATION

Fetal Position: Right 05
RIBS

Unique Fetal Id.: 10

(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT

VERTEBRAL COLUMN

(SKELETAL) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; DISTAL CAUDAL
VERTEBRAE MALALIGNED

SKULL

(SKELETAL) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED
AND/OR FUSED

ABDOMEN

(VISCERAL) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE

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UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal:	588	Unique Fetal Id.:	1
Fetal Position:	Left 01 *		
THORACIC CAVITY	(VISCERAL)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
SKULL	(SKELETAL)	SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED HYOID, ANOMALY - MALFORMATION; RIGHT ARCH ABSENT/UNOSSIFIED	
TAIL	(EXTERNAL)	TAIL, ANOMALY - MALFORMATION; BENT	
ABDOMEN	(VISCERAL)	GALL BLADDER, VARIATION - VARIATION; SMALL	
HEAD	(EXTERNAL)	FACE, FACIAL BLEB(S) - MALFORMATION; LEFT	
Comments:		SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: BENT TAIL--CAUDAL VERTEBRAE MALFORMED AND MALALIGNED	
Fetal Position:	Left 02 *	Unique Fetal Id.:	2
STERNUM	(SKELETAL)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
SKULL	(SKELETAL)	SKULL, ANOMALY - MALFORMATION; MACROSTOMIA CONFIRMED:SKULL BONES MALFORMED AND/OR FUSED HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED	
TAIL	(EXTERNAL)	TAIL, ANOMALY - MALFORMATION; BENT	
HEAD	(EXTERNAL)	MOUTH, MACROSTOMIA - MALFORMATION FACE, FACIAL BLEB(S) - MALFORMATION; RIGHT	
Comments:		SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: BENT TAIL--DISTAL VERTEBRAE MALALIGNED	

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UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 588 (CONT.)
Fetal Position: Right 01 * Unique Fetal Id.: 3
SKULL (Skel) HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED
TAIL (EXTERNAL) TAIL, ANOMALY - MALFORMATION; BENT
ABDOMEN (VISCERAL) GALL BLADDER, VARIATION - VARIATION; SMALL
Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: BENT TAIL--
MEDIAL VERTEBRAE MALALIGNED
Fetal Position: Right 02 * Unique Fetal Id.: 4
SKULL (Skel) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED
AND/OR FUSED
HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED
TAIL (EXTERNAL) TAIL, ANOMALY - MALFORMATION; BENT
Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: BENT
TAIL--MEDIAL VERTEBRAE MALALIGNED AND MALFORMED
Fetal Position: Right 03 * Unique Fetal Id.: 5
SKULL (Skel) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED
AND/OR FUSED
HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED

APPENDIX D

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 588 (CONT.)
 Fetal Position: Right 04 * Unique Fetal Id.: 6
 THORACIC CAVITY
 (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION;
 ACCESSORY RIGHT SUBCLAVIAN

RIBS (Skel) RIB 13, RUDIMENTARY - VARIATION; RIGHT

SKULL (Skel) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED
 AND/OR FUSED

TAIL (EXTERNAL) TAIL, ANOMALY - MALFORMATION; SHORT, BENT

HEAD (EXTERNAL) MOUTH, MACROSTOMIA - MALFORMATION
 FACE, FACIAL BLEB(S) - MALFORMATION; RIGHT

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: MACROSTOMIA;
 SHORT, BENT TAIL--CAUDAL VERTEBRAE MALFORMED, MALALIGNED
 AND/OR FUSED

Fetal Position: Right 05 * Unique Fetal Id.: 7
 RIBS (Skel) RIB 13, FULL - VARIATION; BILATERAL

STERNUM (Skel) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT

SKULL (Skel) SKULL, ANOMALY - MALFORMATION; SKULL BONE MALFORMED AND/OR FUSED
 HYOID, ANOMALY - MALFORMATION; RIGHT ARCH MALPOSITIONED,
 LEFT ARCH ABSENT/UNOSSIFIED

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: BENT
 TAIL--CAUDAL VERTEBRAE MALALIGNED

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UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal:	589	Unique Fetal Id.:	5
Fetal Position:	Right 01 *		
NECK	(EXTERNAL) NECK, BLEB(S) - MALFORMATION; VENTRAL, BILATERAL		
THORACIC CAVITY	HEART, HEART AND/OR GREAT VESSEL, ANOMALY - MALFORMATION; TRANSPOSITION OF GREAT VESSELS, COARCTATION OF THE AORTIC ARCH		
(VISCERAL)			
RIBS	RIB 13, FULL - VARIATION; BILATERAL		
(Skel)			
VERTEBRAL COLUMN	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
(Skel)			
SKULL	HYOID, ANOMALY - MALFORMATION; BODY MALFORMED; ARCHES UNOSSIFIED/ABSENT		
(Skel)			
TAIL	(EXTERNAL) TAIL, ANOMALY - MALFORMATION; ABSENT		
(EXTERNAL)			
ABDOMEN	(VISCERAL) URETER(S), RETROCAVAL - VARIATION; RIGHT		
(VISCERAL)			
HEAD	(EXTERNAL) HEAD, MICROCEPHALY - MALFORMATION PINNA (E), PINNA (E) ANOMALY - MALFORMATION; SMALL, MALPOSITIONED, BILATERAL MOUTH, MICROSTOMIA - MALFORMATION MOUTH, TONGUE/MANDIBLE ANOMALY - MALFORMATION; TONGUE ATTACHED TO MANDIBLE JAW, MAXILLAE, MICROGNATHIA - MALFORMATION JAW, MANDIBLE, MICROGNATHIA - MALFORMATION FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL		
(EXTERNAL)			
Comments:	SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: MICROCEPHALY, MICROGNATHIA (MAXILLAE), MANDIBULAR MICROGNATHIA AND MICROSTOMIA--SKULL BONES MALFORMED AND/OR FUSED; TAIL ABSENT--PROXIMAL CAUDAL VERTEBRAE MALALIGNED, MALFORMED AND/OR ABSENT		

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UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 589 (CONT.)

Fetal Position: Right 02 *

Unique Fetal Id.: 6

NECK

(EXTERNAL) NECK, BLEB(S) - MALFORMATION; VENTRAL, BILATERAL

THORACIC CAVITY

(VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION;
RETROESOPHAGEAL RIGHT SUBCLAVIAN

RIBS

(Skel) RIB 13, FULL - VARIATION; BILATERAL

STERNUM

(Skel) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
2-5, SLIGHT TO MODERATE

VERTEBRAL COLUMN

(Skel) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; DISTAL VERTEBRAE
MALFORMED AND MALALIGNED

SKULL

(Skel) HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES ABSENT/UNOSSIFIED

ABDOMEN

(VISCERAL) URETER(S), RETROCAVAL - VARIATION; RIGHT
SPLEEN, SMALL IN SIZE - VARIATION

HEAD

(EXTERNAL) HEAD, MICROCEPHALY - MALFORMATION
PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL,
MALPOSITIONED, BILATERAL
MOUTH, MICROSTOMIA - MALFORMATION
MOUTH, PALATE, CLEFT PALATE - MALFORMATION
JAW, MAXILLAE, MICROGNATHIA - MALFORMATION
JAW, MANDIBLE, MICROGNATHIA - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Comments:

SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: MICROCEPHALY,
MICROGNATHIA (MAXILLAE), MANDIBULAR MICROGNATHIA, CLEFT
PALATE AND MICROSTOMIA-- SKULL BONES MALFORMED AND/OR FUSED

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UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 589 (CONT.)

Fetal Position: Right 04 *
NECK

Unique Fetal Id.: 8

(EXTERNAL) NECK, BLEB(S) - MALFORMATION; VENTRAL

RIBS

(Skel) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skel)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE
MALALIGNED AND/OR MALFORMED

SKULL

(Skel)

HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES
ABSENT/UNOSSIFIED

HEAD

(EXTERNAL)

HEAD, MICROCEPHALY - MALFORMATION
PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL AND
MALPOSITIONED, BILATERAL
MOUTH, MICROSTOMIA - MALFORMATION
MOUTH, PALATE, CLEFT PALATE - MALFORMATION
JAW, MAXILLAE, MICROGNATHIA - MALFORMATION
JAW, MANDIBLE, MICROGNATHIA - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Comments:

SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: MICROCEPHALY,
MICROGNATHIA (MAXILLAE), MANDIBULAR MICROGNATHIA,
MICROSTOMIA AND CLEFT PALATE-- SKULL BONES MALFORMED AND/OR
FUSED

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UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal:	590	Unique Fetal Id.:	2
Fetal Position:	Left 02 *		
ANUS	(EXTERNAL) ANUS, ANAL ATRESIA - MALFORMATION		
NECK	(EXTERNAL) NECK, BLEB(S) - MALFORMATION; VENTRAL		
VERTEBRAL COLUMN	(Skel) VERTEBRAE/RIBS, ANOMALY - MALFORMATION; INVOLVING THORACIC VERTEBRAE AND RIBS 7-12 AND LUMBAR VERTEBRAE 1-7 AND SACRAL VERTEBRAE 1-4		
SKULL	(Skel) HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED		
TAIL	(EXTERNAL) TAIL, ANOMALY - MALFORMATION; SHORT, STUBBY		
ABDOMEN	(VISCERAL) KIDNEY(S), HYDRONEPHROSIS - VARIATION; LEFT URINARY BLADDER, DISTENDED - VARIATION; SEVERE URETER(S), DISTENDED - VARIATION; RIGHT KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; RIGHT; SMALL, MALFORMED, AND UNASCENDED		
HEAD	(EXTERNAL) HEAD, MICROCEPHALY - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL AND MALPOSITIONED, BILATERAL JAW, MAXILLAE, MICROGNATHIA - MALFORMATION JAW, MANDIBLE, MICROGNATHIA - MALFORMATION FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL		
Comments:	SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: MICROCEPHALY, MICROGNATHIA (MAXILLAE), MANDIBULAR MICROGNATHIA -- SKULL BONES MALFORMED AND/OR FUSED; SHORT TAIL -- ALL CAUDAL VERTEBRAE ABSENT.		

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UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 590 (CONT.)

Fetal Position: Left 04 *

NECK

Unique Fetal Id.: 4

(VISCERAL) THYMUS, VARIATION - VARIATION; HEMORRHAGIC

RIBS

(Skel) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skel)

VERTEBRAE, ANOMALY - MALFORMATION; INVOLVING LUMBAR
VERTEBRAE 4-7 AND SACRAL VERTEBRAE 1-2.

SKULL

(Skel)

HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES
UNOSSIFIED/ABSENT.

TAIL

(EXTERNAL)

TAIL, ANOMALY - MALFORMATION; SHORT

HEAD

(EXTERNAL)

HEAD, MICROCEPHALY - MALFORMATION
PINNA (E), PINNA (E) ANOMALY - MALFORMATION; SMALL AND
MALPOSITIONED, BILATERAL
JAW, MAXILLAE, MICROGNATHIA - MALFORMATION
JAW, MANDIBLE, MICROGNATHIA - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Comments:

SKELETAL CONFIRMATION OF MICROCEPHALY, MANDIBULAR
MICROGNATHIA, AND MICROGNATHIA (MAXILLAE) -- SKULL BONES
MALFORMED AND/OR FUSED; SHORT TAIL -- CAUDAL VERTEBRAE
MALFORMED, MALALIGNED AND/OR FUSED.

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UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 590 (CONT.)

Fetal Position: Right 02 *

NECK

Unique Fetal Id.: 6

(VISCERAL) THYMUS, VARIATION - VARIATION; HEMORRHAGIC

THORACIC CAVITY

(VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS

(skel) RIB 13, FULL - VARIATION; BILATERAL

STERNUM

(skel) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
3-5, SLIGHT TO MODERATE

VERTEBRAL COLUMN

(skel) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(skel) HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES
ABSENT/UNOSSIFIED

ABDOMEN

(VISCERAL) URETER(S), DISTENDED - VARIATION; RIGHT, SEVERE
SPLEEN, SMALL IN SIZE - VARIATION
KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION;
LEFT, MALFORMED, SMALL, UNASCENDED

HEAD

(EXTERNAL) HEAD, MICROCEPHALY - MALFORMATION
PINNA(E), PINNA(E) ANOMALY - MALFORMATION;
MALPOSITIONED, BILATERAL
MOUTH, PALATE, CLEFT PALATE - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Comments:

SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: MICROCEPHALY AND
CLEFT PALATE -- SKULL BONES MALFORMED AND/OR FUSED; SHORT
TAIL -- CAUDAL VERTEBRAE MALFORMED AND/OR MALALIGNED.

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UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
 INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 591	Unique Fetal Id.: 1
Fetal Position: Left 01	
NECK	(EXTERNAL) NECK, BLEB(S) - MALFORMATION; VENTRAL, LEFT
VERTEBRAL COLUMN	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
(Skel)	
SKULL	SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED.
(Skel)	HYOID, ANOMALY - MALFORMATION; LEFT ARCH ABSENT/UNOSSIFIED
HEAD	
(EXTERNAL)	PINNA (E), PINNA (E) ANOMALY - MALFORMATION; SMALL, BILATERAL
	FACE, FACIAL BLEB(S) - MALFORMATION; LEFT
Fetal Position: Left 02	Unique Fetal Id.: 2
SKULL	
(Skel)	SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED; CONFIRMATION OF MICROGNATHIA (MAXILLAE) AND MACROSTOMIA.
	HYOID, ANOMALY - MALFORMATION; ARCHES MALFORMED AND MALPOSITIONED
HEAD	
(EXTERNAL)	MOUTH, MACROSTOMIA - MALFORMATION
	JAW, MAXILLAE, MICROGNATHIA - MALFORMATION
	FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

APPENDIX D

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 591 (CONT.)	Unique Fetal Id.: 3
Fetal Position: Left 03	
NECK	(EXTERNAL) NECK, BLEB(S) - MALFORMATION; VENTRAL, BILATERAL
STERNUM	
(skel)	STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3-5, SLIGHT
SKULL	
(skel)	SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED; CONFIRMING MICROGNATHIA (MAXILLAE) AND MANDIBULAR MICROGNATHIA.
	HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED.
ABDOMEN	
(VISCERAL)	GALL BLADDER, VARIATION - VARIATION; SMALL
HEAD	
(EXTERNAL)	PINNA (E), PINNA (E) ANOMALY - MALFORMATION; SMALL, MALPOSITIONED, BILATERAL
	JAW, MAXILLAE, MICROGNATHIA - MALFORMATION
	JAW, MANDIBLE, MICROGNATHIA - MALFORMATION
	FACE, FACIAL BLEB(S) - MALFORMATION; LEFT
Fetal Position: Right 01 *	Unique Fetal Id.: 4
NECK	(EXTERNAL) NECK, BLEB(S) - MALFORMATION; VENTRAL, BILATERAL
THORACIC CAVITY	
(VISCERAL)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK
STERNUM	
(skel)	STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2, SLIGHT
VERTEBRAL COLUMN	
(skel)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
	VERTEBRAE, ANOMALY - MALFORMATION; INVOLVING LUMBAR
	VERTEBRAE 8 AND ALL SACRAL AND CAUDAL VERTEBRAE (PROXIMAL AND MEDIAL).

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UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 591 (CONT.) Unique Fetal Id.: 4 (CONT.)
 Fetal Position: Right 01

SKULL (skel) HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED, BODY MALFORMED.

ABDOMEN (VISCERAL) GALL BLADDER, VARIATION - VARIATION; SMALL

HEAD (EXTERNAL) HEAD, MICROCEPHALY - MALFORMATION MOUTH, MICROSTOMIA - MALFORMATION; VERY JAW, MAXILLAE, MICROGNATHIA - MALFORMATION JAW, MANDIBLE, MICROGNATHIA - MALFORMATION

Comments: SKELETAL CONFIRMATION OF MICROSTOMIA, MICROCEPHALY, MICROGNATHIA (MAXILLAE), AND MANDIBULAR MICROGNATHIA--SKULL BONES MALFORMED AND/OR FUSED.

Fetal Position: Right 03 Unique Fetal Id.: 6
 NECK (EXTERNAL) NECK, BLEB(S) - MALFORMATION; VENTRAL, BILATERAL

THORACIC CAVITY (VISCERAL) HEART, HEART AND/OR GREAT VESSEL, ANOMALY - MALFORMATION; BULBOUS AORTIC ARCH

VERTEBRAL COLUMN (skel) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (skel) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED, CONFIRMING MICROGNATHIA (MAXILLAE) AND MANDIBULAR MICROGNATHIA. HYOID, ANOMALY - MALFORMATION; BODY MALFORMED ARCHES ABSENT/UNOSSIFIED

ABDOMEN (VISCERAL) URETER(S), DISTENDED - VARIATION; LEFT, SLIGHT KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; RIGHT KIDNEY ABSENT, RIGHT URETER ABSENT

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UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 591 (CONT.)
 Fetal Position: Right 03 Unique Fetal Id.: 6 (CONT.)
 HEAD
 (EXTERNAL) PINNA (E), PINNA (E) ANOMALY - MALFORMATION; SMALL AND MALPOSITIONED, BILATERAL
 JAW, MAXILLAE, MICROGNATHIA - MALFORMATION
 JAW, MANDIBLE, MICROGNATHIA - MALFORMATION
 FACE, FACIAL BLEB (S) - MALFORMATION; BILATERAL

Fetal Position: Right 04 * Unique Fetal Id.: 7
 NECK
 (EXTERNAL) NECK, BLEB (S) - MALFORMATION; VENTRAL, BILATERAL

SKULL
 (Skel)
 HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES UNOSSIFIED/ABSENT.

HEAD
 (EXTERNAL) HEAD, MICROCEPHALY - MALFORMATION
 PINNA (E), PINNA (E) ANOMALY - MALFORMATION; SMALL AND MALPOSITIONED, BILATERAL
 JAW, MAXILLAE, MICROGNATHIA - MALFORMATION
 JAW, MANDIBLE, MICROGNATHIA - MALFORMATION
 FACE, FACIAL BLEB (S) - MALFORMATION; BILATERAL

Comments:
 SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: MICROCEPHALY, MICROGNATHIA (MAXILLAE), MANDIBULAR MICROGNATHIA -- SKULL BONES MALFORMED AND/OR FUSED.

Fetal Position: Right 05 * Unique Fetal Id.: 8
 SKULL
 (Skel)
 SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED; CONFIRMING MICROGNATHIA (MAXILLAE), MANDIBULAR MICROGNATHIA, AND MACROSTOMIA
 HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES MALFORMED OR MALPOSITIONED

TAIL
 (EXTERNAL) TAIL, ANOMALY - MALFORMATION; SHORT, KINKY

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UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 591 (CONT.)

Fetal Position: Right 05 Unique Fetal Id.: 8 (CONT.)
ABDOMEN
(VISCERAL) GALL BLADDER, VARIATION - VARIATION; SMALL

HEAD

(EXTERNAL) PINNA (E), PINNA (E) ANOMALY - MALFORMATION; SMALL AND
MALPOSITIONED, BILATERAL
MOUTH, MACROSTOMIA - MALFORMATION
JAW, MAXILLAE, MICROGNATHIA - MALFORMATION
JAW, MANDIBLE, MICROGNATHIA - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Comments:

SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: SHORT
TAIL--PROXIMAL VERTEBRAE MALFORMED AND MALALIGNED.

Fetal Position: Right 06 Unique Fetal Id.: 9

SKULL

(Skel) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED
AND/OR FUSED; CONFIRMING MICROGNATHIA (MAXILLAE) AND
MACROSTOMIA.
HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES
MALPOSITIONED, ABSENT/UNOSSIFIED

ABDOMEN

(VISCERAL) GALL BLADDER, VARIATION - VARIATION; SMALL

HEAD

(EXTERNAL) PINNA (E), PINNA (E) ANOMALY - MALFORMATION; SMALL
MOUTH, MACROSTOMIA - MALFORMATION
JAW, MAXILLAE, MICROGNATHIA - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

APPENDIX D

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 592
Fetal Position: Left 01 * Unique Fetal Id.: 1

NECK (EXTERNAL) NECK, BLEB(S) - MALFORMATION; VENTRAL, BILATERAL

RIBS (Skel) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

STERNUM (Skel) STERNEBRA(E), FUSED - MALFORMATION; 3-5

VERTEBRAL COLUMN (Skel) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skel) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED
HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES UNOSSIFIED/ABSENT

ABDOMEN (VISCERAL) KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; LEFT KIDNEY; SMALL AND UNASCENDED

HEAD (EXTERNAL) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL AND MALPOSITIONED, BILATERAL

APPENDIX D

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 592 (CONT.)	Unique Fetal Id.: 2
Fetal Position: Left 02 *	
ANUS	(EXTERNAL) ANUS, ANAL ATRESIA - MALFORMATION
STERNUM	
(Skel)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT
SKULL	
(Skel)	SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED
TAIL	
(EXTERNAL)	TAIL, ANOMALY - MALFORMATION; SHORT, RUDIMENTARY
ABDOMEN	
(VISCERAL)	KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; KIDNEY BILATERAL; UNASCENDED AND MALFORMED
HEAD	
(EXTERNAL)	PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL AND MALPOSITIONED, BILATERAL FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL
Comments:	SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: SHORT TAIL--CAUDAL VERTEBRAE 3 AND REMAINING VERTEBRAE ABSENT
Fetal Position:	Left 03
RIBS	
(Skel)	RIB 13, FULL - VARIATION; BILATERAL
SKULL	
(Skel)	SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED; MICROGNATHIA (MAXILLAE) AND MICROSTOMIA CONFIRMED HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED

APPENDIX D

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 592 (CONT.) Unique Fetal Id.: 3 (CONT.)
Fetal Position: Left 03
HEAD (EXTERNAL) PINNA (E), PINNA (E) ANOMALY - MALFORMATION; SMALL AND MALPOSITIONED, BILATERAL MOUTH, MICROSTOMIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL
Fetal Position: Left 04 * Unique Fetal Id.: 4
STERNUM (Skel) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT
VERTEBRAL COLUMN (Skel) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
SKULL (Skel) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED, LEFT HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED
TAIL (EXTERNAL) TAIL, ANOMALY - MALFORMATION; SHORT, SLIGHT
ABDOMEN (VISCERAL) KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; RIGHT KIDNEY UNASCENDED; LEFT KIDNEY SMALL, MALFORMED, AND UNASCENDED
HEAD (EXTERNAL) PINNA (E), PINNA (E) ANOMALY - MALFORMATION; SMALL, BILATERAL
Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: SHORT TAIL--CAUDAL VERTEBRAE MALFORMED AND/OR MALALIGNED

APPENDIX D

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 592 (CONT.)

Fetal Position: Right 01 *
ANUS

Unique Fetal Id.: 5

(EXTERNAL) ANAL OPENING, SMALL IN SIZE - MALFORMATION

RIBS (Skel) RIB 13, FULL - VARIATION; BILATERAL

SKULL (Skel) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED
HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES UNOSSIFIED/ABSENT

TAIL (EXTERNAL) TAIL, ANOMALY - MALFORMATION; ABSENT

HEAD (EXTERNAL) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL, BILATERAL

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: TAIL ABSENT--SACRAL VERTEBRAE MALFORMED; CAUDAL VERTEBRAE ABSENT

VISCERAL OBSERVATIONS NOT RECORDED

Fetal Position: Right 03
NECK Unique Fetal Id.: 7

(EXTERNAL) NECK, BLEB(S) - MALFORMATION; VENTRAL

RIBS (Skel) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN (Skel) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skel) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED; MACROSTOMIA, MICROGNATHIA (MAXILLAE), MANDIBULAR MICROGNATHIA CONFIRMED
HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED

APPENDIX D

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 592 (CONT.)
Fetal Position: Right 03 Unique Fetal Id.: 7 (CONT.)
ABDOMEN
(VISCERAL) URETER(S), RETROCAVAL - VARIATION; RIGHT SIDE

HEAD
(EXTERNAL) PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL AND MALPOSITIONED
MOUTH, MACROSTOMIA - MALFORMATION
JAW, MAXILLAE, MICROGNATHIA - MALFORMATION
JAW, MANDIBLE, MICROGNATHIA - MALFORMATION
FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL

Fetal Position: Right 04 * Unique Fetal Id.: 8
ANUS
(EXTERNAL) ANUS, ANAL ATRESIA - MALFORMATION; HEMATOCYST (.3mm) ATTACHED TO ANAL

RIBS
(Skel) RIB 13, FULL - VARIATION; BILATERAL

STERNUM
(Skel) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
4 AND 5, SLIGHT TO MODERATE

VERTEBRAL COLUMN
(Skel) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL
(Skel) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED
AND/OR FUSED
HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED

TAIL
(EXTERNAL) TAIL, ANOMALY - MALFORMATION; ABSENT

ABDOMEN
(VISCERAL) KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION;
UNASCENDED, MALFORMED, AND SMALL IN SIZE; RIGHT

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UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 592 (CONT.)
 Fetal Position: Right 04 Unique Fetal Id.: 8 (CONT.)
 HEAD (EXTERNAL) PINNA (E), PINNA (E) ANOMALY - MALFORMATION; SMALL

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: TAIL ABSENT--SACRAL VERTEBRAE MALFORMED AND FUSED, CAUDAL VERTEBRAE ABSENT

Animal: 594
 Fetal Position: Right 03 * Unique Fetal Id.: 4
 RIBS (Skel) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

STERNUM (Skel) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT

VERTEBRAL COLUMN (Skel) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (Skel) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND/OR FUSED; MACROSTOMIA CONFIRMED HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES ABSENT/UNOSSIFIED

TAIL (EXTERNAL) TAIL, ANOMALY - MALFORMATION; BENT

ABDOMEN (VISCERAL) KIDNEY (S) AND/OR URETER (S), ANOMALY - MALFORMATION; RIGHT KIDNEY; ENLARGED, MALFORMED, AND UNASCENDED. LEFT KIDNEY SMALL, MALFORMED, AND UNASCENDED.

HEAD (EXTERNAL) PINNA (E), PINNA (E) ANOMALY - MALFORMATION; BILATERAL; SMALL AND MALPOSITIONED MOUTH, MACROSTOMIA - MALFORMATION FACE, FACIAL BLEB (S) - MALFORMATION; BILATERAL

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: BENT TAIL--MEDIAL CAUDAL VERTEBRAE MALFORMED AND MALALIGNED

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UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 594 (CONT.)	Unique Fetal Id.: 6
Fetal Position: Right 05 *	
NECK	(EXTERNAL) NECK, BLEB(S) - MALFORMATION; VENTRAL
VERTEBRAL COLUMN	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
(Skel)	CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; DISTAL VERTEBRAE MALALIGNED
SKULL	HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES MALPOSITIONED, ABSENT/UNOSSIFIED
(Skel)	
ABDOMEN	GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE
(VISCERAL)	KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; LEFT KIDNEY VERY SMALL IN SIZE
HEAD	HEAD, MICROCEPHALY - MALFORMATION
(EXTERNAL)	PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL; SMALL AND MALPOSITIONED, BILATERAL
	MOUTH, PALATE, CLEFT PALATE - MALFORMATION
	FACE, FACIAL BLEB(S) - MALFORMATION; BILATERAL
Comments:	SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: MICROCEPHALY AND CLEFT PALATE--SKULL BONES MALFORMED AND FUSED
Animal: 595	Unique Fetal Id.: 1
Fetal Position: Left 01	
THORACIC CAVITY	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION;
(VISCERAL)	ACCESSORY LEFT SUBCLAVIAN
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	RIB 13, FULL - VARIATION; BILATERAL
(Skel)	
SKULL	HYOID ARCH(ES), BENT - VARIATION; LEFT, MODERATE
(Skel)	

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UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 595 (CONT.)	Unique Fetal Id.: 3
Fetal Position: Left 03	
RIBS	
(Skel) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM	
(Skel) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY	
VERTEBRAL COLUMN	
(Skel) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 01	Unique Fetal Id.: 4
RIBS	
(Skel) RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skel) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; MEDIAL VERTEBRAE MALALIGNED	
SKULL	
(Skel) HYOID, ANOMALY - MALFORMATION; ARCHES MALPOSITIONED	
Fetal Position: Right 02	Unique Fetal Id.: 5
VERTEBRAL COLUMN	
(Skel) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 03	Unique Fetal Id.: 6
RIBS	
(Skel) RIB 13, RUDIMENTARY - VARIATION; RIGHT	
STERNUM	
(Skel) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY	
Fetal Position: Right 04	Unique Fetal Id.: 7
RIBS	
(Skel) RIB 13, RUDIMENTARY - VARIATION; LEFT, WITH NO ARTICULATING HEAD	
ABDOMEN	
(VISCERAL) URETER(S), RETROCAVAL - VARIATION; RIGHT SIDE	

APPENDIX D

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 597
 Fetal Position: Left 01 Unique Fetal Id.: 1
 THORACIC CAVITY
 (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION;
 ACCESSORY LEFT SUBCLAVIAN

ABDOMEN
 (VISCERAL) SPLEEN, SMALL IN SIZE - VARIATION

Fetal Position: Left 02 * Unique Fetal Id.: 2
 RIBS (Skel) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (Skel) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

TAIL
 (EXTERNAL) TAIL, ANOMALY - MALFORMATION; SHORT

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: SHORT
 TAIL--DISTAL VERTEBRAE MALALIGNED

Fetal Position: Right 01 Unique Fetal Id.: 4
 RIBS (Skel) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (Skel) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 02 Unique Fetal Id.: 5
 RIBS (Skel) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (Skel) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
 CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; DISTAL VERTEBRAE
 MALALIGNED

SKULL (Skel) HYOID ARCH(ES), BENT - VARIATION; LEFT, SLIGHT

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UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 597 (CONT.)	Unique Fetal Id.: 6
Fetal Position: Right 03	
THORACIC CAVITY (VISCERAL)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK
RIBS (Skel)	RIB 13, FULL - VARIATION; BILATERAL
STERNUM (Skel)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT
VERTEBRAL COLUMN (Skel)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; DISTAL VERTEBRAE MALALIGNED
Fetal Position: Right 04	Unique Fetal Id.: 7
RIBS (Skel)	RIB 13, FULL - VARIATION; LEFT
Animal: 598	Unique Fetal Id.: 1
Fetal Position: Left 01	
THORACIC CAVITY (VISCERAL)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; ACCESSORY LEFT SUBCLAVIAN
RIBS (Skel)	RIB 13, FULL - VARIATION; BILATERAL; RIGHT WITH NO ARTICULATING HEAD
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS (Skel)	RIB 13, FULL - VARIATION; BILATERAL
STERNUM (Skel)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
VERTEBRAL COLUMN (Skel)	CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; DISTAL CAUDAL VERTEBRAE MALALIGNED

APPENDIX D

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 598 (CONT.)	Unique Fetal Id.: 3
Fetal Position: Left 03	
RIBS	
(Skel) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skel) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; DISTAL VERTEBRAE MALALIGNED	
Fetal Position: Right 01	Unique Fetal Id.: 4
RIBS	
(Skel) RIB 13, RUDIMENTARY - VARIATION; LEFT, WITH NO ARTICULATING HEAD	
VERTEBRAL COLUMN	
(Skel) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; DISTAL VERTEBRAE MALALIGNED AND FUSED	
Fetal Position: Right 02	Unique Fetal Id.: 5
VERTEBRAL COLUMN	
(Skel) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; DISTAL VERTEBRAE MALFORMED AND MALALIGNED	
Fetal Position: Right 03	Unique Fetal Id.: 6
RIBS	
(Skel) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(Skel) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; DISTAL VERTEBRAE MALALIGNED	
Fetal Position: Right 05	Unique Fetal Id.: 8
VERTEBRAL COLUMN	
(Skel) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; DISTAL VERTEBRAE MALALIGNED	
Fetal Position: Right 06	Unique Fetal Id.: 9
RIBS	
(Skel) RIB 13, FULL - VARIATION; BILATERAL	

APPENDIX D

UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 598 (CONT.)
 Fetal Position: Right 07 * Unique Fetal Id.: 10
 TAIL (EXTERNAL) TAIL, ANOMALY - MALFORMATION; BENT

Comments: SKELETAL CONFIRMATION OF EXTERNAL FINDINGS: BENT
 TAIL--DISTAL CAUDAL VERTEBRAE MALALIGNED

Animal: 599
 Fetal Position: Right 01 Unique Fetal Id.: 1
 RIBS (Skel) RIB 13, RUDIMENTARY - VARIATION; LEFT
 7TH CERVICAL RIB, PRESENT - VARIATION; LEFT

VERTEBRAL COLUMN
 (Skel) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; DISTAL VERTEBRAE
 MALALIGNED

Fetal Position: Right 02 Unique Fetal Id.: 2
 VERTEBRAL COLUMN
 (Skel) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; DISTAL VERTEBRAE
 FUSED

Fetal Position: Right 03 Unique Fetal Id.: 3
 STERNUM (Skel) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY

VERTEBRAL COLUMN
 (Skel) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; DISTAL VERTEBRAE
 FUSED

Fetal Position: Right 04 Unique Fetal Id.: 4
 STERNUM (Skel) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
 4 AND 5 SLIGHT

SKULL (Skel) SKULL, ANOMALY - MALFORMATION; SKULL BONES FUSED

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UIC/TRL STUDY NO.: 156 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 5: 300 MG/KG/DAY (RETINOL PALMITATE)

Animal: 600
Fetal Position: Right 01 Unique Fetal Id.: 1
RIBS (Skel) RIB 13, FULL - VARIATION; RIGHT, RUDIMENTARY; LEFT, FULL

SKULL (Skel) HYOID ARCH(ES), BENT - VARIATION; BILATERAL, SLIGHT

Fetal Position: Right 02 Unique Fetal Id.: 2
RIBS (Skel) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

Fetal Position: Right 03 Unique Fetal Id.: 3
RIBS (Skel) RIB 13, FULL - VARIATION; RIGHT, RUDIMENTARY; LEFT, FULL

VERTEBRAL COLUMN (Skel) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

APPENDIX DD

UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 602 Unique Fetal Id.: 1
 Fetal Position: Left 01
 STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5

ABDOMEN (VISCERAL) KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, MODERATE.

Fetal Position: Left 02 Unique Fetal Id.: 2
 ABDOMEN (VISCERAL) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE.

Fetal Position: Left 03 Unique Fetal Id.: 3
 RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT (NO ARTICULATING HEAD).

ABDOMEN (VISCERAL) SPLEEN, SMALL IN SIZE - VARIATION

Fetal Position: Left 05 Unique Fetal Id.: 5
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL

SKULL (SKELETAL) HYOID ARCH(ES), BENT - VARIATION; RIGHT, SLIGHT

Fetal Position: Right 01 Unique Fetal Id.: 6
 RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL (LEFT NO ARTICULATING HEAD)

Fetal Position: Right 02 * Unique Fetal Id.: 7
 THORACIC CAVITY (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK.

RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

ABDOMEN (VISCERAL) SPLEEN, SMALL IN SIZE - VARIATION

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 602 (CONT.)
Fetal Position: Right 03 Unique Fetal Id.: 8
THORACIC CAVITY
(VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK.

Fetal Position: Right 04 Unique Fetal Id.: 9
RIBS
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL (NO ARTICULATING HEAD)

STERNUM
(SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5

Fetal Position: Right 05
LATE RESORPTION: CROWN-RUMP LENGTH: 21 mm

Fetal Position: Right 06 Unique Fetal Id.: 11
THORACIC CAVITY
(VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK.

STERNUM
(SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5

ABDOMEN
(VISCERAL) SPLEEN, SMALL IN SIZE - VARIATION

Fetal Position: Right 07
LATE RESORPTION: CROWN-RUMP LENGTH: 20 mm

Animal: 603
Fetal Position: Left 01 Unique Fetal Id.: 1
RIBS
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

STERNUM
(SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
4, SLIGHT

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 603 (CONT.)
Fetal Position: Left 03 Unique Fetal Id.: 3
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

ABDOMEN
(VISCERAL) KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, MODERATE.

Fetal Position: Right 01 Unique Fetal Id.: 4
RIBS (SKELETAL) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY

Fetal Position: Right 02 Unique Fetal Id.: 5
RIBS (SKELETAL) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL

Fetal Position: Right 04 * Unique Fetal Id.: 7
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

STERNUM
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

Animal: 604
Fetal Position: Left 01 Unique Fetal Id.: 1
THORACIC CAVITY
(VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK.

Fetal Position: Left 03 Unique Fetal Id.: 3
STERNUM
(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
4 AND 5, SLIGHT

APPENDIX DD

UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 604 (CONT.) Unique Fetal Id.: 4
Fetal Position: Right 01
THORACIC CAVITY (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK.

RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT
Fetal Position: Right 02 Unique Fetal Id.: 5
RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT

STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5
Fetal Position: Right 03 Unique Fetal Id.: 6
RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

Fetal Position: Right 04 Unique Fetal Id.: 7
RIBS (SKELETAL) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY (NO ARTICULATING HEAD)

Fetal Position: Right 05 Unique Fetal Id.: 8
RIBS (SKELETAL) RIB 12, RUDIMENTARY - VARIATION; RIGHT

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 25 PRESACRAL VERTEBRAE - VARIATION
Animal: 605 Unique Fetal Id.: 1
Fetal Position: Left 01
RIBS (SKELETAL) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL

STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 605 (CONT.)
 Fetal Position: Left 02 Unique Fetal Id.: 2
 STERNUM
 (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5

Fetal Position: Left 03 Unique Fetal Id.: 3
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Left 04 Unique Fetal Id.: 4
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL

STERNUM
 (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 03 Unique Fetal Id.: 7
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY

STERNUM
 (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5

Fetal Position: Right 04 Unique Fetal Id.: 8
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY

Animal: 606
 Fetal Position: Left 02 Unique Fetal Id.: 2
 STERNUM
 (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6

Fetal Position: Left 04 Unique Fetal Id.: 4
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 606 (CONT.)		Unique Fetal Id.: 5
Fetal Position: Right 01		
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT	
STERNUM	(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6	
Fetal Position: Right 02		Unique Fetal Id.: 6
STERNUM	(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6	
Fetal Position: Right 03		Unique Fetal Id.: 7
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
STERNUM	(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6	
Animal: 607		Unique Fetal Id.: 2
Fetal Position: Left 02		
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY	
STERNUM	(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6	
Animal: 608		Unique Fetal Id.: 1
Fetal Position: Left 01		
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY; RIGHT, FULL	
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT	
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT, WITH NO ARTICULATING HEAD	

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 608 (CONT.) Unique Fetal Id.: 4
Fetal Position: Right 01
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 02 Unique Fetal Id.: 5
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 03 Unique Fetal Id.: 6
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 04 Unique Fetal Id.: 7
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Animal: 609 Unique Fetal Id.: 1
Fetal Position: Left 01
RIBS (SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT RUDIMENTARY

VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 03 Unique Fetal Id.: 3
RIBS (SKELETAL) RIB 13, FULL - VARIATION; LEFT

VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 609 (CONT.)
 Fetal Position: Right 01 Unique Fetal Id.: 4
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 03 Unique Fetal Id.: 6
 STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 AND 6

Fetal Position: Right 04 Unique Fetal Id.: 7
 VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (SKELETAL) HYOID ARCH(ES), BENT - VARIATION; LEFT, SLIGHT; RIGHT, MODERATE

Fetal Position: Right 05
 LATE RESORPTION: CROWN-RUMP LENGTH: 27 mm

Fetal Position: Right 06
 LATE RESORPTION: CROWN-RUMP LENGTH: 50 mm

Fetal Position: Right 07 Unique Fetal Id.: 10
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

HINDLIMBS (SKELETAL) TALUS, UNOSSIFIED - VARIATION; BILATERAL

ABDOMEN (VISCERAL) KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, MODERATE.

Fetal Position: Right 08 Unique Fetal Id.: 11
 STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 AND 6

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 610			
Fetal Position:	Left 02	Unique Fetal Id.:	2
RIBS			
	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL		
Fetal Position:	Left 03	Unique Fetal Id.:	3
RIBS			
	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL		
Fetal Position:	Right 02	Unique Fetal Id.:	5
RIBS			
	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL		
Fetal Position:	Right 03	Unique Fetal Id.:	6
VERTEBRAL COLUMN			
	(SKELETAL) VERTEBRAE/RIBS, ANOMALY - MALFORMATION; INVOLVING THORACIC VERTEBRAE AND RIBS 9-12; 13TH RUDIMENTARY RIB, RIGHT		
Animal: 611			
Fetal Position:	Left 02	Unique Fetal Id.:	2
RIBS			
	(SKELETAL) RIB 13, FULL - VARIATION; LEFT		
VERTEBRAL COLUMN			
	(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position:	Left 05	Unique Fetal Id.:	5
RIBS			
	(SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY		
VERTEBRAL COLUMN			
	(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION		
Fetal Position:	Left 06	Unique Fetal Id.:	6
RIBS			
	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL, WITH NO ARTICULATING HEAD, BILATERAL		

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 611 (CONT.)	Unique Fetal Id.: 7
Fetal Position: Left 07	
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN	(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
Fetal Position: Right 01	Unique Fetal Id.: 8
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
Fetal Position: Right 02	Unique Fetal Id.: 9
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT, WITH NO ARTICULATING HEAD
Fetal Position: Right 03	Unique Fetal Id.: 10
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
Fetal Position: Right 04	Unique Fetal Id.: 11
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
STERNUM	(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 AND 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY
VERTEBRAL COLUMN	(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
Fetal Position: Right 05	Unique Fetal Id.: 12
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN	(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 611 (CONT.) Unique Fetal Id.: 13
Fetal Position: Right 06
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 07 Unique Fetal Id.: 14
RIBS (SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY
WITH NO ARTICULATING HEAD

STERNUM
(SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY

VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Animal: 612 Unique Fetal Id.: 1
Fetal Position: Left 01
RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

STERNUM
(SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
4, SLIGHT

Fetal Position: Right 02 Unique Fetal Id.: 3
RIBS (SKELETAL) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY; RIGHT, FULL

Fetal Position: Right 04 Unique Fetal Id.: 5
SKULL (SKELETAL) HYOID ARCH (ES), BENT - VARIATION; RIGHT, SLIGHT

Fetal Position: Right 05 Unique Fetal Id.: 6
VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE/RIBS, ANOMALY - MALFORMATION; INVOLVING THORACIC
VERTEBRAE AND RIBS 10-13; 13TH FULL RIB, RIGHT; 27
PRESACRAL VERTEBRAE

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 613 Unique Fetal Id.: 1
Fetal Position: Left 01
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 02 Unique Fetal Id.: 2
THORACIC CAVITY (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT

STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

SKULL (SKELETAL) HYOID BODY, UNOSSIFIED - VARIATION

Fetal Position: Left 03 Unique Fetal Id.: 3
THORACIC CAVITY (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK.

RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 613 (CONT.)
Fetal Position: Right 01 Unique Fetal Id.: 4
RIBS (SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT RUDIMENTARY

VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 02 Unique Fetal Id.: 5
THORACIC CAVITY HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
(VISCERAL) CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK.

RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 03 Unique Fetal Id.: 6
THORACIC CAVITY HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
(VISCERAL) CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK.

RIBS (SKELETAL) RIB 13, FULL - VARIATION; LEFT

STERNUM (SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

VERTEBRAL COLUMN
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Animal: 614
Fetal Position: Left 01 Unique Fetal Id.: 1
RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

Fetal Position: Left 02 Unique Fetal Id.: 2
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 615 (CONT.) Unique Fetal Id.: 3
Fetal Position: Left 03
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
Fetal Position: Left 04 Unique Fetal Id.: 4
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
STERNUM (SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT TO MODERATE
VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
Fetal Position: Right 02 Unique Fetal Id.: 6
STERNUM (SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4, SLIGHT
STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 AND 6
Fetal Position: Right 03 Unique Fetal Id.: 7
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
STERNUM (SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5 AND 6
VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
Fetal Position: Right 04 Unique Fetal Id.: 8
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
STERNUM (SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 616			
Fetal Position: Left 02		Unique Fetal Id.: 2	
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; RIGHT		
Fetal Position: Left 03		Unique Fetal Id.: 3	
THORACIC CAVITY	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK.		
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL		
Fetal Position: Left 04		Unique Fetal Id.: 4	
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT		
Fetal Position: Left 05		Unique Fetal Id.: 5	
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL		
ABDOMEN	(VISCERAL) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE.		
Fetal Position: Right 01		Unique Fetal Id.: 6	
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL		
ABDOMEN	(VISCERAL) GALL BLADDER, VARIATION - VARIATION; ABSENT		
Fetal Position: Right 02		Unique Fetal Id.: 7	
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL		
Fetal Position: Right 03		Unique Fetal Id.: 8	
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT		
STERNUM	(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4 AND 5, SLIGHT		

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 616 (CONT.)
 Fetal Position: Right 04 Unique Fetal Id.: 9
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 05 Unique Fetal Id.: 10
 RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT

STERNUM
 (SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
 2-4, SLIGHT

Fetal Position: Right 06 Unique Fetal Id.: 11
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Animal: 617
 Fetal Position: Left 01 Unique Fetal Id.: 1
 STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY

Fetal Position: Left 03 Unique Fetal Id.: 3
 STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY

Fetal Position: Left 04 Unique Fetal Id.: 4
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

STERNUM
 (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

ABDOMEN
 (VISCERAL) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE.

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 617 (CONT.) Unique Fetal Id.: 5
Fetal Position: Left 05
RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL, WITH NO ARTICULATING HEADS

ABDOMEN (VISCERAL) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE.

Fetal Position: Left 06
LATE RESORPTION: CROWN-RUMP LENGTH: 80 MM

Fetal Position: Left 07 Unique Fetal Id.: 7
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

ABDOMEN (VISCERAL) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE.

Fetal Position: Right 01 Unique Fetal Id.: 8
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 03 Unique Fetal Id.: 10
THORACIC CAVITY (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK.

RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL
STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY

Animal: 618 Unique Fetal Id.: 1
Fetal Position: Left 01
RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 618 (CONT)
 Fetal Position: Left 02 Unique Fetal Id.: 2
 RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT, WITH NO
 ARTICULATING HEAD

Fetal Position: Left 04 Unique Fetal Id.: 4
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 05 Unique Fetal Id.: 5
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 02 Unique Fetal Id.: 7
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 03 Unique Fetal Id.: 8
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 04
 LATE RESORPTION: CROWN-RUMP LENGTH: 65 mm

Fetal Position: Right 05 Unique Fetal Id.: 10
 RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

Fetal Position: Right 06 Unique Fetal Id.: 11
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY

ABDOMEN
 (VISCERAL) SPLEEN, SMALL IN SIZE - VARIATION

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 618 (CONT.)
 Fetal Position: Right 07 Unique Fetal Id.: 12
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

ABDOMEN
 (VISCERAL) SPLEEN, SMALL IN SIZE - VARIATION

Animal: 619
 Fetal Position: Left 02 Unique Fetal Id.: 2
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Left 03 Unique Fetal Id.: 3
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 04 Unique Fetal Id.: 4
 EYES
 (VISCERAL) AROUND IRIS, HEMORRHAGIC RING - VARIATION; LEFT

Fetal Position: Left 06 Unique Fetal Id.: 6
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN
 (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 01 Unique Fetal Id.: 7
 RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

Fetal Position: Right 03 Unique Fetal Id.: 9
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; RIGHT

EYES
 (VISCERAL) EYE(S), IRIS BOMBE' - MALFORMATION; LEFT

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

Animal: 619 (CONT.)
Fetal Position: Right 04 Unique Fetal Id.: 10
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 05
LATE RESORPTION: CROWN-RUMP LENGTH: 34 mm

Animal: 620
Fetal Position: Left 03 Unique Fetal Id.: 3
THORACIC CAVITY (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

Fetal Position: Right 01 Unique Fetal Id.: 4
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 25/16 MG BASE/KG/DAY

Animal: 621		Unique Fetal Id.: 1
Fetal Position: Left 01		
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN		
	(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT RUDIMENTARY	
Fetal Position: Left 04		Unique Fetal Id.: 4
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Left 05		Unique Fetal Id.: 5
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT, WITH NO ARTICULATING HEAD	
Fetal Position: Right 01		Unique Fetal Id.: 6
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 02		Unique Fetal Id.: 7
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 03		Unique Fetal Id.: 8
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; LEFT	
STERNUM		
	(SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Fetal Position: Right 04		Unique Fetal Id.: 9
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 25/16 MG BASE/KG/DAY

Animal: 623	Unique Fetal Id.: 1
Fetal Position: Left 01	
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
STERNUM	(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2-4, SLIGHT TO MODERATE
VERTEBRAL COLUMN	(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN	(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
Fetal Position: Left 04	Unique Fetal Id.: 4
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
Fetal Position: Left 05	Unique Fetal Id.: 5
THORACIC CAVITY	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
(VISCERAL)	CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK
Fetal Position: Left 07	Unique Fetal Id.: 7
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; RIGHT, FULL; LEFT, RUDIMENTARY WITH NO ARTICULATING HEAD
STERNUM	(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
ABDOMEN	(VISCERAL) SPLEEN, SMALL IN SIZE - VARIATION

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 25/16 MG BASE/KG/DAY

Animal: 623 (CONT.) Unique Fetal Id.: 9
 Fetal Position: Right 01
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; RIGHT
 STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
 VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
 ABDOMEN (VISCERAL) SPLEEN, SMALL IN SIZE - VARIATION
 Fetal Position: Right 03 Unique Fetal Id.: 11
 THORACIC CAVITY (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; LEFT, WITH NO ARTICULATING HEAD
 STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
 Fetal Position: Right 04 Unique Fetal Id.: 12
 STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
 ABDOMEN (VISCERAL) SPLEEN, SMALL IN SIZE - VARIATION
 Fetal Position: Right 05 * Unique Fetal Id.: 13
 Comments: VISCERAL OBSERVATIONS NOT RECORDED
 STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
 SKULL (SKELETAL) HYOID ARCH(ES), BENT - VARIATION; LEFT, SEVERE

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 25/16 MG BASE/KG/DAY

Animal: 626		Unique Fetal Id.: 1
Fetal Position: Left 01		
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY; RIGHT, FULL	
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY; RIGHT, FULL (WITH NO ARTICULATING HEADS)	
STERNUM	(SKELETAL) STERNEBRA(S), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT, WITH NO ARTICULATING HEAD	
Fetal Position: Left 04		Unique Fetal Id.: 4
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Left 05		Unique Fetal Id.: 5
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 01		Unique Fetal Id.: 6
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
ABDOMEN	(VISCERAL) KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, MODERATE	
Fetal Position: Right 02		Unique Fetal Id.: 7
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; LEFT	
ABDOMEN	(VISCERAL) KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, MODERATE SPLEEN, SMALL IN SIZE - VARIATION	

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 25/16 MG BASE/KG/DAY

Animal: 627	Unique Fetal Id.: 1
Fetal Position: Left 01	
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
SKULL	(SKELETAL) HYOID ARCH(ES), BENT - VARIATION; LEFT, MODERATE
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	(SKELETAL) RIB(S), FUSED - MALFORMATION; 7-8, PROXIMAL TO MEDIAL RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
Fetal Position: Left 04	Unique Fetal Id.: 4
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
Fetal Position: Left 05	Unique Fetal Id.: 5
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT
Fetal Position: Left 06	Unique Fetal Id.: 6
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
Fetal Position: Left 07	Unique Fetal Id.: 7
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL; LEFT WITH NO ARTICULATING HEAD
SKULL	(SKELETAL) HYOID ARCH(ES), BENT - VARIATION; BILATERAL, SLIGHT

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 25/16 MG BASE/KG/DAY

Animal: 627 (CONT.) Unique Fetal Id.: 8
 Fetal Position: Right 01
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; RIGHT

SKULL
 (SKELETAL) HYOID ARCH(ES), BENT - VARIATION; LEFT, MODERATE
 Fetal Position: Right 02 Unique Fetal Id.: 9
 RIBS
 (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Animal: 629 Unique Fetal Id.: 3
 Fetal Position: Left 03
 THORACIC CAVITY
 (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

Fetal Position: Left 05 Unique Fetal Id.: 5
 THORACIC CAVITY
 (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

Fetal Position: Left 06 Unique Fetal Id.: 6
 THORACIC CAVITY
 (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

Fetal Position: Right 03 Unique Fetal Id.: 9
 RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL; WITH NO
 ARTICULATING HEADS

Animal: 632 Unique Fetal Id.: 2
 Fetal Position: Left 02
 RIBS
 (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 25/16 MG BASE/KG/DAY

Animal: 632 (CONT.)
 Fetal Position: Left 04 Unique Fetal Id.: 4
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

STERNUM (SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
 Fetal Position: Right 02 Unique Fetal Id.: 6
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; RIGHT

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
 Fetal Position: Right 03 Unique Fetal Id.: 7
 STERNUM (SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
 Fetal Position: Right 04 Unique Fetal Id.: 8
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Animal: 633
 Fetal Position: Left 01 Unique Fetal Id.: 1
 SKULL (SKELETAL) HYOID ARCH(ES), BENT - VARIATION; BILATERAL, MODERATE
 Fetal Position: Left 03 Unique Fetal Id.: 3
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

SKULL (SKELETAL) HYOID ARCH(ES), BENT - VARIATION; LEFT, SEVERE
 Fetal Position: Left 04 Unique Fetal Id.: 4
 SKULL (SKELETAL) HYOID ARCH(ES), BENT - VARIATION; BILATERAL, SLIGHT TO MODERATE

ABDOMEN (VISCERAL) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 25/16 MG BASE/KG/DAY

Animal: 633 (CONT.)	Unique Fetal Id.: 5
Fetal Position: Left 05	
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL
STERNUM	(SKELETAL) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 4-5, SLIGHT
SKULL	(SKELETAL) HYOID ARCH(ES), BENT - VARIATION; BILATERAL, MODERATE
Fetal Position: Right 01	Unique Fetal Id.: 6
STERNUM	(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY
Fetal Position: Right 03	Unique Fetal Id.: 8
SKULL	(SKELETAL) HYOID ARCH(ES), BENT - VARIATION; RIGHT, MODERATE
Animal: 634	
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
Fetal Position: Right 01	Unique Fetal Id.: 7
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
Fetal Position: Right 02	Unique Fetal Id.: 8
STERNUM	(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 25/16 MG BASE/KG/DAY

Animal: 634 (CONT.) Unique Fetal Id.: 9
 Fetal Position: Right 03
 THORACIC CAVITY
 (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
 STERNUM (SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY
 Fetal Position: Right 04 Unique Fetal Id.: 10
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
 Fetal Position: Right 05 Unique Fetal Id.: 11
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY

STERNUM (SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY
 Fetal Position: Right 06 Unique Fetal Id.: 12
 STERNUM (SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY
 Fetal Position: Right 07 Unique Fetal Id.: 13
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

Animal: 635 Unique Fetal Id.: 2
 Fetal Position: Left 02
 STERNUM (SKELETAL) STERNEBRA (E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
 4, SLIGHT
 STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
 Fetal Position: Left 04 Unique Fetal Id.: 4
 RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 25/16 MG BASE/KG/DAY

Animal: 635 (CONT.)		Unique Fetal Id.: 5
Fetal Position: Left 05		
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Left 06		Unique Fetal Id.: 6
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
STERNUM		
(SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY		
Fetal Position: Right 01		Unique Fetal Id.: 7
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY	
Fetal Position: Right 02		Unique Fetal Id.: 8
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 03		Unique Fetal Id.: 9
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Right 04		Unique Fetal Id.: 10
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; RIGHT, WITH NO ARTICULATING HEAD	
Animal: 636		
Fetal Position: Left 01		Unique Fetal Id.: 1
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT	
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS	(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT	
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY WITH NO ARTICULATING HEAD	

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 25/16 MG BASE/KG/DAY

Animal: 636 (CONT.)	Unique Fetal Id.: 4
Fetal Position: Right 01	
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
STERNUM	(SKELETAL) STERNEBRA(E), MALALIGNED, SEVERE - MALFORMATION; 5, SEVERE; 2, 3 AND 6, SLIGHT
VERTEBRAL COLUMN	(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
ABDOMEN	(VISCERAL) GALL BLADDER, VARIATION - VARIATION; ABSENT
Fetal Position: Right 02	Unique Fetal Id.: 5
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN	(SKELETAL) CENTRA, EXTRA SITE OF OSSIFICATION - MALFORMATION; ANTERIOR TO CENTRUM 1
Fetal Position: Right 05	Unique Fetal Id.: 8
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
Animal: 638	
Fetal Position: Left 01	Unique Fetal Id.: 1
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
ABDOMEN	(VISCERAL) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	(SKELETAL) RIB 13, FULL - VARIATION; RIGHT

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 25/16 MG BASE/KG/DAY

Animal: 638 (CONT.) Unique Fetal Id.: 4
 Fetal Position: Left 04
 ABDOMEN (VISCERAL) SPLEEN, SMALL IN SIZE - VARIATION

Fetal Position: Left 05 Unique Fetal Id.: 5
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL (SKELETAL) HYOID ARCH(ES), BENT - VARIATION; LEFT, MODERATE

ABDOMEN (VISCERAL) SPLEEN, SMALL IN SIZE - VARIATION

Fetal Position: Left 06 Unique Fetal Id.: 6
 ABDOMEN (VISCERAL) SPLEEN, SMALL IN SIZE - VARIATION

Fetal Position: Right 02 Unique Fetal Id.: 8
 RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 03 Unique Fetal Id.: 9
 STERNUM (SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

ABDOMEN (VISCERAL) SPLEEN, SMALL IN SIZE - VARIATION

Fetal Position: Right 04 Unique Fetal Id.: 10
 STERNUM (SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

ABDOMEN (VISCERAL) SPLEEN, SMALL IN SIZE - VARIATION

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 25/16 MG BASE/KG/DAY

Animal: 640	Unique Fetal Id.: 1
Fetal Position: Left 01	
RIBS	
(SKELETAL) RIB 13, RUDIMENTARY - VARIATION; LEFT, WITH NO ARTICULATING HEAD	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
ABDOMEN	
(VISCERAL) KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, MODERATE URETER(S), RETROCAVAL - VARIATION; RIGHT GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE	
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Left 03	Unique Fetal Id.: 3
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Left 04	Unique Fetal Id.: 4
RIBS	
(SKELETAL) RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN	
(SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 25/16 MG BASE/KG/DAY

Animal: 640 (CONT.) Unique Fetal Id.: 5
Fetal Position: Left 05
RIBS (SKELETAL) RIB 13, RUDIMENTARY - VARIATION; BILATERAL
VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
SKULL (SKELETAL) HYOID BODY, UNOSSIFIED - VARIATION
Fetal Position: Left 06 Unique Fetal Id.: 6
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
STERNUM (SKELETAL) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
Fetal Position: Right 01 Unique Fetal Id.: 7
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
Fetal Position: Right 02 Unique Fetal Id.: 8
RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO. 156A DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 25/16 MG BASE/KG/DAY

Animal: 640 (CONT.) Unique Fetal Id.: 9
Fetal Position: Right 03
THORACIC CAVITY
(VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
STERNUM (SKELETAL) STERNEBRA (E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
Fetal Position: Right 04 Unique Fetal Id.: 10
THORACIC CAVITY (VISCERAL) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS (SKELETAL) RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN (SKELETAL) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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APPENDIX 6
Protocol and Amendments

DRAFT

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-10D
Study No.: 156

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR238605 SUCCINATE IN RABBITS

1.0 PURPOSE OF THE STUDY:

The purpose of this study is to evaluate the embryo/fetal toxicity and the teratogenic potential of WR238605 Succinate in rabbits. The protocol conforms to the standards of the U.S. Food and Drug Administration, the requirements of the Committee on Safety of Medicines in Great Britain, and the Organization for Economic Cooperation and Development. The protocol for this study was approved by the UIC Animal Care Committee (Appendix 1).

2.0 SPONSOR:

2.1 Name: U.S. Army Medical Materiel
Development Activity

2.2 Address: Fort Detrick
Frederick, MD 21702-5009

2.3 Representative: George J. Schieferstein, Ph.D.

3.0 TESTING FACILITY:

3.1 Name: Toxicology Research Laboratory (TRL)

3.2 Address: University of Illinois at Chicago (UIC)
Department of Pharmacology
1940 W. Taylor St.
Chicago, Illinois 60612 - 7353

3.3 Study Director: Barry S. Levine, D.Sc., D.A.B.T.

4.0 DATES:

4.1 Proposed Initiation of In-Life Phase: 01/02/95

4.2 Proposed Completion of In-Life Phase: 08/08/95

4.3 Proposed Study Completion Date
(Draft Final Report): 10/30/95

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Contract No.: DAMD17-92-C-2001
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5.0 TEST ARTICLE

- 5.1 Name or Code No: WR238605 Succinate (base mole fraction = 0.8)
8-[4-Amino-1-methylbutylamino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethyl-phenoxy)quinoline succinate
CAS #106635-81-8
Bottle number BM12562
- 5.2 TRL Chemical No: 0720614
- 5.3 Physical Description: Pale yellow powder
- 5.4 Storage Conditions to Maintain Stability:
- 5.4.1 Temperature: 0 to 4°C.
- 5.4.2 Humidity: Ambient conditions.
- 5.4.3 Light: Protect from light; amber bottle or silver foil covering.
- 5.4.4 Special Requirements: None.
- 5.5 Special Handling Procedures: Standard safety precautions will be followed including gloves, eye protection, mask, and lab coats.
- 5.6 Log of Test Article: The amount, date, identity of person(s) removing aliquots and the purpose for which each aliquot of the test article was removed from the batch will be documented. At termination of the study, all unused test article will be returned to the Sponsor.

6.0 PERSONNEL:

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
Reproductive Toxicologist	Ashraf F. Youssef, M.D., Ph.D.
Reproductive Scientist	Roberto A. Matamoros, D.V.M., Ph.D.
Teratologist (PAI)	Michael D. Mercieca, B.S.
Analytical Chemist	Adam Negrusz, Ph.D.
Clinical Veterinarian	James Artwohl, D.V.M., M.S., D.A.C.L.A.M.
Veterinarian Support	Documented in raw data
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Nancy Dinger, B.S.
Chemistry Specialist	Thomas Tolhurst, B.S.
Quality Assurance	Ronald C. Schoenbeck

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7.0 TEST SYSTEM:

- 7.1 Species: Rabbit
- 7.2 Strain: New Zealand White (Pasteurella Free)
- 7.3 Sex(s)/Number: 100 time-mated females (day 0 = day of observed mating)
- 7.4 Weight of Animals: ~3.0 - 4.0 kg at start of study
- 7.5 Age of Animals: ~5 to 6 months at study initiation.
- 7.6 Source of Animals: HRP, Inc., Denver, PA.
- 7.7 Justification for Selection of Test System: The FDA requires the use of two animal species, one being a non-rodent, in preclinical developmental toxicity studies. The rabbit is a standard and accepted non-rodent species for regulatory developmental toxicology studies, and is specified by the Sponsor. In addition, the New Zealand white rabbit was selected because it has demonstrated sensitivity to developmental toxicants and historical data and experience exist.
- 7.8 Procedure for Unique Identification of Test System: Each animal will be given a facility-unique number (ear tag) by the Supplier, and a separate study-unique number (ear tag) upon arrival at UIC. This latter number will also appear on a cage card visible on the front of each cage. The cage card will additionally contain the study number, test or control article identification, dose level, and treatment group. Raw data records and specimens will also be identified by the unique animal number.
- 7.9 Housing: The animals will be housed in an AAALAC-accredited facility. Animals will be singly housed in stainless steel cages in a temperature (61-69°F) and humidity (30 - 70%) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 0.32 m² area and 38.0 cm height, is adequate to house rabbits for this study as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23.
- 7.10 Quarantine Procedure: Animals will be quarantined for at least 3 days, from receipt until dosing is initiated on day 6 of gestation. During the quarantine period the animals will be observed daily for signs of illness and all unusual observations will be reported to the Study Director, Toxicologist or Veterinarian. Animals will be examined during quarantine and approved for use by the veterinarian prior to being placed on test. Any sickly animal will be either eliminated prior to the test animal selection process or replaced by a healthy animal following this procedure but prior to initiation of treatment under the direction of the Study Director or Toxicologist. Quarantine release will be documented on the Clinical Veterinarian Log by a veterinarian prior to study initiation.

- 7.11 Food: The animals will be fasted on the day of arrival. They will receive approximately 25 g of Purina High Fiber Certified Rabbit Chow #5325 (PMI Feeds, Inc., St. Louis, MO) on the second day, which will be gradually increased over a few days to approximately 100-130 g/day. This regimen is recommended by the animal supplier (HRP, Inc.) to reduce the incidence of intestinal problems. On the days of measured food consumption, an exact amount of 130 g will be provided.
- 7.12 Water: Tap water from an automatic watering system in which the room distribution lines are flushed daily will be provided *ad libitum* from arrival until termination. The water is untreated with additional chlorine or HCl.
- 7.13 There are no known contaminants in the feed or water which are expected to influence the study. A copy of the feed certification will be kept with the study records. The results of the most current comprehensive chemical analyses of Chicago water are documented in files maintained by Quality Assurance.
- 7.14 It is not known if the animals will experience pain or distress during the study. Analgesic or anesthetic agents will confound the ability to determine the toxic potential of the test article, and therefore will not be used. If an animal is in severe pain or distress, following consultation with the veterinary staff, it will be euthanized in accordance with standard operating procedures.

8.0 EXPERIMENTAL DESIGN:

8.1 Treatment Groups:

<u>Group No.</u>	<u>Treatment</u>	<u>Dose Level (mg base/kg/day)</u>	<u>Number of Females*</u>
1	Vehicle	0	20
2	WR238605 Succinate	2	20
3	WR238605 Succinate	7	20
4	WR238605 Succinate	25	20
5**	Vitamin A (Retinol Palmitate)	75,000 IU/kg/day (= 300 mg/kg/day)	20

* Presumed pregnant

** The positive control agent, will be administered orally at the specified dose on days 9 and 10 of gestation at a dosing volume of 1 ml/kg.

The high dose (25 mg base/kg/day) was retested in 20 presumed pregnant rabbits. Due to excessive mortality/abortion, the dose was lowered to 16 mg base/kg/day on gestation day 15 or 16 (stagger-started over two days). A concurrent vehicle control was administered to another group of 20 presumed pregnant rabbits.

Dose levels were selected on the basis of a range-finding study in rabbits (UIC/TRL Study No. 155). The number of animals, 20/dose level, is the number of animals required by the 1966 FDA Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use (Goldenthal Guidelines), and is the number of animals indicated by the Sponsor in Task Order UIC-10.

- 8.2 Frequency and Route of Administration of Test Article: The test article will be administered once daily by gavage during the period of major organogenesis, gestation days 6 through 18. It will be given at a dosing volume of 1 ml/kg. The control group will receive the vehicle at the same dosing volume. The specific volume to be administered will be adjusted on the basis of each animal's most recent body weight.
- 8.3 Justification of Route(s): The oral route is a convenient and accepted procedure for administering a specific amount of a test article to each animal. It mimics potential human exposure conditions and is specified by the Sponsor.
- 8.4 Procedure to Control Bias during the Assignment of Animals to Treatment Groups: During the quarantine/pretest period, animals judged to be healthy and meeting acceptable body weight requirements will be assigned to the study at random using a randomization procedure on the basis of body weight.
- 8.5 Test Article Vehicle: 1% Methylcellulose/0.2% Tween 80.
- 8.6 Test Article Dosage Form Preparation and Analyses: The dosage formulations of the test article will be prepared once at the beginning of the study. Stability data obtained from a previous study (UIC/TRL Study No. 047) indicated that dosing suspensions are stable at least for two weeks. Homogeneity data obtained from UIC/TRL Study No. 047 demonstrated that the test article suspensions are homogeneous (coefficients of variation for sampling in the top, middle and bottom of several test suspensions were typically less than 4%).

The stock test article suspension will be prepared by suspending the appropriate quantity of test article in the vehicle. All dosing suspensions will be stored at 0 - 4°C. Samples of the dosage formulations will be analyzed for test article concentration prior to use. Only samples within 10% of their intended concentration will be used. The dosing suspensions will be re-analyzed at the end of the dosing period.

- 8.7 Frequency of Observations, Test Analyses and Measurements:
- 8.7.1 Mortality Check: All animals will be observed twice daily, at least six hours apart for moribundity/mortality.
- 8.7.2 Clinical Signs: All animals will be observed daily for clinical signs of toxicity approximately 1-2 hours after dosing (days 6-18), and in the morning after completion of the dosing period (days 19-29). Moribund animals will be sacrificed on that day and the uterine contents will be examined as described in section 8.7.6.
- 8.7.4 Body Weights: Individual body weights will be recorded on day 0 of gestation, at randomization, and on gestation days 6 - 18, 24 and 29.
- 8.7.5 Food Consumption: Food consumption for all animals will be measured during the following 24 hour intervals: days 7/8, 9/10, 11/12, 14/15, 17/18, 23/24, 28/29.

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8.7.6 Sacrifice: On day 29 of presumed gestation, all surviving female rabbits will be killed by intravenous injection of sodium pentobarbital (50 mg/kg) via the marginal ear vein. Any female showing signs of abortion ($GD < 28$) or premature delivery ($GD \geq 28$) will be euthanized on the same day and evaluated as in Sections 8.8.6 - 8.8.8.

8.7.7 Cesarean-Sectioning Observations: The abdominal and thoracic cavities will be opened by a ventral midline incision and the contents examined. In gravid animals, the ovaries will be examined. The number of corpora lutea on each ovary will be recorded (ovaries discarded after evaluation). The gravid uterus will be examined and weighed. The number and location of viable and nonviable fetuses* *in utero*, early and late resorptions** and the total number of implantation sites will be recorded.

The uterine position of each fetus will be documented using the following procedure. All implantation sites, including resorptions, will be numbered in consecutive fashion beginning and similarly with the right distal uterine horn, noting the position of the cervix. Maternal tissues will only be saved for histopathological examination in 10% neutral buffered formalin as deemed necessary by the gross findings. The carcass of each dam will then be discarded.

*A viable fetus is defined as one which responds to stimuli. A non viable fetus is defined as a term fetus, which does not respond to stimuli *in utero* or is not breathing.

**An early resorption is defined as one in which it is not grossly evident that organogenesis has occurred. A late resorption is defined as one in which it is grossly evident that organogenesis has occurred. A fetus with evident autolysis is considered a late resorption.

8.7.8 Confirmation of Pregnancy: Uteri from females that appear nongravid will be opened and placed for approximately 10 minutes in ammonium sulfide solution (10%) for detection of possible implantation sites. If any implantation sites are detected, the ovaries will be examined as in 8.7.7.

8.7.9 Necropsy: Rabbits which die will be examined for the cause of death. Rabbits which require termination due to moribund condition will be killed and examined. Necropsy will occur on the same calendar day on which death or termination occurs. Examination will not be performed if precluded by postmortem autolysis. Pregnancy status and uterine contents will be recorded. Maternal tissues with gross lesions appropriate for retention will be fixed in neutral buffered 10% formalin for possible future evaluation. Exception: (Parovarian cysts will be discarded; these are common, spontaneous lesions in rabbits). Viscera which appear normal will be discarded. Naturally-delivered pups will be examined to the extent possible using the same methods described for fetuses.

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8.7.10 Fetal Gross Observations: Fetuses will be removed from the uterus and placed in individual containers. After sex and body weights are recorded, each fetus will be individually identified noting litter, uterine placement and study number.

8.7.11 Fetal Morphological Examination:

8.7.11.1 External: A detailed examination of each fetus will be conducted to include the eyes, palate, trunk and extremities. Any abnormal finding will be recorded. Late resorptions will be recorded and the tissue discarded or kept in formalin 10% as deemed necessary by the Study Director or the Reproductive Toxicologist.

8.7.11.2 Visceral Evaluation: All fetuses will be euthanized by an intraperitoneal injection of a 40% solution of sodium pentobarbital (0.4 ml/fetus). Fetuses will be examined for visceral anomalies and sexed internally employing the Staples' fresh tissue dissection techniques (Staples, 1974). Fetal examination will include evaluation of the eyes and the brain by a mid-sagittal section. At the completion of the visceral evaluation, fetuses will be eviscerated, skinned, and stored in 95% ethyl alcohol.

8.7.11.3 Skeletal Evaluation: All fetuses will be evaluated for skeletal anomalies with the exception of the fetuses from the initial 25 mg base/kg/day dose group. Those fetuses will remain in 95% ethyl alcohol until the Sponsor provides written directions for either the evaluation or disposal of those fetal tissues. The remaining fetal carcasses from all other groups will be macerated in a 2% potassium hydroxide solution, stained with Alizarin Red S, and cleared in 25% glycerin (Dawson, 1926). At the completion of the skeletal evaluation, the skeletal preparations will be stored in 99.5% glycerin and 0.5% phenol.

8.7.12 Statistical Analyses: Maternal body weights, weight gains, absolute uterine weight, and fetal body weights will be analyzed by a one-way analysis of variance. If a significant F ratio is obtained ($p \leq 0.05$), Dunnett's test will be used for pair-wise comparisons to the control group.

The incidence of fetal abnormalities will be examined in terms of the fetal and litter percentages (% abnormal fetuses/group & % abnormal litters/group). Abnormalities will include malformations in addition to variations. The proportions of litters with abnormalities and male to female fetal sex ratios will be compared by using the Chi-square test criterion with Yate's correction for 2 x 2 contingency tables and or Fisher's exact probability test.

Maternal food consumption data, the numbers of resorptions, non viable fetuses, viable fetuses, *corpora lutea* (C.L.), implantations, preimplantation loss* and postimplantation loss** will be compared using the Kruskal-Wallis test. If a significant effect is seen ($p \leq 0.05$), the Mann-Whitney U test will be used for pair-wise comparisons to the control group.

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*Preimplantation loss = # C.L. - # implantations

**Postimplantation loss = # implantations - # live fetuses

Statistical analysis will be conducted on the retest data comparing the retest 25/16 mg base/kg/day group to its concurrent vehicle control. Other statistical analyses will be conducted as deemed necessary and will be documented in the raw data.

C-section and fetal morphological data from pregnant animals that do not survive to the scheduled terminal sacrifice (i.e., animals found dead, sacrificed moribund, aborting, or delivering early), will not be included in the statistical analysis. C-section data from all animals will be used to determine the incidence of pregnancy.

In addition to the written report, summary data tables of parameters and variability will be transmitted to the Sponsor on magnetic media (computer diskette) in "ASCII" form. The transcribed data on disk will no longer be considered GLP compliant.

9.0 RECORDS TO BE MAINTAINED:

All data generated during the conduct of the study, except those that are generated as direct computer input, shall be recorded directly, promptly, and accurately in ink in bound books with prenumbered pages or on worksheets that shall be bound during or at the conclusion of the nonclinical laboratory study. All appropriate computer and machine output shall be bound during or at the conclusion of the study. All data entries shall be dated on the day of entry and signed or initialed by the person entering the data.

Any changes in entries for whatever reason (e.g., to correct an error or transposition) shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of data input. In computer driven collection systems, the operator responsible for direct data input shall be identified at the time of data input. Any changes in computer entries for whatever reason (e.g., to correct an error or transposition) shall be made in such a manner so as not to obscure the original entry, if possible, shall indicate the reason for such change, and shall be dated by the responsible individual.

All recorded data shall be reviewed, signed, and dated by a knowledgeable person, other than the person making the entry, to assure adherence to procedures and to verify observations.

Upon completion of the study and submission of the final report, all raw data, documentation, specimens, test article reserves and other materials necessary to reconstruct the study will be stored in the TRL archives maintained by Quality Assurance.

All changes or revisions, and reasons therefore, to this protocol once it is approved shall be documented, signed by the Study Director and Sponsor, dated and maintained with the protocol.

10.0 REGULATORY REQUIREMENTS:

This study will be performed in compliance with the UIC/TRL Quality Assurance Program designed to conform with FDA Good Laboratory Practice Regulations and EPA Good Laboratory Practice Standards.

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Will this study be submitted to a regulatory agency? Yes If so, to which agency(ies)? Food and Drug Administration

Does the Sponsor Request that remaining test article be returned? Possibly; direction will be provided by the Sponsor.

Does the Sponsor request that samples of the test article/carrier mixture(s) be returned to the Sponsor? No

11.0 REFERENCES:

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

Dunnett, CW (1955). A multiple comparison procedure for comparing several treatments with a control. J. Amer. Stat. Assoc. 50:1096-1129.

DTSC (1992). The assessment of developmental and reproductive risks. Toxicology and Risk Assessment Section, Department of Toxic Substances Control (DTSC), California Environmental Protection Agency, Sacramento, CA. Review Draft dated March, 1992.

EPA (1984b). Guideline for the health assessment of suspect developmental toxicants. Draft document from the Office of Research and Development, EPA, Washington, D.C.

EPA (1985). Hazard evaluation division standard evaluation procedure: Teratology Studies. U.S. Environmental Protection Agency, Office of Pesticide Programs, document EPA-540/9.85.018.

FDA (1982). Toxicological principles for safety assessment of direct food additives and color additives used in food. Bureau of Foods, Food and Drug Administration, Washington, D.C.

Gad, S and Weil, CS (1988). Statistics and Experimental Design for Toxicologists, 2nd ed. pp53-70, 147-176, Telforel Press. Caldwell, NJ.

Hayes, W (1989). Principles and Methods of Toxicology, pp 311-361, Raven press. New York, NY.

HRP, Inc. Rabbit quality and consistency. HRP NZW time-mated conception rates. (9/3/92).

Snedecot, GW and Cochran, WG (1967). Variance test for homogeneity of the binomial distribution. Statistical Method, 6th Edition, pp. 240-241, Iowa State University Press. Ames, IA.

Staples, RE (1974). Detection of visceral alterations in mammalian fetuses. Teratol. 9: A-37.

U.S. Department of Health and Human Services (1985). Guide for the Care and Use of Laboratory Animals. Prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources. Commission on Life Sciences, National Research Council. Public Health Service, National Institutes of Health, NIH Publications No. 86-23.

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U.S. Environmental Protection Agency (1991). Guidelines for developmental toxicity risk assessment. Notice. Fed. Regist. 56: 63798-63826.

U.S. Food and Drug Administration (1966). Guidelines for reproduction studies for safety evaluation of drugs for human use.

Wilson, JG (1965). Methods for administering drugs and detecting malformations in experimental animals. *In: Teratology Principles and Techniques* (Wilson, J.G. and Warkany, J., eds.). pp. 262-277, Un. Chicago Press. Chicago, IL.

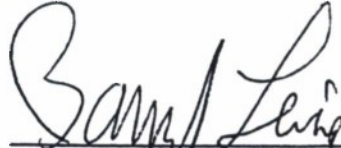
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STUDY NO: <u>154</u> INITIAL: <u>AW</u>
DATE: <u>10-3-56</u>

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Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-10D
Study No.: 156

12.0 PROTOCOL APPROVAL:

STUDY DIRECTOR:


Barry S. Levine, D.Sc., D.A.B.T.


6/28/94
Date

QUALITY ASSURANCE:


Ronald Schoenbeck

6/29/94
Date

SPONSOR APPROVAL:


George J. Schieferstein, Ph.D.
Contracting Officer's
Representative (COR)

7/5/94
Date

COMMENTS FROM THE COR:

Office of the Vice Chancellor for Research (M/C 672)
310 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227
(312) 996-4995

Appendix 1

June 22, 1994

Barry S. Levine
Pharmacology
312 BGRC, M/C 868

Dear Dr. Levine:

The modifications requested in your correspondence of June 15, 1994 pertaining to your approved protocol ACC: #93-077-13: "Developmental Toxicity (Segment II) Study of WR238605 in Rabbits" have been reviewed in accordance with the Animal Care and Use Policies of the University of Illinois at Chicago. You will be pleased to know that the modifications were approved on June 20, 1994 and consequently the records of Animal Care Committee will be revised to reflect these changes.

Thank you for complying with the Animal Care Policies and Procedures of UIC.

Sincerely yours,


Josephine B. Miller, Ph.D.
Chair, Animal Care Committee

JBM:st
xc: BRL

Study No: 156

Title: Developmental Toxicity (Segment II) Study of WR238605 Succinate in Rabbits

1. Page 1 Section 4.0

Add the following dates:

Proposed Initiation of In-life Phase (Day 0): 01/02/95

Proposed Completion of In-life Phase: 02/03/95

Proposed Study Completion Date
(Draft Final Report): 05/03/95

Reason: Dates were not finalized when the protocol was submitted.

2. Page 2 Section 6.0

Add the following to personnel

Lead Technician Nancy Dinger, B.S.

Reason: To reflect changes in personnel.

3. Page 4 Section 8.1

A. The following doses were assigned to Groups 1-5:

<u>Group No.</u>	<u>Treatment</u>	<u>Dose Level</u> <u>(mg base/kg/day)</u>
1	Vehicle	0
2	WR238605 Succinate	2
3	WR238605 Succinate	7
4	WR238605 Succinate	25
5	(Retinol Palmitate)	75,000 IU/kg/day (=300 mg/kg/day)

B. Change "will be" to "were" in the first sentence of the paragraph.

Reason: A. The doses of the test article have now been determined and the teratogenic dose in rabbits of Retinol Palmitate was reduced based on preliminary studies performed by TRL.

B. To reflect that the dose range-finding study has been done, from which dose levels were chosen.

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4. Page 5 Section 8.5

Change the concentration of Tween 80 in the vehicle from 0.4% to 0.2%.

Reason: Less foaming provides easier chemical analysis of the dosage formulation.

5. Page 5 Section 8.6

Add the phrase "at least" to the second sentence to read "At least for two weeks"

Reason: To reflect the actual stability of the dosing suspensions for more than two weeks.

6. Page 5 Section 8.7.4

Change gestation days for body weight measurements to be days 6-18, 24 and 29.

Reason: Change in procedure.

7. Page 6 Section 8.7.6

Add the following sentence to the end of the section "any female showing signs of abortion (GD<28) or premature delivery (GD≥28) will be euthanized on the same day and evaluated as in sections 8.7.7 - 8.7.9"

Reason: To explain the procedure.

8. Page 6 Section 8.7.7

Replace the sentence "and continuing from the proximal to distal right uterine horn" by the sentence "and similarly with the right distal uterine horn, noting the position of the cervix."

Reason: To clarify the procedure.

9. Page 6 Section 8.7.8

Change the ammonium sulfide solution concentration from 0.5% to 10%.

Reason: To match the Pathology Associate, Inc., standard operating procedure.

PROTOCOL AMENDMENT

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Title: Developmental Toxicity (Segment II) Study of WR238605 Succinate in Rabbits

10. Page 7 Section 8.7.11.2

Replace the section after the first sentence to read as follows:

All fetuses will be euthanized by I.P. injection of 40% solution of sodium pentobarbital (0.4 ml/fetus). Fetal examination will include evaluation of the eyes and the brain by a mid-coronal section. The remaining carcass will be retained in 95% ethyl alcohol.

Reason: To clarify procedure.

11. Page 7 Section 8.7.11.3

Change the end of the first sentence to read "...subsequent staining with Alizarin Red S for evaluation of the fetal skeletons (Dawson, 1926). Skeletal preparations will be stored in 99.5% glycerin and 0.5% phenol and will be retained".

Reason: Alizarin Red S is a preferred technical method with similar evaluation efficiency to the double staining method and is less time consuming. The phenol is added to prevent molding.

12. Page 7, 8 Section 8.7.12

Replace the first three paragraphs by the following:

Maternal body weights, weight gains, relative uterine weight (% body weight), and fetal body weights will be analyzed by a one-way analysis of variance. If a significant F ratio is obtained ($p \leq 0.05$), Dunnett's test will be used for pairwise comparisons to the control group.

The incidence of fetal abnormalities will be examined in terms of the fetal and litter percentages (% abnormal fetuses/group & % abnormal litters/group). Abnormalities will include malformations in addition to variations. The proportions of litters with abnormalities and male to female fetal sex ratios will be compared by using the Chi-square test criterion with Yate's correction for 2 x 2 contingency tables and or Fisher's exact probability test.

Maternal food consumption data, the numbers of resorptions, non viable fetuses, viable fetuses, *corpora lutea* (C.L.), implantations, preimplantation loss* and postimplantation loss** will be compared using the Kruskal-Wallis test. If a significant effect is seen ($p \leq 0.05$), the Mann-Whitney U test will be used for pairwise comparisons to the control group.

*Preimplantation loss = #C.L. - #implantations

**Postimplantation loss = #implantations - # live fetuses

PROTOCOL AMENDMENT

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Other statistical analyses will be conducted as deemed necessary and will be documented in the raw data.

Only data from pregnant animals will be included in the evaluation or the statistical analysis. In animals with abortion or premature delivery, uterine weight will not be included in the statistical analysis.

Reason: To represent more appropriately the statistical analysis procedures.

13. Page 9 Section 11.0

Delete Lang LP (1993) reference.

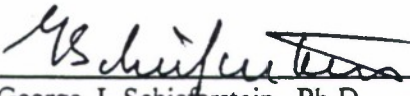
Reason: Irrelevant to the study.

STUDY DIRECTOR



Barry S. Levine, D.Sc., D.A.B.T. 1/11/95
Date

SPONSOR APPROVAL



George J. Schieferstein, Ph.D. 1/17/95
Date

PROTOCOL AMENDMENT

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Study No: 156
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Title: Developmental Toxicity (Segment II) Study of WR238605 Succinate in Rabbits

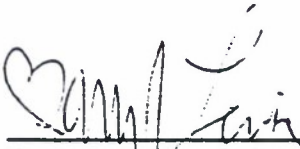
14. Page 7 Section 8.7.11.2

At the sentence before the last sentence replace "mid-coronal" by "mid-sagittal"

Reason: Change in procedure with similar outcome of the results.

Approvals:

STUDY DIRECTOR:



Barry S. Levine, D.Sc., D.A.B.T.

2/16/95
Date

SPONSOR APPROVAL:



George J. Schieferstein, Ph.D.

3/3/95
Date

Study No.: 156
 Title: Developmental Toxicity (Segment II) Study of WR238605 Succinate in Rabbits

15. Page 1 Section 4.0

Replace the dates of the proposed completion of in-life phase and proposed study completion date as follows:

4.2	<u>Proposed Completion of In-Life Phase:</u>	08/08/95
4.3	<u>Proposed Study Completion Date</u> <u>(Draft Final Report):</u>	10/30/95

Reason: Due to an apparent formulation analysis problem, the Sponsor requested further evaluation of the high dose.

16. Page 4 Section 8.1

Add the following after the Table of treatment groups:

The high dose (25 mg base/kg/day) was retested in 20 presumed pregnant rabbits. Due to excessive mortality/abortion, the dose was lowered to 16 mg base/kg/day on gestation day 15 or 16 (stagger-started over two days). A concurrent vehicle control was administered to another group of 20 presumed pregnant rabbits.

Reason: Due to an apparent formulation analysis problem, the Sponsor requested further evaluation of the high dose. However, excessive mortality in that group necessitated reducing the dose from 25 to 16 mg base/kg/day on gestation day 15/16.

17. Page 7 Section 8.7.11.2

Replace this section with the following:

Visceral Evaluation: All fetuses will be euthanized by an intraperitoneal injection of a 40% solution of sodium pentobarbital (0.4 ml/fetus). Fetuses will be examined for visceral anomalies and sexed internally employing the Staples' fresh tissue dissection techniques (Staples, 1974). Fetal examination will include evaluation of the eyes and the brain by a mid-sagittal section. At the completion of the visceral evaluation, fetuses will be eviscerated, skinned, and stored in 95% ethyl alcohol.

Reason: To clarify the procedure for preparing fetal tissues for visceral evaluation and for storage in ethyl alcohol.

18. Page 7 Section 8.7.11.3

Replace this section with the following:

Skeletal Evaluation: All fetuses will be evaluated for skeletal anomalies with the exception of the fetuses from the initial 25 mg base/kg/day dose group. Those fetuses will remain in 95% ethyl alcohol until the Sponsor provides written directions for either the evaluation or disposal of those fetal tissues. The remaining fetal carcasses from all other groups will be macerated in a 2% potassium hydroxide solution, stained with Alizarin Red S, and cleared in 25% glycerin (Dawson, 1926). At the completion of the skeletal evaluation, the skeletal preparations will be stored in 99.5% glycerin and 0.5% phenol.

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Reason: A. Following discussions with the Sponsor, it has been determined that skeletal evaluations will not be conducted on fetuses obtained from the initial 25 mg base/kg/day group. Those fetuses will be stored until such time that the Sponsor directs either evaluation or disposal of those tissues.

B. To clarify the procedures for preparing fetal tissues for skeletal evaluation.

19. Page 7 Section 8.7.12

In the first sentence change "relative uterine weight (% body weight)" to "absolute uterine weight".

Reason: To clarify that the absolute uterine weight will be statistically analyzed.

20. Page 7 Section 8.7.12

Insert the following sentence at the beginning of paragraph four: "Statistical analysis will be conducted on the retest data comparing the retest 25/16 mg base/kg/day group to its concurrent vehicle control.

Reason: To clarify that the statistical analysis for the data from the retest will be separate from the initial study groups.

21. Page 8 Section 8.7.12

Delete the 1st paragraph on this page and replace with the following:

C-section and fetal morphological data from pregnant animals that do not survive to the scheduled terminal sacrifice (i.e., animals found dead, sacrificed moribund, aborting, or delivering early), will not be included in the statistical analysis. C-section data from all animals will be used to determine the incidence of pregnancy.

Reason: To clarify what information will not be included in statistical analysis.

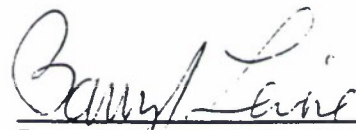
22. Page 9 Section 11.0

Delete "Kimmel, CA and Trammel, C (1981)... Stain Technol. 56:271-273" from the references.

Reason: This reference does not pertain to the techniques used in this study.

APPROVALS:

STUDY DIRECTOR


Barry S. Levine, D.Sc., D.A.B.T.

10/3/95
Date

SPONSOR APPROVAL


George J. Schieferstein, Ph.D.

10/5/95
Date

DRAFT

PROTOCOL AMENDMENT

Study No.: 156
Title: Developmental Toxicity (Segment II) Study of WR238605 Succinate in Rabbits

23. Page 6 Section 8.7.6

Change the last line to read as follows: "Any female showing signs of abortion ($GD < 28$) or premature delivery ($GD \geq 28$) will be euthanized on the same day and evaluated as in Sections 8.7.7 and 8.7.8, with the exception that the gravid uterus will not be weighed."

Reason: To clarify cesarean-section observations for rabbits that abort or deliver prematurely.

24. Page 6 Section 8.7.9

Delete the 5th sentence and replace it with the following: "Cesarean-section observations will be performed as in Sections 8.7.7 and 8.7.8, with the exception that the gravid uterus will not be weighed."

Reason: To clarify cesarean-section observations for rabbits which die or are terminated due to moribund condition.


25. Page 7 Section 8.7.10

Change the first line to read as follows: "At scheduled sacrifice, fetuses will be removed from the uterus. . ."

Reason: To clarify that fetal observations will be performed only on fetuses from animals sacrificed on presumed gestation day 29.

APPROVALS:

STUDY DIRECTOR



Barry S. Levine, D.Sc., D.A.B.T.

10/31/95
Date

SPONSOR APPROVAL

George Schieferstein, P.h.D.

Date

DRAFT

APPENDIX 7
Study Deviations

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR238605 SUCCINATE IN RABBITS

D R A F T

Study Deviations*

<u>Deviation Type</u>	<u>Specific Deviation</u>	<u>Effect on Study</u>
Protocol	One female in the initial high dose group was given hay on 01/25/95 to supplement its diet. All animals in the retest high dose group were given hay from 07/24/95 through the end of the study (08/08/95) to supplement their diet. Additionally, all but three animals were gavaged with a slurry of pelleted food in distilled water on 07/27/95, 07/28/95, and 08/01/95.	None, since this was done to encourage the animals to eat and potentially enhanced survival in the high dose group.
Protocol	The animal room temperature was out of range on several occasions.	None, deviations were minimal.
Protocol	In the first week of the retest of the high dose, the suspension was analyzed prior to use and at the end of the first week. In the second week, the high dose was lowered. The 25 mg base/kg/day suspension was analyzed prior to use and after use (mid-week two), while the 16 mg base/kg/day suspension was analyzed prior to use (mid-week 2) and after use (end week 2).	None, more frequent analyses were performed to more closely monitor the suspensions and because the dose was lowered.
Protocol	Food consumption was recorded on gestation days 8/9 instead of 7/8 for animal no. 545 (7 mg base/kg/day group), nos. 612, 614, 616, 618, 619 (0 mg base/kg/day), and nos. 632, 633, 635, 637, 640 (25/16 mg base/kg/day).	None.
Protocol	Corpora lutea were inadvertently not recorded for animal no. 565 (premature delivery; 25 mg base/kg/day).	None.

*The detailed "Deviation Reports" are contained in the raw data which are archived at the Toxicology Research Laboratory, University of Illinois at Chicago, Department of Pharmacology, 1940 W. Taylor St., Chicago, IL 60612.

The above deviations did not affect the integrity of the study.

Barry S. Levine, D.Sc.,D.A.B.T.

Date