

DRAFT

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-7N
Study No.: 138

Title Page

Study Report for Task Order No. UIC-7N
DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS
Sponsor: U.S. Army Medical Materiel
Development Activity
Test Article: WR242511 Tartrate
Contract No.: DAMD17-92-C-2001

Study Director

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

In-Life Phase Completed On

December 02, 1994

Performing Laboratory

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This study evaluated the embryo/fetal toxicity and the teratogenic potential of WR242511 tartrate in time-mated New Zealand White (Pasteurella Free) female rabbits. Doses were 0, 0.5, 1.3, and 3.5 mg base/kg/day administered by gavage during gestation days (GD) 6 - 18 (GD0 = day of observed mating). In addition, a positive control group was administered retinol palmitate, 300 mg/kg/day, on GD9 and 10 by gavage. Apparent toxicity of the test article was limited to one abortion in the mid dose (GD27) and one premature delivery (GD29) in the high dose. No other toxic effects were seen in either the pregnant females or in the fetuses. In a previous dose range-finding study (UIC/TRL Study No. 137), early fatality of all 5 females was observed at 6 mg base/kg/day, while 2.5 mg base/kg/day showed marginal toxicity (slight decrease in female fetal weights). Accordingly, the high dose in the present study was chosen between 2.5 and 6 mg base/kg/day to induce marginal maternal toxicity, but to avoid excessive maternal fatality. Although overt maternal toxicity was not apparent in high dose animals in the present investigation, based on the results of the dose range-finding test it is believed that a dose somewhat higher than 3.5 mg base/kg/day would have resulted in excessive mortality. In the positive control group, marginal decreases in weight gain, a significant decrease in uterine weights, and significant increases in the number of early resorptions and % post-implantation loss were observed. Fetal toxicity was seen in the positive control group as a significant decrease in the number of viable fetuses and a significant increase in external and internal anomalies. Since neither overt maternal toxicity nor fetal toxicity was observed in WR242511 dose groups, 3.5 mg base/kg/day was considered at or near the no-observed effect level (NOEL) for both fetal and maternal toxicity in rabbits. In a previously conducted developmental toxicity study in rats, 2 mg base/kg/day was considered the NOEL for fetal toxicity while 0.5 mg base/kg/day was considered the NOEL for maternal toxicity (UIC/TRL Study No. 144). Taken together, rats demonstrated greater sensitivity to WR242511 than rabbits. In the rat teratology study, WR242511 did not demonstrate a developmental hazard to rat fetuses except in maternally toxic doses. Fetal body weights were reduced, but treatment-related malformations were not observed.					
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STATEMENT OF COMPLIANCE

To the best of my knowledge, Study No. 138 entitled " Developmental Toxicity (Segment II) Study of WR242511 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 demonstrated 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
WR242511 IN RABBITS

STUDY NO. 138

DIRECTOR: BARRY S. LEVINE

INITIATION DATE: 11/19/93

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 11/22/93, TO STUDY DIR 11/22/93, TO MGMT 11/22/93
PHASES: PROTOCOL REVIEW

INSPECT ON 11/4/94, TO STUDY DIR 11/4/94, TO MGMT 11/7/94
PHASES: ROOM ENVIRONMENT, QUARANTINE, LICK-IT CHECK AND TEST
ARTICLE PREPARATION

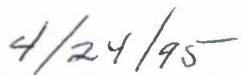
INSPECT ON 11/7/94, TO STUDY DIR 11/7/94, TO MGMT 11/8/94
PHASES: BODY WEIGHT, FOOD CONSUMPTION AND DOSING

INSPECT ON 2/8/95, TO STUDY DIR 2/8/95, TO MGMT 2/8/95
PHASES: RAW DATA AND DRAFT REPORT FROM THE ANALYTICAL LAB

INSPECT ON 3/7-8/95, TO STUDY DIR 3/8/95, TO MGMT 3/16/95
PHASES: RAW DATA

INSPECT ON 4/19-21/95, TO STUDY DIR 4/21/95, TO MGMT 4/24/95
PHASES: DRAFT REPORT


QUALITY ASSURANCE


DATE

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Signature Page

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

TRL Chemical No.: 1720614

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

Test Article: WR242511 Tartrate

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

Testing Facility: TOXICOLOGY RESEARCH LABORATORY (TRL)
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Barry S. Levine, D.Sc., D.A.B.T.
Study Director

Date

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

Date

In-life Phase Initiation: October 31, 1994

Dosing Initiation: November 06, 1994

In-Life Completion: December 02, 1994

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1. SUMMARY

This study evaluated the embryo/fetal toxicity and the teratogenic potential of WR242511 tartrate in time-mated New Zealand White (Pasteurella Free) female rabbits. Doses were 0, 0.5, 1.3, and 3.5 mg base/kg/day administered by gavage during gestation days (GD) 6 - 18 (GD0 = day of observed mating). In addition, a positive control group was administered retinol palmitate, 300 mg/kg/day, on GD9 and 10 by gavage. The results are summarized in Table 1. One female in the high dose prematurely delivered on GD29 and one female in the mid dose aborted on GD27. No other maternal toxic manifestations were observed in any WR242511 dose level. In addition, fetal toxicity was not apparent. In the positive control group, one female aborted on GD22. Other manifestations of toxicity in this group were a marginal decrease in weight gain during dosing; significant decreases in uterine weight and viable fetuses; and significant increases in post-implantation loss, early resorptions and fetuses with external, visceral and skeletal malformations.

With the exception of one abortion and one premature delivery in test article-treated animals, toxicity was not apparent in either the does or their fetuses. Based on the results of this study, the highest dose tested (3.5 mg base/kg/day) was considered at or near the no observed effect level for both maternal and fetal toxicity in rabbits. Since 6 mg base/kg/day in a previously conducted dose range-finding study was lethal to 5/5 animals, it is believed that a dose in excess of 3.5 mg base/kg/day in the present investigation would have resulted in excessive mortality.

2. INTRODUCTION

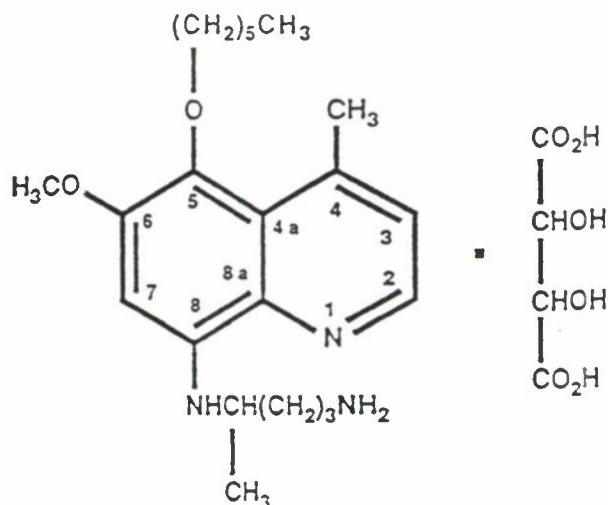
This study was conducted to evaluate the embryo/fetal toxicity and the teratogenic potential of the test article in New Zealand white rabbits. The test article was administered by daily gavage to time-mated females during gestation days 6 - 18. The fetuses were delivered by Cesarean section on gestation day 29. All fetuses were examined for external anomalies and by Staples' technique for visceral anomalies and then fixed in ethyl alcohol (95%) for subsequent skeletal examinations. 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. This study was stagger-started over four days and was initiated on October 31, 1994 (observation of mating). Dosing was initiated (stagger-started) on November 06, 1994 (GD6) and the in-life portion was terminated on December 02, 1994 (GD29).

3. MATERIALS AND METHODS

3.1 Test Article

WR242511 tartrate (Bottle Lot No. BM 05816), a fine, yellow powder, was received on June 16, 1993 from Herner & Co. and was previously assigned an in-house chemical number (1720614). The chemical name of the test article is 8-[(4-amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline DL-tartrate and the mole fraction of the base is 0.71. It was stored at -20 to -15°C and ambient humidity

in the freezer, and was protected from light (the container was wrapped in aluminum foil). The chemical structure follows.



The test article was initially identified by GC-MS and the purity was determined to be greater than 99.6%. 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.

3.2 Animals

A total of one-hundred and twenty female New Zealand White (Pasteurella Free) rabbits were obtained from HRP, Inc., Denver, PA, on November 1 & 4, 1994 (30 and 90 animals, respectively). The animals were $\approx$ 6 months old upon arrival at the UIC AAALAC-accredited animal facility (date of birth 04/30/94). 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 (approx. 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. Tap water from an automatic watering system in which the room distribution lines were flushed daily was provided *ad libitum* from arrival until 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

Animals were mated on four consecutive days at the supplier's facility. The day of mating was considered gestation day 0 (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 gestation day 0 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. 137) 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	WR242511	0.5	20
3	WR242511	1.3	20
4	WR242511	3.5	20
5**	Vitamin A (Retinol Palmitate)	75,000 IU/kg/day (= 300 mg/kg/day)	20

* Presumed pregnant

** The positive control agent (suspended in water at 300 mg/ml and prepared fresh daily) was administered orally at the specified dose on days 9 and 10 of gestation at a dosing volume of 1 ml/kg.

The test article was administered by gavage once daily during gestation days 6 through 18. The dosing suspensions were administered at a dosing volume of 1 ml/kg. A stock test article suspension (20 mg/ml) was prepared weekly by suspending the appropriate quantity of the test article in the vehicle (aqueous 1% methylcellulose/0.2% Tween 80). Daily dosage formulations were prepared by diluting the stock to the appropriate concentration.

The stock and dosing suspensions were kept at 0 - 4°C. Samples of the dosage formulations used at the beginning and at the end of the dosing period were analyzed for test article concentration. Only samples within 10% of their intended concentration were used. Stability data obtained from a previous study (UIC/TRL Study No. 107) indicated that the stock formulation was stable for two weeks and the dosing suspensions were stable for 48 hours. Homogeneity data obtained from UIC/TRL Study No. 107 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 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 immediately prior to dosing and in the afternoon, and in the afternoon after the dosing period ceased.

On GD29, all 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 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 has 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. All fetuses were euthanized by ip injection of a 40% solution of sodium pentobarbital ($\approx$ 0.4 ml/fetus). 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 freshly examined by the Staples' technique for visceral anomalies including a mid-sagittal section between the eyes (Staples, 1974). All fetuses were then skinned and eviscerated. Following staining with Alizarin Red S and then cleared in glycerin as recommended by Dawson, 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, absolute 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.

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

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

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

Uterine weight, fetal body weights and fetal sex in animals with abortion/premature delivery were not included in the statistical analysis.

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 dosing suspensions were within 10% of their target concentrations at the beginning and at the end of the dosing period.

4.2 Mortality/Clinical Signs

The summary of clinical signs of toxicity is in Table 3. Individual signs are in Appendix 2.

No animal died in this study. One female in the mid dose (i.e., 1.3 mg base/kg/day) aborted on GD27 and one female in the high dose (i.e., 3.5 mg base/kg/day) had a premature delivery on GD29. In addition, one female in the positive control group aborted and was subsequently sacrificed on GD22. Neither abortion nor premature delivery was associated with or preceded by any marked maternal toxicity.

4.3 Maternal Body Weights

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

No significant change in body weight/weight gain was observed in the WR242511 treatment groups. A marginal, but significant decrease in weight gain was observed in the positive control group from day 9 to day 10, (i.e., following the first of the two daily doses).

4.4 Food Consumption

The summary of mean daily food consumption is in Table 6. Individual food consumption data are contained in Appendix 4.

No decrease in food consumption was observed in any group throughout the study.

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.

All animals were pregnant except for three females in the positive control group. In the mid dose group, the female which aborted had 6 fetuses. Only one fetus could be externally evaluated and appeared normal; the rest of the fetuses were cannibalized. In the positive control group, the female which aborted had 10 fetuses with 5 apparently normal while the others were cannibalized. All aborted fetuses were discarded after examination.

4.6 Fetal Observations

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

Treatment related abnormalities were not observed in fetuses of pregnant rabbits dosed with WR242511. In the positive control group (i.e., 300 mg/kg/day retinol palmitate on GD9 & 10), observations included a significant decrease in the number of viable fetuses and significant increases in % post-implantation loss, early resorptions and fetuses with external, skeletal, and visceral anomalies. Anomalies were observed mainly in the skull, caudal vertebrae, hyoid bone and in the urinary system.

5. DISCUSSION/CONCLUSION

This study evaluated the embryo/fetal toxicity and the teratogenic potential of WR242511 tartrate in time-mated New Zealand White (Pasteurella Free) female rabbits. Doses were 0, 0.5, 1.3, and 3.5 mg base/kg/day administered by gavage during gestation days (GD) 6 - 18 (GD0 = day of observed mating). In addition, a positive control group was administered retinol palmitate, 300 mg/kg/day, on GD9 and 10 by gavage. The results are summarized in Table 1.

Apparent toxicity of the test article was limited to one abortion in the mid dose (GD27) and one premature delivery (GD29) in the high dose. No other toxic effects were seen in either the pregnant females or in the fetuses. In a previous dose range-finding study (UIC/TRL Study No. 137), early fatality of all 5 females was observed at 6 mg base/kg/day, while 2.5 mg base/kg/day showed marginal toxicity (slight decrease in female fetal weights). Accordingly, the high dose in the present study was chosen between 2.5 and 6 mg base/kg/day to induce marginal maternal toxicity, but to avoid excessive maternal fatality. Although overt maternal toxicity was not apparent in high dose animals in the present investigation, based on the results of the dose range-finding test it is believed that a dose somewhat higher than 3.5 mg base/kg/day would have resulted in excessive mortality.

In the positive control group, marginal decreases in weight gain, a significant decrease in uterine weights, and significant increases in the number of early resorptions and % post-implantation loss

were observed. Fetal toxicity was seen in the positive control group as a significant decrease in the number of viable fetuses and a significant increase in external and internal anomalies.

Since neither overt maternal toxicity nor fetal toxicity was observed in WR242511 dose groups, 3.5 mg base/kg/day was considered at or near the no-observed effect level (NOEL) for both fetal and maternal toxicity in rabbits. In a previously conducted developmental toxicity study in rats, 2 mg base/kg/day was considered the NOEL for fetal toxicity while 0.5 mg base/kg/day was considered the NOEL for maternal toxicity (UIC/TRL Study No. 144). Taken together, rats demonstrated greater sensitivity to WR242511 than rabbits. In the rat teratology study, WR242511 did not demonstrate a developmental hazard to rat fetuses except in maternally toxic doses. Fetal body weights were reduced, but treatment-related malformations were not observed.

6. PERSONNEL

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
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Reproductive Scientist	Roberto A. Matamoros, D.V.M., Ph.D.
Analytical Chemist	Adam Negrusz, Ph.D.
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Veterinarian Support	Documented in raw data
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Documented in raw data
Chemistry Specialist	Thomas Tolhurst, B.S.
Quality Assurance	Ronald C. Schoenbeck

Report preparation was assisted by Dr. Ashraf Youssef, Ms. Soudabeh Soura and Mr. Mukesh Pitroda.

7. 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 WR242511 IN RABBITS

Summary of Toxic Responses

	WR242511				Retinol Palmitate
Dose Level (mg base/kg/day)	0.0	0.5	1.3	3.5	300*
Number of Females Pregnant (Non-pregnant)	20(0)	20(0)	20(0)	20(0)	17(3)
Term Litters (Early pregnancy termination)	20(0)	20(0)	19(1)*	19(1)*	16(1)*
Clinical Signs	-	NE	NE	NE	NE
Maternal Body Weight Gain	-	NE	NE	NE	↓(?)
Food Consumption	-	NE	NE	NE	NE
Uterine Weight	-	NE	NE	NE	↓
Early Resorptions	-	NE	NE	NE	↑
Post-implantation Loss	-	NE	NE	NE	↑
Decrease in Fetal Body Weight (♂/♀)	-/-	NE/NE	NE/NE	NE/NE	NE/NE
Viable Fetuses	-	NE	NE	NE	↓
Total Loss/Litter	-	NE	NE	NE	↑
External Malformations	-	NE	NE	NE	↑
Skeletal malformations	-	NE	NE	NE	↑
Visceral Malformations	-	NE	NE	NE	↑

CONCLUSIONS

This study evaluated the embryo/fetal toxicity and the teratogenic potential of WR242511 tartrate in time-mated New Zealand White (Pasteurella Free) female rabbits. Doses were 0, 0.5, 1.3, and 3.5 mg base/kg/day administered by gavage during gestation days (GD) 6 - 18 (GD0 = day of observed mating). In addition, a positive control group was administered retinol palmitate, 300 mg/kg/day, on GD9 and 10 by gavage. Apparent toxicity of the test article was limited to one abortion in the mid dose (GD27) and one premature delivery (GD29) in the high dose. No other toxic effects were seen in either the pregnant females or in the fetuses. In a previous dose range-finding study (UIC/TRL Study No. 137), early fatality of all 5 females was observed at 6 mg base/kg/day, while 2.5 mg base/kg/day showed marginal toxicity (slight decrease in female fetal weights). Accordingly, the high dose in the present study was chosen between 2.5 and 6 mg base/kg/day to induce marginal maternal toxicity, but to avoid excessive maternal fatality. Although overt maternal toxicity was not apparent in high dose animals in the present investigation, based on the results of the dose range-finding test it is believed that a dose somewhat higher than 3.5 mg base/kg/day would have resulted in excessive mortality. In the positive control group, marginal decreases in weight gain, a significant decrease in uterine weights, and significant increases in the number of early resorptions and % post-implantation loss were observed. Fetal toxicity was seen in the positive control group as a significant decrease in the number of viable fetuses and a significant increase in external and internal anomalies. Since neither overt maternal toxicity nor fetal toxicity was observed in WR242511 dose groups, 3.5 mg base/kg/day was considered at or near the no-observed effect level (NOEL) for both fetal and maternal toxicity in rabbits. In a previously conducted developmental toxicity study in rats, 2 mg base/kg/day was considered the NOEL for fetal toxicity while 0.5 mg base/kg/day was considered the NOEL for maternal toxicity (UIC/TRL Study No. 144). Taken together, rats demonstrated greater sensitivity to WR242511 than rabbits. In the rat teratology study, WR242511 did not demonstrate a developmental hazard to rat fetuses except in maternally toxic doses. Fetal body weights were reduced, but treatment-related malformations were not observed.

NE = No effect

(?) = Possible Effect

*mg/kg/day on GD9 & 10

*Aborted/Premature Delivery

Table 2

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITSDosage Formulation Analyses^a

Target Concentration (mg base/ml)	GD 6 ^b	% Target	Target Concentration (mg base/ml)	GD 18 ^c	% Target
0	0	-	0	0	-
0.5	0.46 ± 0.00	92.0	0.5	0.47 ± 0.00	94.0
1.3	1.26 ± 0.00	96.9	1.3	1.24 ± 0.01	95.4
3.5	3.28 ± 0.01	93.7	3.5	3.47 ± 0.01	99.1

^aMean ± standard deviation for triplicate runs.^bGestation Day 6 (first day of dosing)^cGestation Day 18 (last day of dosing)

Table 3
DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

SUMMARY OF CLINICAL SIGNS

STUDY: 138

SEX: FEMALE

	DOSE: (mg base/kg/day)	0	0.5	1.3	3.5	300 mg/kg/day ^a
	GROUP:	1-F	2-F	3-F	4-F	5-F
Scheduled Sacrifice		20	20	19	19	19
Animal Aborted/Sacrificed		0	0	1	0	1
Premature Delivery		0	0	0	1	0
Total Number of Animals		20	20	20	20	20

^aRetinol Palmitate given on GD9 and GD10 only

Table 4

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

SUMMARY OF BODY WEIGHTS (Kilograms) (Maternal)

STUDY: 138

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day)	D	D.5	1.3	3.5	300 mg/kg/day ^a
	GROUP:	1-F	2-F	3-F	4-F	5-F
DAY 0	MEAN	3.53	3.53	3.57	3.57	3.54
	S.D.	0.229	0.234	0.256	0.206	0.251
	N	20	19	20	19	17
DAY 5	MEAN	3.42	3.40	3.41	3.42	3.41
	S.D.	0.215	0.235	0.250	0.189	0.257
	N	20	19	20	19	17
DAY 6	MEAN	3.38	3.40	3.41	3.43	3.42
	S.D.	0.231	0.242	0.253	0.174	0.295
	N	20	19	20	19	17
DAY 7	MEAN	3.35	3.37	3.40	3.42	3.41
	S.D.	0.222	0.232	0.251	0.175	0.281
	N	20	19	20	19	17
DAY 8	MEAN	3.37	3.39	3.40	3.41	3.41
	S.D.	0.226	0.221	0.240	0.184	0.277
	N	20	19	20	19	17
DAY 9	MEAN	3.38	3.39	3.42	3.42	3.44
	S.D.	0.220	0.217	0.245	0.175	0.271
	N	20	19	20	19	17
DAY 10	MEAN	3.40	3.40	3.41	3.41	3.41
	S.D.	0.242	0.225	0.250	0.200	0.254
	N	20	19	20	19	17
DAY 11	MEAN	3.41	3.42	3.44	3.44	3.40
	S.D.	0.232	0.221	0.243	0.188	0.246
	N	20	19	20	19	17
DAY 12	MEAN	3.43	3.45	3.47	3.47	3.42
	S.D.	0.243	0.223	0.236	0.181	0.264
	N	20	19	20	19	17
DAY 13	MEAN	3.44	3.46	3.50	3.47	3.47
	S.D.	0.267	0.216	0.247	0.192	0.272
	N	20	19	20	19	17

* P less than .05

** P less than .01

Analysis of Variance using DUNNETT'S Procedure

^a Retinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 138

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0	0.5	1.3	3.5	300 mg/kg/day ^a
		1-F	2-F	3-F	4-F	5-F
DAY 14	MEAN	3.48	3.50	3.53	3.51	3.49
	S.D.	0.258	0.219	0.239	0.194	0.265
	N	20	19	20	19	17
DAY 15	MEAN	3.51	3.53	3.55	3.53	3.53
	S.D.	0.264	0.223	0.253	0.198	0.296
	N	20	19	20	19	17
DAY 16	MEAN	3.52	3.55	3.55	3.54	3.55
	S.D.	0.260	0.222	0.240	0.208	0.312
	N	20	19	20	19	17
DAY 17	MEAN	3.51	3.56	3.56	3.54	3.54
	S.D.	0.260	0.244	0.241	0.221	0.299
	N	20	19	20	19	17
DAY 18	MEAN	3.52	3.55	3.54	3.53	3.54
	S.D.	0.255	0.230	0.239	0.243	0.308
	N	20	19	20	19	17
DAY 24	MEAN	3.61	3.61	3.59	3.63	3.58
	S.D.	0.251	0.253	0.284	0.242	0.278
	N	20	19	20	19	16
DAY 29	MEAN	3.65	3.66	3.68	3.67	3.64
	S.D.	0.262	0.221	0.250	0.223	0.274
	N	20	19	19	19	16

* P less than .05

** P less than .01

Analysis of Variance using DUNNETT'S Procedure

^a Retinol Palmitate given on GD9 and GD10 only

Table 5

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

SUMMARY OF WEIGHT GAINS (Kilograms) (Maternal)

STUDY: 138

SEX: FEMALE

PERIOD ^a	DOSE: (mg base/kg/day)	0	0.5	1.3	3.5	300 mg/kg/day ^c
	GROUP:	1-F	2-F	3-F	4-F	5-F
DAY 7 ^b	MEAN	-0.03	-0.03	-0.01	-0.01	-0.01
	S.D.	0.080	0.090	0.047	0.079	0.064
	N	20	19	20	19	17
DAY 8	MEAN	0.02	0.01	-0.01	-0.01	0.01
	S.D.	0.035	0.040	0.047	0.057	0.048
	N	20	19	20	19	17
DAY 9	MEAN	0.01	0.01	0.02	0.01	0.03
	S.D.	0.042	0.048	0.048	0.053	0.041
	N	20	19	20	19	17
DAY 10	MEAN	0.02	0.00	-0.01	-0.01	-0.03**
	S.D.	0.043	0.055	0.029	0.062	0.045
	N	20	19	20	19	17
DAY 11	MEAN	0.01	0.02	0.03	0.03	-0.01
	S.D.	0.050	0.039	0.036	0.067	0.028
	N	20	19	20	19	17
DAY 12	MEAN	0.02	0.03	0.03	0.03	0.03
	S.D.	0.044	0.035	0.051	0.039	0.031
	N	20	19	20	19	17
DAY 13	MEAN	0.01	0.01	0.04	0.01	0.04
	S.D.	0.044	0.032	0.033	0.059	0.031
	N	20	19	20	19	17
DAY 14	MEAN	0.04	0.04	0.02	0.03	0.03
	S.D.	0.044	0.030	0.052	0.054	0.029
	N	20	19	20	19	17
DAY 15	MEAN	0.02	0.03	0.03	0.02	0.04
	S.D.	0.030	0.028	0.046	0.038	0.044
	N	20	19	20	19	17
DAY 16	MEAN	0.02	0.02	0.00	0.01	0.02
	S.D.	0.027	0.035	0.033	0.057	0.038
	N	20	19	20	19	17

* P less than .05

** P less than .01

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 WR242511 IN RABBITS

DRAFT

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 138

SEX: FEMALE

PERIOD ^a	DOSE: (mg base/kg/day) GROUP:	0	0.5	1.3	3.5	300 mg/kg/day ^b
		1-F	2-F	3-F	4-F	5-F
DAY 17	MEAN	-0.01	0.01	0.01	0.00	-0.01
	S.D.	0.035	0.040	0.032	0.042	0.045
	N	20	19	20	19	17
DAY 18	MEAN	0.00	-0.01	-0.02	-0.01	0.00
	S.D.	0.029	0.029	0.023	0.039	0.038
	N	20	19	20	19	17
DAY 24	MEAN	0.09	0.05	0.06	0.10	0.03
	S.D.	0.060	0.102	0.158	0.063	0.083
	N	20	19	20	19	16
DAY 29	MEAN	0.05	0.06	0.06	0.04	0.06
	S.D.	0.048	0.085	0.055	0.063	0.053
	N	20	19	19	19	16
TOTAL GAIN	MEAN	0.27	0.27	0.28	0.24	0.20
	S.D.	0.112	0.149	0.090	0.149	0.127
	N	20	19	19	19	16

* P less than .05
** P less than .01

Analysis of Variance using DUNNETT'S Procedure

^aSuccessive periods

^bRetinol Palmitate given on GD9 and GD10 only

Table 6
DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

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SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 138

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day) 0 GROUP:	1-F	0.5 2-F	1.3 3-F	3.5 4-F	300 mg/kg/day ^a 5-F
DAY 8	INTAKE (g)	130	130	126	130	130
	S.D.	0.0	0.0	19.7	0.0	0.0
	N	20	19	20	19	17
DAY 10	INTAKE (g)	130	130	130	130	130
	S.D.	0.0	0.0	0.0	0.0	0.0
	N	20	19	20	19	17
DAY 12	INTAKE (g)	130	130	130	120	130
	S.D.	0.0	0.0	0.0	32.5	0.0
	N	20	19	20	19	17
DAY 15	INTAKE (g)	129	130	129	128	130
	S.D.	6.0	0.0	6.5	6.9	0.0
	N	20	19	20	19	17
DAY 18	INTAKE (g)	130	130	130	116	130
	S.D.	0.0	0.0	0.0	40.9	0.0
	N	20	19	20	19	17
DAY 24	INTAKE (g)	130	130	130	130	130
	S.D.	0.0	0.0	0.0	0.0	0.0
	N	20	19	20	19	16
DAY 29	INTAKE (g)	130	130	130	130	130
	S.D.	0.0	0.0	0.0	0.0	0.0
	N	20	19	19	19	16

^a Retinol Palmitate given on GD9 and GD10 only

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Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-7N
Study No.: 138

Table 7

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

Summary of Cesarean-Section Data and Fetal Evaluations

	WR242511					Retinol Palmitate
	0.0	0.5	1.3	3.5		
Dose Level (mg base/kg/day)						300 ^a
Females Pregnant (Nonpregnant)	20(0)	20(0)	20(0)	20(0)		17(3)
Term Litters (Early Pregnancy Termination)	20(0)	20(0)	19(1)	19(1)		16(1)
Uterine Weight (g) [†]	462.6 ± 70.8	459.5 ± 109.1	451.5 ± 91.4	427.1 ± 104.5		331.0 ± 125.9 ^b
Early Resorptions (No.)	0.5	0.4	0.3	0.8		1.9 ^c
Viable Fetuses (No.)	8.4	8.1	8.1	7.4		5.1 ^d
Post-implantation loss (%)	7.4	3.6	5.7	11.5		29.5 ^c
Total Implantation Loss (%)	10.9	9.4	8.5	18.5		37.8 ^c
Fetal Body Weight (g) [†] - Males	39.5 ± 3.2	40.9 ± 4.1	39.8 ± 4.5	38.0 ± 6.29		40.1 ± 5.11
- Females	39.4 ± 4.0	41.1 ± 4.4	39.6 ± 5.0	38.2 ± 4.70		40.8 ± 5.03
Litters with External Malformations (%)	0(0)	0(0)	0(0)	1(5.3)		13(86.7) ^d
Litters with Skeletal Malformations (%)	2(10)	3(15.8)	0(0)	1(5.9)		13(86.7) ^d
Litters with Visceral Malformations (%)	1(5)	1(5.3)	3(15.8)	1(5.9)		6(40) ^d

^amg/kg/day on GD9 and GD10

^bStatistically significant from vehicle control group using ANOVA/Dunnett's test ($p \leq 0.05$)

^cStatistically significant from vehicle control group using Kruskal-Wallis/Mann-Whitney U test ($p \leq 0.05$)

^dStatistically significant from vehicle control group using the Fisher's Exact Test the Chi-square test ($p \leq 0.05$)

[†]Mean ± SD

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APPENDIX 1

Analytical Chemistry Report

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DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

UIC/TRL STUDY NUMBER 138

Part I: Identity, Purity and Stability Study of WR242511

Part II: Dosing Formulations Analysis of WR242511 in 1%
Methylcellulose/0.2% Tween 80

Analysts: Adam Negrusz
A. Karl Larsen, Jr.

Study Site: Drug Disposition Research Laboratory
College of Pharmacy
University of Illinois at Chicago
Chicago, Illinois 60612

Sponsor: Toxicology Research Laboratory
University of Illinois at Chicago
Chicago, Illinois 60612

Report Prepared by: Dr. Adam Negrusz

Report Prepared: January 31, 1995

Approved: January 31, 1995
Dr. Eugene F. Woods, Ph.D. *E. Woods*
Laboratory Director

Part I: Identity, Purity and Stability Study of WR242511

Objective

The objective of this study was to confirm the identity, establish the purity and stability of WR242511.

Identification

GC-MS System

Gas Chromatograph:	Hewlett-Packard Series II
Mass Selective Detector:	Hewlett-Packard Model 5970
Analytical Column:	30 m x 0.25 mm ID, DB-5 with a 3 micron film thickness.
GC Parameters:	Injector temp. 250°C, oven temp. 70°C initial, 280°C final, 15°C/minute ramp, carrier gas - helium, flow rate 2 ml/minute, split ratio 10:1

Procedure

Subject sample (WR242511 tartrate) was submitted by the Toxicology Research Laboratory. The sample was dissolved in methanol to a concentration of 0.71 µg base/ml and a 2 µl aliquot was injected on the column. The MSD scanned from 40 amu to 400 amu at a rate of 1 scan per second.

Results - GC-MS

The mass spectrum indicates a molecular ion m/e 373 which is in agreement with the WR242511 free base molecular weight. Major fragments of WR242511 sample are m/e 84, 175, 203, 288.

Figure 1 shows the mass spectrum of the WR242511 sample.

Purity

Experimental

The subject sample (WR242511 tartrate) was supplied by the Toxicology Research Laboratory and stored at -20°C when it was not analyzed.

Description

A fine yellow powder, no obvious odor.

Spectrum

An ultraviolet spectrum (Figure 2) recorded on a Shimadzu Spectronic 200 UV spectrometer (dual beam) was obtained from a 14.2 μg base/ml solution of WR242511 prepared in mobile phase. The sample was found with maximal absorptivity observed at 212 nm and 264 nm.

HPLC System

Solvent Delivery System:	Perkin-Elmer Series 3B Pump
Injector:	Rheodyne 7125 with 50 μl sample loop
Analytical Column:	Spherisorb CN 5 μ , 250 mm x 4.6 mm (Alltech)
Detector:	Perkin-Elmer LC-55B UV Detector, 225 nm, 264 nm
Integrator:	Spectra-Physics SP4270 Integrator
Mobile Phase:	20% methanol, 50% acetonitrile, 30% 0.01 M ammonium formate (in water), pH 3.0 (adjusted with 88% formic acid), flow 1.5 ml/minute

Procedure

Six solutions of WR242511 were prepared as follows. Twenty five mg of WR242511 tartrate sample was weighed into a 25 ml volumetric flask. The sample was dissolved in and the volume brought to mark with mobile phase. A 25 μl aliquot of each solution was immediately chromatographed at 225 nm and next at 264 nm.

Calculation of Results

Quantitations were based on the assumption of equal detector response per unit weight of all UV-absorbing components. Areas of WR242511 and other detectable components in the subject sample chromatograms were employed in the following equation to calculate the percentage of WR242511 present in the sample:

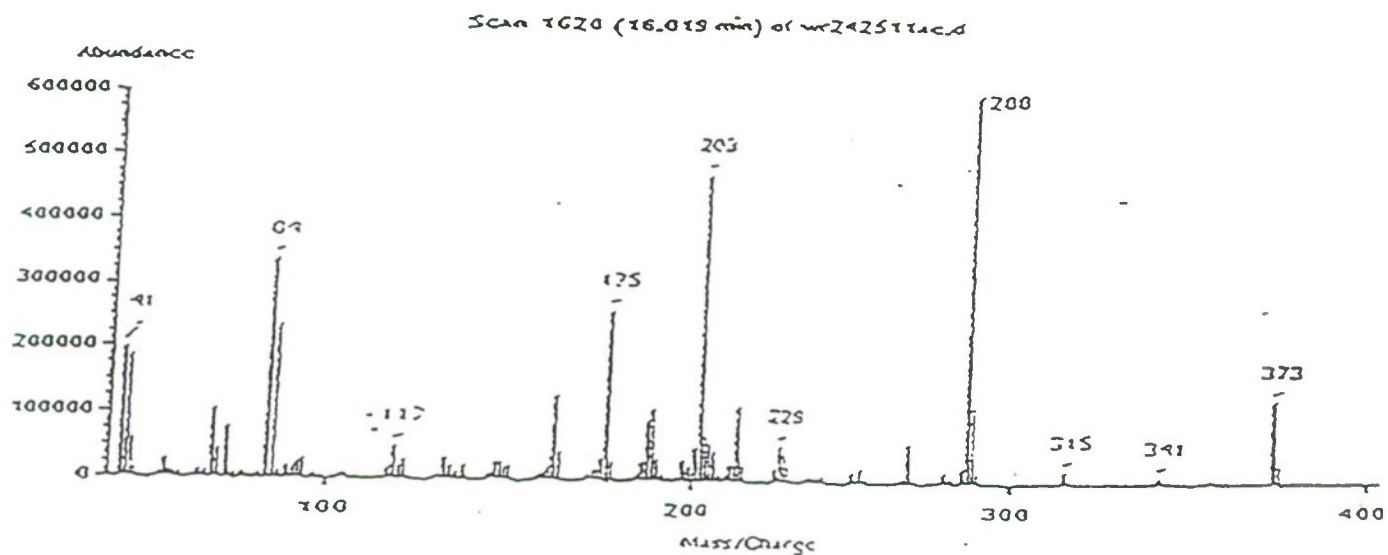
$$\% \text{PURITY} = (\text{area of WR242511} / \text{total area}) \times 100$$

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Results

Typical chromatograms are shown in Figure 3. The subject samples were found to contain less than 1% of one UV-absorbing impurity (225 nm). At 264 nm no visible impurities were observed. Percent purity of initial WR242511 sample was found to be 99.63%, standard deviation - 0.02%, terminal 99.46% $\pm$ 0.04%. The assay results are presented in Tables 1 and 2.

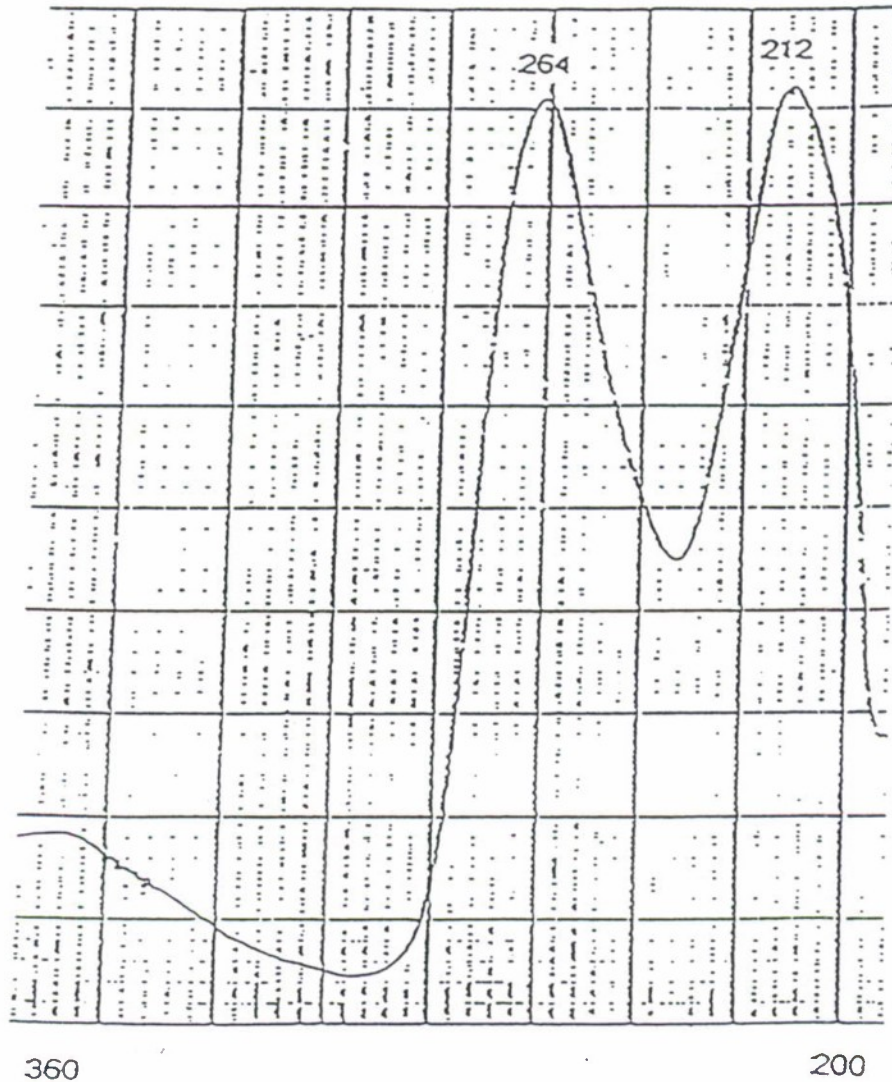
FIGURE 1
MASS SPECTRUM OF WR242511 SAMPLE



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FIGURE 2

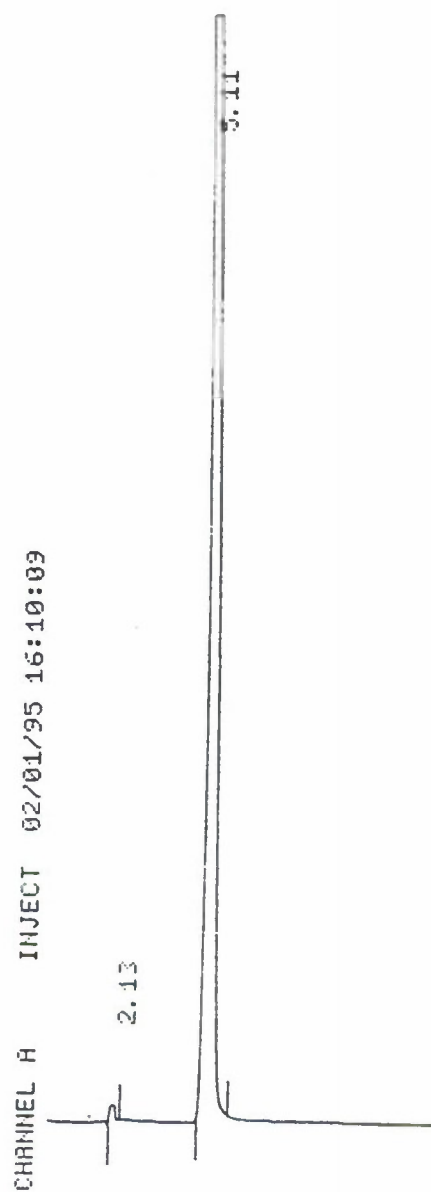
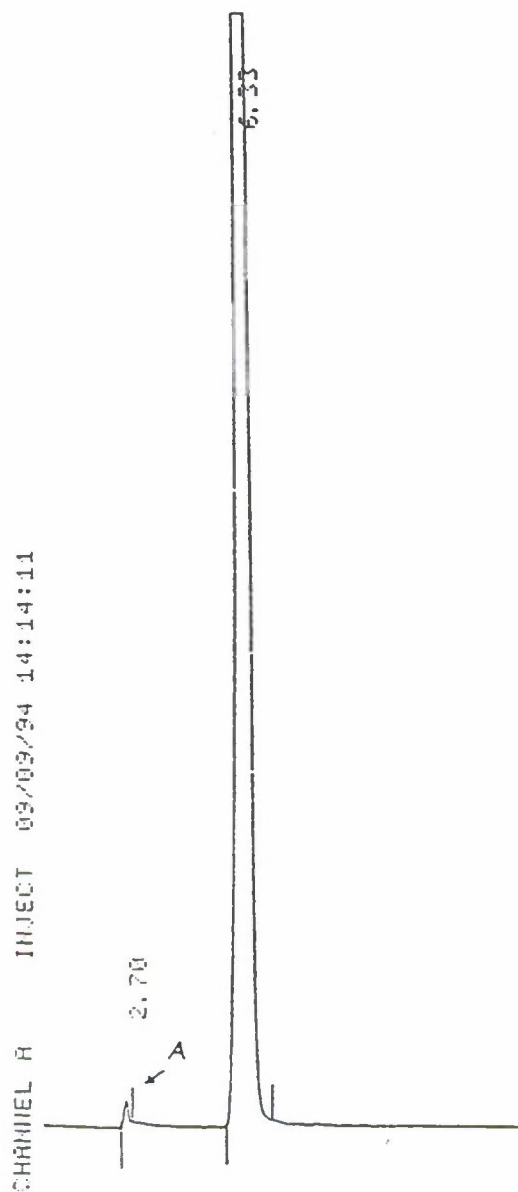
ULTRAVIOLET SPECTRUM OF WR242511



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FIGURE 3

CHROMATOGRAMS OF WR242511 SAMPLE, CONC. 0.71 MG BASE/ML, 225 NM,
A - INITIAL SAMPLE, B - TERMINAL SAMPLE



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Table 1

Purity Data for WR242511
Initial Sample

Solutions

Peak Identity	1	2	3	4	5	6
A	3229	3089	3167	3535	3451	3438
WR242511	880964	873460	902359	904336	881062	888791
% Purity	99.635	99.648	99.650	99.611	99.610	99.615

Mean $\pm$ S.D. - 99.63 $\pm$ 0.02

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Table 2

Purity Data for WR242511
Terminal Sample

Solutions

Peak Identity	1	2	3	4	5	6
A	3215	3204	3537	3467	3141	3488
WR242511	653986	635077	652265	644740	626757	644418
% Purity	99.466	99.498	99.461	99.465	99.501	99.384

Mean $\pm$ S.D. - 99.46 $\pm$ 0.04

Part II: Dosing Formulations Analysis of WR242511 in 1% Methylcellulose/0.2% Tween 80

Introduction

Samples from Study No. 138 were submitted by the Toxicology Research Laboratory to the Drug Disposition Research Laboratory for the quantitation of WR242511 in dosing formulations. Samples were received on November 6 and on November 18, 1994. All samples submitted were analyzed by high performance liquid chromatography by a previously described analytical method (see report Study No. 107 from February 21, 1994, Part II and Part IV).

Results

Results of dosing formulations for Study No. 138 are found in Table 3. All dosing formulations analyzed were within 10% of their target values.

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Table 3

Results of Dosing Formulations Analysis for Study No. 138

November 6, 1994

Sample Identification	Target Concentration (mg base/ml)	Mean Concentration ± S.D. (mg base/ml)
WHITE	0	0
ORANGE WITH BLACK DOT	0.5	0.4635 ± 0.0031
PINK WITH BLACK DOT	1.3	1.2626 ± 0.0032
GREEN WITH BLACK DOT	3.5	3.2783 ± 0.0145

November 18, 1994

Sample Identification	Target Concentration (mg base/ml)	Mean Concentration ± S.D. (mg base/ml)
WHITE	0	0
ORANGE WITH BLACK DOT	0.5	0.4680 ± 0.0035
PINK WITH BLACK DOT	1.3	1.2442 ± 0.0085
GREEN WITH BLACK DOT	3.5	3.4676 ± 0.0145

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APPENDIX 2

Individual Maternal Clinical Signs

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

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INDIVIDUAL CLINICAL SIGNS

STUDY: 138
DAY 6-DAY 29

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

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
401	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
402	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
403	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
404	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
405	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
406	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
407	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
408	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
409	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
410	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
411	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
412	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
413	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

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INDIVIDUAL CLINICAL SIGNS

STUDY: 138
DAY 6-DAY 29

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

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
414	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
415	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
416	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
417	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
418	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
419	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
420	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 138
DAY 6-DAY 29

GROUP: 2-F SEX: FEMALE
DOSE: 0.5 (mg base/kg/day)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
421	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
422	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
423	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
424	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
425	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
426	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
427	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
428	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
429	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
430	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
431	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
432	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
433	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 138
DAY 6-DAY 29

GROUP: 2-F
DOSE: 0.5(mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
434	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
435	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
436	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
437	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
438	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
439	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
440	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 138
DAY 6-DAY 29

GROUP: 3-F
DOSE: 1.3 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
441	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
442	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
443	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
444	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
445	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
446	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
447	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
448	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
449	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
450	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
451	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
452	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
453	Animal Aborted/Sacrificed Normal			DAY 27 DAY 6-DAY 26

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 138
DAY 6-DAY 29

GROUP: 3-F
DOSE: 1.3 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
454	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
455	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
456	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
457	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
458	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
459	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
460	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 138
DAY 6-DAY 29

GROUP: 4-F
DOSE: 3.5 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
461	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
462	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
463	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
464	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
465	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
466	Normal Premature Delivery			DAY 6-DAY 28 DAY 29
467	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
468	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
469	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
470	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
471	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
472	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
473	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 138
DAY 6-DAY 29

GROUP: 4-F
DOSE: 3.5 (mg base/kg/day)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
474	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
475	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
476	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
477	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
478	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
479	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29
480	Normal Scheduled Sacrifice			DAY 6-DAY 28 DAY 29

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 138
DAY 6-DAY 29

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

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
481	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
482	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
483	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
484	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
485	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
486	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
487	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
488	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
489	Animal Aborted/Sacrificed Normal			DAY 22 DAY 9-DAY 23
490	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
491	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
492	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
493	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29

^a Retinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 138
DAY 6-DAY 29

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

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
494	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
495	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
496	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
497	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
498	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
499	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29
500	Normal Scheduled Sacrifice			DAY 9-DAY 28 DAY 29

^a Retinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

INCIDENCE OF OBSERVATIONS

STUDY: 138

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0 1-F	0.5 2-F	1.3 3-F	3.5 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
Normal		20 100%	20 100%	20 100%	20 100%	20 100%
DAY 13						
No. Observed		20	20	20	20	20
Normal		20 100%	20 100%	20 100%	20 100%	20 100%
DAY 14						
No. Observed		20	20	20	20	20
Normal		20 100%	20 100%	20 100%	20 100%	20 100%
DAY 15						
No. Observed		20	20	20	20	20
Normal		20 100%	20 100%	20 100%	20 100%	20 100%

^a Retinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 138

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0 1-F	0.5 2-F	1.3 3-F	3.5 4-F	300 mg/kg/day ^a 5-F
DAY 16						
No. Observed		20	20	20	20	20
Normal		20 100%	20 100%	20 100%	20 100%	20 100%
DAY 17						
No. Observed		20	20	20	20	20
Normal		20 100%	20 100%	20 100%	20 100%	20 100%
DAY 18						
No. Observed		20	20	20	20	20
Normal		20 100%	20 100%	20 100%	20 100%	20 100%
DAY 19						
No. Observed		20	20	20	20	20
Normal		20 100%	20 100%	20 100%	20 100%	20 100%
DAY 20						
No. Observed		20	20	20	20	20
Normal		20 100%	20 100%	20 100%	20 100%	20 100%
DAY 21						
No. Observed		20	20	20	20	20
Normal		20 100%	20 100%	20 100%	20 100%	20 100%
DAY 22						
No. Observed		20	20	20	20	20
Normal		20 100%	20 100%	20 100%	20 100%	20 100%
Animal Aborted/Sacrificed		0	0	0	0	1 5%
DAY 23						
No. Observed		20	20	20	20	20
Normal		20 100%	20 100%	20 100%	20 100%	20 100%
DAY 24						
No. Observed		20	20	20	20	19
Normal		20 100%	20 100%	20 100%	20 100%	19 100%
DAY 25						
No. Observed		20	20	20	20	19
Normal		20 100%	20 100%	20 100%	20 100%	19 100%

^a Retinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 138

SEX: FEMALE

PERIOD	DOSE: (mg base/kg/day) GROUP:	0 1-F	0.5 2-F	1.3 3-F	3.5 4-F	300 mg/kg/day ^a 5-F
DAY 26						
No. Observed		20	20	20	20	19
Normal		20 100%	20 100%	20 100%	20 100%	19 100%
DAY 27						
No. Observed		20	20	20	20	19
Normal		20 100%	20 100%	19 95%	20 100%	19 100%
Animal Aborted/Sacrificed		0	0	1 5%	0	0
DAY 28						
No. Observed		20	20	19	20	19
Normal		20 100%	20 100%	19 100%	20 100%	19 100%
DAY 29						
No. Observed		20	20	19	20	19
Scheduled Sacrifice		20 100%	20 100%	19 100%	19 95%	19 100%
Premature Delivery		0	0	0	1 5%	0

^a Retinol Palmitate given on GD9 and GD10 only

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APPENDIX 3

Individual Maternal Body Weight and Weight Gain Data

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DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 138

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
401	3.69	3.49	3.59	3.40	3.45	3.41	3.50	3.46	3.51	3.57	3.61	3.64
402	3.79	3.66	3.59	3.61	3.59	3.69	3.73	3.74	3.82	3.84	3.82	3.88
403	3.64	3.41	3.49	3.34	3.44	3.40	3.43	3.51	3.55	3.56	3.59	3.54
404	3.06	3.13	3.06	2.98	3.02	3.03	3.05	3.04	3.08	3.06	3.15	3.16
405	3.52	3.42	3.46	3.25	3.32	3.37	3.33	3.41	3.39	3.38	3.43	3.47
406	3.76	3.63	3.55	3.56	3.60	3.57	3.63	3.61	3.69	3.72	3.74	3.81
407	3.52	3.38	3.35	3.41	3.38	3.37	3.38	3.37	3.40	3.30	3.44	3.48
408	3.72	3.54	3.45	3.51	3.51	3.49	3.55	3.43	3.45	3.51	3.49	3.49
409	3.28	3.03	2.99	3.03	3.03	3.06	3.08	3.07	3.07	3.06	3.11	3.12
410	3.36	3.18	3.12	3.09	3.08	3.07	3.09	3.11	3.10	3.10	3.12	3.17
411	3.42	3.34	3.32	3.26	3.27	3.29	3.33	3.32	3.32	3.25	3.35	3.42
412	3.14	3.12	2.92	2.99	3.02	3.10	3.01	3.11	3.12	3.10	3.13	3.13
413	3.84	3.70	3.61	3.54	3.56	3.62	3.72	3.70	3.68	3.74	3.84	3.84
414	3.82	3.60	3.67	3.64	3.71	3.72	3.75	3.76	3.75	3.79	3.88	3.93
415	3.60	3.42	3.49	3.46	3.50	3.47	3.50	3.48	3.54	3.57	3.56	3.58
416	3.45	3.48	3.43	3.37	3.38	3.43	3.42	3.49	3.38	3.45	3.50	3.52
417	3.25	3.11	3.09	3.10	3.09	3.11	3.10	3.09	3.12	3.11	3.16	3.15
418	3.60	3.56	3.46	3.51	3.54	3.49	3.49	3.52	3.54	3.59	3.61	3.62
419	3.72	3.78	3.68	3.69	3.67	3.67	3.69	3.67	3.75	3.79	3.79	3.79
420	3.42	3.33	3.31	3.28	3.26	3.27	3.26	3.27	3.29	3.32	3.33	3.36
MEAN	3.53	3.42	3.38	3.35	3.37	3.38	3.40	3.41	3.43	3.44	3.48	3.51
S.D.	0.229	0.215	0.231	0.222	0.226	0.220	0.242	0.232	0.243	0.267	0.258	0.264
N	20	20	20	20	20	20	20	20	20	20	20	20

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 138

GROUP: 1-F

SEX: FEMALE

DOSE: 0 (mg base/kg/day)

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

401	3.67	3.67	3.65	3.71	3.78
402	3.87	3.88	3.86	4.02	4.07
403	3.60	3.66	3.59	3.71	3.75
404	3.17	3.17	3.19	3.30	3.31
405	3.45	3.46	3.46	3.55	3.62
406	3.82	3.74	3.81	4.01	4.02
407	3.51	3.48	3.48	3.58	3.60
408	3.52	3.49	3.48	3.50	3.48
409	3.11	3.10	3.10	3.21	3.24
410	3.21	3.20	3.20	3.30	3.31
411	3.39	3.40	3.44	3.51	3.54
412	3.20	3.16	3.19	3.34	3.34
413	3.84	3.84	3.85	3.81	3.91
414	3.96	3.93	3.92	3.97	3.99
415	3.57	3.61	3.62	3.72	3.70
416	3.55	3.54	3.56	3.77	3.83
417	3.18	3.18	3.18	3.27	3.31
418	3.66	3.59	3.59	3.69	3.84
419	3.78	3.82	3.79	3.80	3.88
420	3.35	3.37	3.34	3.42	3.57
MEAN	3.52	3.51	3.52	3.61	3.65
S.D.	0.260	0.260	0.255	0.251	0.262
N	20	20	20	20	20

---: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 138

GROUP: 2-F

SEX: FEMALE

DOSE: 0.5 (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
421	3.50	3.48	3.52	3.32	3.42	3.55	3.42	3.48	3.54	3.53	3.60	3.65
422	3.42	3.21	3.33	3.23	3.26	3.25	3.24	3.21	3.27	3.30	3.32	3.34
423	3.68	3.42	3.53	3.42	3.40	3.41	3.41	3.46	3.47	3.51	3.54	3.59
424	3.48	3.30	3.42	3.32	3.30	3.33	3.32	3.35	3.39	3.42	3.41	3.46
425	--	--	--	--	--	--	--	--	--	--	--	--
426	3.46	3.26	3.23	3.25	3.24	3.25	3.25	3.31	3.31	3.30	3.34	3.33
427	3.64	3.65	3.49	3.56	3.63	3.57	3.63	3.70	3.67	3.71	3.76	3.79
428	3.56	3.44	3.51	3.31	3.36	3.37	3.37	3.40	3.37	3.43	3.45	3.44
429	3.17	3.06	3.00	3.05	3.06	3.07	3.08	3.09	3.15	3.18	3.23	3.24
430	3.62	3.39	3.36	3.41	3.45	3.37	3.48	3.53	3.57	3.51	3.57	3.59
431	3.78	3.63	3.67	3.71	3.66	3.68	3.61	3.66	3.76	3.72	3.76	3.79
432	3.44	3.44	3.26	3.38	3.36	3.40	3.41	3.45	3.46	3.52	3.61	3.70
433	3.78	3.66	3.69	3.69	3.65	3.65	3.66	3.66	3.69	3.73	3.75	3.77
434	3.34	3.34	3.22	3.29	3.29	3.34	3.33	3.30	3.38	3.36	3.45	3.51
435	3.38	3.10	3.06	3.09	3.15	3.15	3.16	3.20	3.22	3.23	3.26	3.27
436	4.08	3.89	3.87	3.80	3.78	3.82	3.86	3.83	3.85	3.85	3.87	3.84
437	3.40	3.45	3.42	3.38	3.39	3.33	3.35	3.38	3.42	3.41	3.47	3.51
438	3.82	3.66	3.70	3.69	3.71	3.66	3.73	3.66	3.74	3.74	3.76	3.80
439	3.12	2.94	3.00	2.96	2.97	2.99	3.00	2.99	3.01	3.04	3.07	3.09
440	3.35	3.31	3.29	3.20	3.26	3.30	3.20	3.26	3.31	3.32	3.29	3.32
MEAN	3.53	3.40	3.40	3.37	3.39	3.39	3.40	3.42	3.45	3.46	3.50	3.53
S.D.	0.234	0.235	0.242	0.232	0.221	0.217	0.225	0.221	0.223	0.216	0.219	0.223
N	19	19	19	19	19	19	19	19	19	19	19	19

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 138

GROUP: 2-F

SEX: FEMALE

DOSE: 0.5 (mg base/kg/day)

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

421	3.64	3.66	3.63	3.88	3.87
422	3.35	3.35	3.34	3.40	3.28
423	3.62	3.57	3.57	3.65	3.70
424	3.44	3.47	3.48	3.36	3.51
425	--	--	--	--	b
426	3.36	3.34	3.35	3.45	3.48
427	3.80	3.82	3.79	3.95	4.00
428	3.49	3.47	3.47	3.60	3.62
429	3.28	3.27	3.22	3.27	3.33
430	3.63	3.69	3.65	3.66	3.67
431	3.85	3.88	3.90	3.86	3.90
432	3.73	3.78	3.75	3.74	3.79
433	3.81	3.85	3.86	3.88	3.92
434	3.42	3.44	3.45	3.58	3.62
435	3.31	3.29	3.33	3.14	3.45
436	3.87	3.92	3.87	3.99	3.99
437	3.53	3.61	3.60	3.62	3.71
438	3.81	3.78	3.75	3.78	3.82
439	3.13	3.08	3.12	3.22	3.39
440	3.39	3.34	3.38	3.52	3.56

MEAN 3.55 3.56 3.55 3.61 3.66

S.D. 0.222 0.244 0.230 0.253 0.221

N 19 19 19 19 19

--: Data Unavailable

b: Scheduled Sacrifice

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 138

GROUP: 3-F

SEX: FEMALE

DOSE: 1.3 (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
441	3.50	3.45	3.56	3.54	3.52	3.47	3.39	3.50	3.54	3.68	3.59	3.75
442	3.23	3.00	3.17	3.13	3.10	3.12	3.12	3.16	3.18	3.21	3.27	3.23
443	3.80	3.75	3.84	3.77	3.73	3.73	3.76	3.72	3.83	3.89	3.84	3.90
444	3.55	3.34	3.35	3.31	3.28	3.34	3.35	3.37	3.40	3.45	3.46	3.51
445	3.63	3.45	3.41	3.36	3.45	3.38	3.38	3.43	3.54	3.58	3.63	3.67
446	3.43	3.42	3.21	3.13	3.15	3.26	3.27	3.35	3.39	3.40	3.46	3.43
447	3.17	3.08	3.03	3.03	3.03	3.00	3.01	3.05	3.07	3.08	3.08	3.08
448	3.52	3.34	3.33	3.37	3.34	3.37	3.39	3.41	3.45	3.49	3.54	3.55
449	3.62	3.57	3.39	3.39	3.43	3.40	3.38	3.42	3.46	3.49	3.52	3.52
450	3.45	3.27	3.24	3.31	3.35	3.38	3.37	3.39	3.39	3.38	3.38	3.40
451	4.06	3.92	4.02	3.97	3.88	3.95	3.95	4.00	4.00	4.02	4.01	4.07
452	3.25	3.04	3.15	3.10	3.15	3.12	3.08	3.13	3.18	3.22	3.26	3.28
453	3.83	3.38	3.53	3.49	3.49	3.52	3.52	3.54	3.57	3.62	3.64	3.70
454	3.59	3.43	3.47	3.45	3.45	3.46	3.45	3.47	3.51	3.55	3.59	3.61
455	3.89	3.50	3.47	3.53	3.57	3.55	3.52	3.59	3.57	3.63	3.60	3.67
456	3.88	3.75	3.69	3.72	3.66	3.72	3.68	3.70	3.77	3.78	3.80	3.81
457	3.18	3.06	3.04	3.07	3.00	3.06	3.06	3.06	3.12	3.13	3.17	3.21
458	3.38	3.31	3.26	3.27	3.28	3.33	3.32	3.31	3.32	3.30	3.34	3.36
459	3.55	3.42	3.39	3.43	3.36	3.42	3.40	3.39	3.40	3.45	3.46	3.46
460	3.83	3.70	3.59	3.66	3.68	3.75	3.81	3.79	3.65	3.69	3.86	3.81
MEAN	3.57	3.41	3.41	3.40	3.40	3.42	3.41	3.44	3.47	3.50	3.53	3.55
S.D.	0.256	0.250	0.253	0.251	0.240	0.245	0.250	0.243	0.236	0.247	0.239	0.253
N	20	20	20	20	20	20	20	20	20	20	20	20

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 138

GROUP: 3-F

SEX: FEMALE

DOSE: 1.3 (mg base/kg/day)

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

441	3.71	3.71	3.67	3.81	3.85
442	3.25	3.27	3.28	3.37	3.44
443	3.85	3.89	3.88	3.93	4.02
444	3.49	3.53	3.50	3.65	3.70
445	3.65	3.63	3.65	3.77	3.89
446	3.48	3.43	3.43	3.47	3.51
447	3.08	3.11	3.11	3.15	3.18
448	3.55	3.53	3.52	3.63	3.67
449	3.47	3.50	3.48	3.60	3.65
450	3.41	3.43	3.42	3.58	3.61
451	4.02	4.06	4.05	4.23	4.21
452	3.32	3.35	3.27	3.40	3.52
453	3.69	3.64	3.62	3.08	--
454	3.60	3.62	3.60	3.45	3.66
455	3.66	3.67	3.63	3.73	3.71
456	3.83	3.87	3.82	3.84	3.82
457	3.21	3.19	3.16	3.22	3.29
458	3.35	3.35	3.35	3.44	3.52
459	3.53	3.55	3.51	3.61	3.67
460	3.84	3.78	3.76	3.91	3.98

MEAN	3.55	3.56	3.54	3.59	3.68
S.D.	0.240	0.241	0.239	0.284	0.250
N	20	20	20	20	19

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 138

GROUP: 4-F

SEX: FEMALE

DOSE: 3.5 (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
461	3.70	3.65	3.62	3.59	3.58	3.54	3.52	3.53	3.58	3.64	3.69	3.73
462	3.42	3.31	3.42	3.24	3.25	3.27	3.26	3.31	3.35	3.37	3.42	3.48
463	3.40	3.20	3.32	3.25	3.23	3.25	3.13	3.28	3.30	3.33	3.35	3.31
464	--	--	--	--	--	--	--	--	--	--	--	--
465	3.66	3.49	3.54	3.51	3.45	3.48	3.42	3.52	3.52	3.44	3.59	3.62
466	3.59	3.55	3.43	3.53	3.51	3.52	3.45	3.57	3.60	3.63	3.65	3.61
467	3.36	3.28	3.27	3.25	3.23	3.26	3.25	3.26	3.26	3.29	3.34	3.34
468	3.56	3.39	3.39	3.46	3.46	3.39	3.47	3.45	3.48	3.54	3.62	3.70
469	3.54	3.45	3.42	3.43	3.43	3.50	3.48	3.51	3.49	3.49	3.52	3.49
470	3.30	3.12	3.16	3.09	3.16	3.14	3.13	3.14	3.17	3.19	3.23	3.25
471	3.80	3.60	3.62	3.60	3.62	3.62	3.60	3.61	3.64	3.67	3.70	3.76
472	3.35	3.16	3.13	3.21	3.20	3.22	3.24	3.22	3.22	3.27	3.31	3.34
473	3.82	3.65	3.67	3.66	3.70	3.64	3.71	3.71	3.71	3.69	3.73	3.74
474	3.48	3.40	3.37	3.41	3.41	3.40	3.41	3.44	3.45	3.48	3.54	3.53
475	3.65	3.49	3.62	3.59	3.57	3.63	3.68	3.72	3.70	3.75	3.75	3.77
476	3.64	3.52	3.44	3.45	3.48	3.45	3.47	3.36	3.49	3.49	3.55	3.55
477	4.11	3.82	3.72	3.72	3.72	3.73	3.80	3.77	3.80	3.84	3.84	3.88
478	3.58	3.22	3.25	3.42	3.22	3.39	3.24	3.42	3.41	3.22	3.29	3.38
479	3.26	3.26	3.24	3.21	3.13	3.12	3.13	3.14	3.22	3.23	3.21	3.22
480	3.61	3.49	3.52	3.40	3.44	3.42	3.35	3.40	3.49	3.45	3.32	3.39
MEAN	3.57	3.42	3.43	3.42	3.41	3.42	3.41	3.44	3.47	3.47	3.51	3.53
S.D.	0.206	0.189	0.174	0.175	0.184	0.175	0.200	0.188	0.181	0.192	0.194	0.198
N	19	19	19	19	19	19	19	19	19	19	19	19

---: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 138

GROUP: 4-F

SEX: FEMALE

DOSE: 3.5 (mg base/kg/day)

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

461	3.74	3.72	3.76	3.76	3.81
462	3.48	3.47	3.48	3.58	3.57
463	3.37	3.33	3.27	3.36	3.38
464	--	--	--	--	b
465	3.61	3.65	3.64	3.75	3.79
466	3.70	3.69	3.70	3.72	3.74
467	3.36	3.35	3.36	3.46	3.48
468	3.67	3.63	3.61	3.70	3.71
469	3.50	3.56	3.53	3.58	3.65
470	3.27	3.26	3.25	3.38	3.40
471	3.75	3.79	3.78	4.05	3.91
472	3.36	3.37	3.36	3.49	3.51
473	3.79	3.85	3.86	4.01	4.05
474	3.55	3.55	3.58	3.64	3.68
475	3.85	3.76	3.83	3.85	3.86
476	3.57	3.53	3.53	3.67	3.79
477	3.87	3.91	3.90	3.92	4.04
478	3.45	3.48	3.42	3.54	3.64
479	3.24	3.22	3.22	3.36	3.41
480	3.21	3.14	3.03	3.10	3.26

MEAN	3.54	3.54	3.53	3.63	3.67
S.D.	0.208	0.221	0.243	0.242	0.223
N	19	19	19	19	19

--: Data Unavailable

b: Scheduled Sacrifice

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 138

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
481	3.65	3.42	3.49	3.43	3.39	3.46	3.39	3.38	3.45	3.50	3.56	3.58
482	3.21	3.06	3.18	3.09	3.11	3.11	3.09	3.10	3.13	3.11	3.13	3.12
483	3.57	3.32	3.44	3.38	3.37	3.40	3.37	3.35	3.38	3.47	3.48	3.45
484	3.99	3.68	3.90	3.82	3.84	3.84	3.73	3.71	3.75	3.80	3.84	3.91
485	--	--	--	--	--	--	--	--	--	--	--	--
486	3.72	3.72	3.65	3.61	3.69	3.71	3.62	3.62	3.65	3.72	3.73	3.87
487	3.19	3.01	2.92	2.94	2.98	2.99	3.00	3.01	2.97	2.99	2.99	2.98
488	3.50	3.43	3.43	3.39	3.45	3.44	3.41	3.39	3.44	3.46	3.49	3.54
489	3.37	3.33	3.12	3.14	3.15	3.15	3.20	3.21	3.20	3.23	3.27	3.33
490	--	--	--	--	--	--	--	--	--	--	--	--
491	--	--	--	--	--	--	--	--	--	--	--	--
492	3.52	3.43	3.32	3.43	3.53	3.52	3.47	3.48	3.49	3.56	3.59	3.62
493	3.29	3.27	3.25	3.20	3.20	3.35	3.30	3.22	3.27	3.32	3.35	3.36
494	3.26	3.13	3.18	3.15	3.10	3.17	3.16	3.13	3.12	3.21	3.29	3.34
495	3.99	3.89	4.02	3.96	3.90	3.95	3.90	3.85	3.93	3.97	3.99	4.11
496	3.80	3.82	3.79	3.78	3.76	3.79	3.77	3.77	3.81	3.83	3.84	3.89
497	3.62	3.44	3.48	3.41	3.45	3.46	3.47	3.49	3.51	3.57	3.54	3.61
498	3.70	3.51	3.47	3.56	3.54	3.53	3.59	3.56	3.55	3.62	3.60	3.64
499	3.31	3.13	3.10	3.13	3.13	3.18	3.12	3.16	3.18	3.19	3.26	3.28
500	3.57	3.37	3.37	3.47	3.40	3.40	3.37	3.36	3.39	3.39	3.42	3.45
MEAN	3.54	3.41	3.42	3.41	3.41	3.44	3.41	3.40	3.42	3.47	3.49	3.53
S.D.	0.251	0.257	0.295	0.281	0.277	0.271	0.254	0.246	0.264	0.272	0.265	0.296
N	17	17	17	17	17	17	17	17	17	17	17	17

--: Data Unavailable

^a Retinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 138

GROUP: 5-F

SEX: FEMALE

DOSE: 300 (mg/kg/day)^a

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

481	3.56	3.52	3.52	3.59	3.66
482	3.18	3.16	3.14	3.20	3.21
483	3.45	3.44	3.44	3.44	3.59
484	3.99	4.01	3.99	3.99	4.01
485	--	--	--	--	b
486	3.94	3.84	3.85	3.84	3.87
487	2.97	2.99	3.01	3.02	3.03
488	3.54	3.54	3.53	3.57	3.59
489	3.34	3.29	3.28	d	d
490	--	--	--	--	b
491	--	--	--	--	b
492	3.64	3.72	3.63	3.68	3.68
493	3.34	3.37	3.35	3.48	3.55
494	3.32	3.29	3.30	3.39	3.45
495	4.17	4.07	4.18	3.96	3.96
496	3.84	3.85	3.83	3.90	3.99
497	3.65	3.65	3.65	3.76	3.76
498	3.70	3.68	3.68	3.74	3.86
499	3.28	3.30	3.29	3.35	3.49
500	3.46	3.45	3.46	3.39	3.51

MEAN 3.55 3.54 3.54 3.58 3.64

S.D. 0.312 0.299 0.308 0.278 0.274

N 17 17 17 16 16

--: Data Unavailable b: Scheduled Sacrifice d: Sacrificed Moribund

^a Retinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

U R A F T

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 138

GROUP: 1-F

SEX: FEMALE

DOSE: 0 (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
401	-0.19	0.05	-0.04	0.09	-0.04	0.05	0.06	0.04	0.03	0.03	0.00
402	0.02	-0.02	0.10	0.04	0.01	0.08	0.02	-0.02	0.06	-0.01	0.01
403	-0.15	0.10	-0.04	0.03	0.08	0.04	0.01	0.03	-0.05	0.06	0.06
404	-0.08	0.04	0.01	0.02	-0.01	0.04	-0.02	0.09	0.01	0.01	0.00
405	-0.21	0.07	0.05	-0.04	0.08	-0.02	-0.01	0.05	0.04	-0.02	0.01
406	0.01	0.04	-0.03	0.06	-0.02	0.08	0.03	0.02	0.07	0.01	-0.08
407	0.06	-0.03	-0.01	0.01	-0.01	0.03	-0.10	0.14	0.04	0.03	-0.03
408	0.06	0.00	-0.02	0.06	-0.12	0.02	0.06	-0.02	0.00	0.03	-0.03
409	0.04	0.00	0.03	0.02	-0.01	0.00	-0.01	0.05	0.01	-0.01	-0.01
410	-0.03	-0.01	-0.01	0.02	0.02	-0.01	0.00	0.02	0.05	0.04	-0.01
411	-0.06	0.01	0.02	0.04	-0.01	0.00	-0.07	0.10	0.07	-0.03	0.01
412	0.07	0.03	0.08	-0.09	0.10	0.01	-0.02	0.03	0.00	0.07	-0.04
413	-0.07	0.02	0.06	0.10	-0.02	-0.02	0.06	0.10	0.00	0.00	0.00
414	-0.03	0.07	0.01	0.03	0.01	-0.01	0.04	0.09	0.05	0.03	-0.03
415	-0.03	0.04	-0.03	0.03	-0.02	0.06	0.03	-0.01	0.02	-0.01	0.04
416	-0.06	0.01	0.05	-0.01	0.07	-0.11	0.07	0.05	0.02	0.03	-0.01
417	0.01	-0.01	0.02	-0.01	-0.01	0.03	-0.01	0.05	-0.01	0.03	0.00
418	0.05	0.03	-0.05	0.00	0.03	0.02	0.05	0.02	0.01	0.04	-0.07
419	0.01	-0.02	0.00	0.02	-0.02	0.08	0.04	0.00	0.00	-0.01	0.04
420	-0.03	-0.02	0.01	-0.01	0.01	0.02	0.03	0.01	0.03	-0.01	0.02
MEAN	-0.03	0.02	0.01	0.02	0.01	0.02	0.01	0.04	0.02	0.02	-0.01
S.O.	0.080	0.035	0.042	0.043	0.050	0.044	0.044	0.044	0.030	0.027	0.035
N	20	20	20	20	20	20	20	20	20	20	20

--: Data Unavailable

^a Successive periods

^b Baseline is day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (kilograms)^a

STUDY: 138

GROUP: 1-F

SEX: FEMALE

DOSE: 0 (mg base/kg/day)

ANIMAL # DAY 18 DAY 24 DAY 29 TOTAL
GAIN

401	-0.02	0.06	0.07	0.19
402	-0.02	0.16	0.05	0.48
403	-0.07	0.12	0.04	0.26
404	0.02	0.11	0.01	0.25
405	0.00	0.09	0.07	0.16
406	0.07	0.20	0.01	0.47
407	0.00	0.10	0.02	0.25
408	-0.01	0.02	-0.02	0.03
409	0.00	0.11	0.03	0.25
410	0.00	0.10	0.01	0.19
411	0.04	0.07	0.03	0.22
412	0.03	0.15	0.00	0.42
413	0.01	-0.04	0.10	0.30
414	-0.01	0.05	0.02	0.32
415	0.01	0.10	-0.02	0.21
416	0.02	0.21	0.06	0.40
417	0.00	0.09	0.04	0.22
418	0.00	0.10	0.15	0.38
419	-0.03	0.01	0.08	0.20
420	-0.03	0.08	0.15	0.26

MEAN 0.00 0.09 0.05 0.27

S.O. 0.029 0.050 0.048 0.112

N 20 20 20 20

--: Data Unavailable

b: Scheduled Sacrifice

^aSuccessive periods

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 138

GROUP: 2-F

SEX: FEMALE

DOSE: 0.5 (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
421	-0.20	0.10	0.13	-0.13	0.06	0.06	-0.01	0.07	0.05	-0.01	0.02
422	-0.10	0.03	-0.01	-0.01	-0.03	0.06	0.03	0.02	0.02	0.01	0.00
423	-0.11	-0.02	0.01	0.00	0.05	0.01	0.04	0.03	0.05	0.03	-0.05
424	-0.10	-0.02	0.03	-0.01	0.03	0.04	0.03	-0.01	0.05	-0.02	0.03
425	--	--	--	--	--	--	--	--	--	--	--
426	0.02	-0.01	0.01	0.00	0.06	0.00	-0.01	0.04	-0.01	0.03	-0.02
427	0.07	0.07	-0.06	0.06	0.07	-0.03	0.04	0.05	0.03	0.01	0.02
428	-0.20	0.05	0.01	0.00	0.03	-0.03	0.06	0.02	-0.01	0.05	-0.02
429	0.05	0.01	0.01	0.01	0.01	0.06	0.03	0.05	0.01	0.04	-0.01
430	0.05	0.04	-0.08	0.11	0.05	0.04	-0.06	0.06	0.02	0.04	0.06
431	0.04	-0.05	0.02	-0.07	0.05	0.10	-0.04	0.04	0.03	0.06	0.03
432	0.12	-0.02	0.04	0.01	0.04	0.01	0.06	0.09	0.09	0.03	0.05
433	0.00	-0.04	0.00	0.01	0.00	0.03	0.04	0.02	0.02	0.04	0.04
434	0.07	0.00	0.05	-0.01	-0.03	0.08	-0.02	0.09	0.06	-0.09	0.02
435	0.03	0.06	0.00	0.01	0.04	0.02	0.01	0.03	0.01	0.04	-0.02
436	-0.07	-0.02	0.04	0.04	-0.03	0.02	0.00	0.02	-0.03	0.03	0.05
437	-0.04	0.01	-0.06	0.02	0.03	0.04	-0.01	0.06	0.04	0.02	0.08
438	-0.01	0.02	-0.05	0.07	-0.07	0.08	0.00	0.02	0.04	0.01	-0.03
439	-0.04	0.01	0.02	0.01	-0.01	0.02	0.03	0.03	0.02	0.04	-0.05
440	-0.09	0.06	0.04	-0.10	0.06	0.05	0.01	-0.03	0.03	0.07	-0.05
MEAN	-0.03	0.01	0.01	0.00	0.02	0.03	0.01	0.04	0.03	0.02	0.01
S.D.	0.090	0.040	0.048	0.055	0.039	0.035	0.032	0.030	0.028	0.035	0.040
N	19	19	19	19	19	19	19	19	19	19	19

--- Data Unavailable

^a Successive periods

^b Baseline is day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 138

GROUP: 2-F

SEX: FEMALE

DOSE: 0.5(mg base/kg/day)

ANIMAL #	DAY 18	DAY 24	DAY 29	TOTAL GAIN
421	-0.03	0.25	-0.01	0.35
422	-0.01	0.06	-0.12	-0.05
423	0.00	0.08	0.05	0.17
424	0.01	-0.12	0.15	0.09
425	--	--	b	--
426	0.01	0.10	0.03	0.25
427	-0.03	0.16	0.05	0.51
428	0.00	0.13	0.02	0.11
429	-0.05	0.05	0.06	0.33
430	-0.04	0.01	0.01	0.31
431	0.02	-0.04	0.04	0.23
432	-0.03	-0.01	0.05	0.53
433	0.01	0.02	0.04	0.23
434	0.01	0.13	0.04	0.40
435	0.04	-0.19	0.31	0.39
436	-0.05	0.12	0.00	0.12
437	-0.01	0.02	0.09	0.29
438	-0.03	0.03	0.04	0.12
439	0.04	0.10	0.17	0.39
440	0.04	0.14	0.04	0.27

MEAN -0.01 0.05 0.06 0.27

S.D. 0.029 0.102 0.085 0.149

N 19 19 19 19

--: Data Unavailable

b: Scheduled Sacrifice

^aSuccessive periods

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 138

GROUP: 3-F

SEX: FEMALE

DOSE: 1.3 (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
441	-0.02	-0.02	-0.05	-0.08	0.11	0.04	0.14	-0.09	0.16	-0.04	0.00
442	-0.04	-0.03	0.02	0.00	0.04	0.02	0.03	0.06	-0.04	0.02	0.02
443	-0.07	-0.04	0.00	0.03	-0.04	0.11	0.06	-0.05	0.06	-0.05	0.04
444	-0.04	-0.03	0.06	0.01	0.02	0.03	0.05	0.01	0.05	-0.02	0.04
445	-0.05	0.09	-0.07	0.00	0.05	0.11	0.04	0.05	0.04	-0.02	-0.02
446	-0.08	0.02	0.11	0.01	0.08	0.04	0.01	0.06	-0.03	0.05	-0.05
447	0.00	0.00	-0.03	0.01	0.04	0.02	0.01	0.00	0.00	0.00	0.03
448	0.04	-0.03	0.03	0.02	0.02	0.04	0.04	0.05	0.01	0.00	-0.02
449	0.00	0.04	-0.03	-0.02	0.04	0.04	0.03	0.03	0.00	-0.05	0.03
450	0.07	0.04	0.03	-0.01	0.02	0.00	-0.01	0.00	0.02	0.01	0.02
451	-0.05	-0.09	0.07	0.00	0.05	0.00	0.02	-0.01	0.06	-0.05	0.04
452	-0.05	0.05	-0.03	-0.04	0.05	0.05	0.04	0.04	0.02	0.04	0.03
453	-0.04	0.00	0.03	0.00	0.02	0.03	0.05	0.02	0.06	-0.01	-0.05
454	-0.02	0.00	0.01	-0.01	0.02	0.04	0.04	0.04	0.02	-0.01	0.02
455	0.06	0.04	-0.02	-0.03	0.07	-0.02	0.06	-0.03	0.07	-0.01	0.01
456	0.03	-0.06	0.06	-0.04	0.02	0.07	0.01	0.02	0.01	0.02	0.04
457	0.03	-0.07	0.06	0.00	0.00	0.06	0.01	0.04	0.04	0.00	-0.02
458	0.01	0.01	0.05	-0.01	-0.01	0.01	-0.02	0.04	0.02	-0.01	0.00
459	0.04	-0.07	0.06	-0.02	-0.01	0.01	0.05	0.01	0.00	0.07	0.02
460	0.07	0.02	0.07	0.06	-0.02	-0.14	0.04	0.17	-0.05	0.03	-0.06
MEAN	-0.01	-0.01	0.02	-0.01	0.03	0.03	0.04	0.02	0.03	0.00	0.01
S.D.	0.047	0.047	0.048	0.029	0.036	0.051	0.033	0.052	0.046	0.033	0.032
N	20	20	20	20	20	20	20	20	20	20	20

--: Data Unavailable

^aSuccessive periods

^bBaseline is day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 138

GROUP: 3-F

SEX: FEMALE

DOSE: 1.3 (mg base/kg/day)

ANIMAL #	DAY 18	DAY 24	DAY 29	TOTAL GAIN
441	-0.04	0.14	0.04	0.29
442	0.01	0.09	0.07	0.27
443	-0.01	0.05	0.09	0.18
444	-0.03	0.15	0.05	0.35
445	0.02	0.12	0.12	0.48
446	0.00	0.04	0.04	0.30
447	0.00	0.04	0.03	0.15
448	-0.01	0.11	0.04	0.34
449	-0.02	0.12	0.05	0.26
450	-0.01	0.16	0.03	0.37
451	-0.01	0.18	-0.02	0.19
452	-0.08	0.13	0.12	0.37
453	-0.02	-0.54	--	-0.45
454	-0.02	-0.15	0.21	0.19
455	-0.04	0.10	-0.02	0.24
456	-0.05	0.02	-0.02	0.13
457	-0.03	0.06	0.07	0.25
458	0.00	0.09	0.08	0.26
459	-0.04	0.10	0.06	0.28
460	-0.02	0.15	0.07	0.39

MEAN	-0.02	0.06	0.06	0.24
S.O.	0.023	0.158	0.055	0.185
N	20	20	19	20

--: Data Unavailable

b: Scheduled Sacrifice

^a Successive periods

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (kilograms)^a

STUDY: 138

GROUP: 4-F

SEX: FEMALE

DOSE: 3.5 (mg base/kg/day)

ANIMAL #	OAY 7 ^b	OAY 8	OAY 9	OAY 10	OAY 11	OAY 12	OAY 13	OAY 14	OAY 15	OAY 16	OAY 17
461	-0.03	-0.01	-0.04	-0.02	0.01	0.05	0.06	0.05	0.04	0.01	-0.02
462	-0.18	0.01	0.02	-0.01	0.05	0.04	0.02	0.05	0.06	0.00	-0.01
463	-0.07	-0.02	0.02	-0.12	0.15	0.02	0.03	0.02	-0.04	0.06	-0.04
464	--	--	--	--	--	--	--	--	--	--	--
465	-0.03	-0.06	0.03	-0.06	0.10	0.00	-0.08	0.15	0.03	-0.01	0.04
466	0.10	-0.02	0.01	-0.07	0.12	0.03	0.03	0.02	-0.04	0.09	-0.01
467	-0.02	-0.02	0.03	-0.01	0.01	0.00	0.03	0.05	0.00	0.02	-0.01
468	0.07	0.00	-0.07	0.08	-0.02	0.03	0.06	0.08	0.08	-0.03	-0.04
469	0.01	0.00	0.07	-0.02	0.03	-0.02	0.00	0.03	-0.03	0.01	0.06
470	-0.07	0.07	-0.02	-0.01	0.01	0.03	0.02	0.04	0.02	0.02	-0.01
471	-0.02	0.02	0.00	-0.02	0.01	0.03	0.03	0.03	0.06	-0.01	0.04
472	0.08	-0.01	0.02	0.02	-0.02	0.00	0.05	0.04	0.03	0.02	0.01
473	-0.01	0.04	-0.06	0.07	0.00	0.00	-0.02	0.04	0.01	0.05	0.06
474	0.04	0.00	-0.01	0.01	0.03	0.01	0.03	0.06	-0.01	0.02	0.00
475	-0.03	-0.02	0.06	0.05	0.04	-0.02	0.05	0.00	0.02	0.08	-0.09
476	0.01	0.03	-0.03	0.02	-0.11	0.13	0.00	0.06	0.00	0.02	-0.04
477	0.00	0.00	0.01	0.07	-0.03	0.03	0.04	0.00	0.04	-0.01	0.04
478	0.17	-0.20	0.17	-0.15	0.18	-0.01	-0.19	0.07	0.09	0.07	0.03
479	-0.03	-0.08	-0.01	0.01	0.01	0.08	0.01	-0.02	0.01	0.02	-0.02
480	-0.12	0.04	-0.02	-0.07	0.05	0.09	-0.04	-0.13	0.07	-0.18	-0.07
MEAN	-0.01	-0.01	0.01	-0.01	0.03	0.03	0.01	0.03	0.02	0.01	0.00
S.O.	0.079	0.057	0.053	0.062	0.067	0.039	0.059	0.054	0.038	0.057	0.042
N	19	19	19	19	19	19	19	19	19	19	19

--: Data Unavailable

^a Successive periods

^b Baseline is day 6

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (kilograms)^a

STUDY: 138

GROUP: 4-F

SEX: FEMALE

DOSE: 3.5 (mg base/kg/day)

ANIMAL #	DAY 18	DAY 24	DAY 29	TOTAL GAIN
461	0.04	0.00	0.05	0.19
462	0.01	0.10	-0.01	0.15
463	-0.06	0.09	0.02	0.06
464	--	--	b	--
465	-0.01	0.11	0.04	0.25
466	0.01	0.02	0.02	0.31
467	0.01	0.10	0.02	0.21
468	-0.02	0.09	0.01	0.32
469	-0.03	0.05	0.07	0.23
470	-0.01	0.13	0.02	0.24
471	-0.01	0.27	-0.14	0.29
472	-0.01	0.13	0.02	0.38
473	0.01	0.15	0.04	0.38
474	0.03	0.06	0.04	0.31
475	0.07	0.02	0.01	0.24
476	0.00	0.14	0.12	0.35
477	-0.01	0.02	0.12	0.32
478	-0.06	0.12	0.10	0.39
479	0.00	0.14	0.05	0.17
480	-0.11	0.07	0.16	-0.26
MEAN	-0.01	0.10	0.04	0.24
S.D.	0.039	0.063	0.063	0.149
N	19	19	19	19

--: Data Unavailable

b: Scheduled Sacrifice

^aSuccessive periods

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 138

GROUP: 5-F

SEX: FEMALE

DOSE: 300 (mg/kg/day)^c

ANIMAL #	DAY 7 ^b	DAY 8	DAY 9	DAY 10	DAY 11	DAY 12	DAY 13	DAY 14	DAY 15	DAY 16	DAY 17
481	-0.06	-0.04	0.07	-0.07	-0.01	0.07	0.05	0.06	0.02	-0.02	-0.04
482	-0.09	0.02	0.00	-0.02	0.01	0.03	-0.02	0.02	-0.01	0.06	-0.02
483	-0.06	-0.01	0.03	-0.03	-0.02	0.03	0.09	0.01	-0.03	0.00	-0.01
484	-0.08	0.02	0.00	-0.11	-0.02	0.04	0.05	0.04	0.07	0.08	0.02
485	--	--	--	--	--	--	--	--	--	--	--
486	-0.04	0.08	0.02	-0.09	0.00	0.03	0.07	0.01	0.14	0.07	-0.10
487	0.02	0.04	0.01	0.01	0.01	-0.04	0.02	0.00	-0.01	-0.01	0.02
488	-0.04	0.06	-0.01	-0.03	-0.02	0.05	0.02	0.03	0.05	0.00	0.00
489	0.02	0.01	0.00	0.05	0.01	-0.01	0.03	0.04	0.06	0.01	-0.05
490	--	--	--	--	--	--	--	--	--	--	--
491	--	--	--	--	--	--	--	--	--	--	--
492	0.11	0.10	-0.01	-0.05	0.01	0.01	0.07	0.03	0.03	0.02	0.08
493	-0.05	0.00	0.15	-0.05	-0.08	0.05	0.05	0.03	0.01	-0.02	0.03
494	-0.03	-0.05	0.07	-0.01	-0.03	-0.01	0.09	0.08	0.05	-0.02	-0.03
495	-0.06	-0.06	0.05	-0.05	-0.05	0.08	0.04	0.02	0.12	0.06	-0.10
496	-0.01	-0.02	0.03	-0.02	0.00	0.04	0.02	0.01	0.05	-0.05	0.01
497	-0.07	0.04	0.01	0.01	0.02	0.02	0.06	-0.03	0.07	0.04	0.00
498	0.09	-0.02	-0.01	0.06	-0.03	-0.01	0.07	-0.02	0.04	0.06	-0.02
499	0.03	0.00	0.05	-0.06	0.04	0.02	0.01	0.07	0.02	0.00	0.02
500	0.10	-0.07	0.00	-0.03	-0.01	0.03	0.00	0.03	0.03	0.01	-0.01
MEAN	-0.01	0.01	0.03	-0.03	-0.01	0.03	0.04	0.03	0.04	0.02	-0.01
S.D.	0.064	0.048	0.041	0.045	0.028	0.031	0.031	0.029	0.044	0.038	0.045
N	17	17	17	17	17	17	17	17	17	17	17

--: Data Unavailable

^aSuccessive periods

^bBaseline is day 6

^cRetinol Palmitate given on GD9 and GD10 only

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL WEIGHT GAIN (Kilograms)^a

STUDY: 138

GROUP: 5-F

SEX: FEMALE

DOSE: 300 (mg/kg/day)^c

ANIMAL #	DAY 18	DAY 24	DAY 29	TOTAL GAIN
----------	--------	--------	--------	------------

481	0.00	0.07	0.07	0.17
482	-0.02	0.06	0.01	0.03
483	0.00	0.00	0.15	0.15
484	-0.02	0.00	0.02	0.11
485	--	--	b	--
486	0.01	-0.01	0.03	0.22
487	0.02	0.01	0.01	0.11
488	-0.01	0.04	0.02	0.16
489	-0.01	d	d	--
490	--	--	b	--
491	--	--	b	--
492	-0.09	0.05	0.00	0.36
493	-0.02	0.13	0.07	0.30
494	0.01	0.09	0.06	0.27
495	0.11	-0.22	0.00	-0.06
496	-0.02	0.07	0.09	0.20
497	0.00	0.11	0.00	0.28
498	0.00	0.06	0.12	0.39
499	-0.01	0.06	0.14	0.39
500	0.01	-0.07	0.12	0.14

MEAN	0.00	0.03	0.06	0.20
S.D.	0.038	0.083	0.053	0.127
N	17	16	16	16

--: Data Unavailable b: Scheduled Sacrifice d: Sacrificed Moribund

^aSuccessive periods

^cRetinol Palmitate given on GD9 and GD10 only

DRAFT

APPENDIX 4

Individual Maternal Food Consumption Data

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 138

GROUP: 1-F

SEX: FEMALE

DOSE: 0 (mg base/kg/day)

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

401	130	130	130	130	130	130	130
402	130	130	130	130	130	130	130
403	130	130	130	130	130	130	130
404	130	130	130	130	130	130	130
405	130	130	130	130	130	130	130
406	130	130	130	130	130	130	130
407	130	130	130	130	130	130	130
408	130	130	130	130	130	130	130
409	130	130	130	130	130	130	130
410	130	130	130	103	130	130	130
411	130	130	130	130	130	130	130
412	130	130	130	130	130	130	130
413	130	130	130	130	130	130	130
414	130	130	130	130	130	130	130
415	130	130	130	130	130	130	130
416	130	130	130	130	130	130	130
417	130	130	130	130	130	130	130
418	130	130	130	130	130	130	130
419	130	130	130	130	130	130	130
420	130	130	130	130	130	130	130

MEAN	130	130	130	129	130	130	130
S.D.	0.0	0.0	0.0	6.0	0.0	0.0	0.0
N	20	20	20	20	20	20	20

---: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 138

GROUP: 2-F

SEX: FEMALE

DOSE: 0.5 (mg base/kg/day)

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

421	130	130	130	130	130	130	130
422	130	130	130	130	130	130	130
423	130	130	130	130	130	130	130
424	130	130	130	130	130	130	130
425	--	--	--	--	--	--	--
426	130	130	130	130	130	130	130
427	130	130	130	130	130	130	130
428	130	130	130	130	130	130	130
429	130	130	130	130	130	130	130
430	130	130	130	130	130	130	130
431	130	130	130	130	130	130	130
432	130	130	130	130	130	130	130
433	130	130	130	130	130	130	130
434	130	130	130	130	130	130	130
435	130	130	130	130	130	130	130
436	130	130	130	130	130	130	130
437	130	130	130	130	130	130	130
438	130	130	130	130	130	130	130
439	130	130	130	130	130	130	130
440	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	19	19	19	19	19	19	19

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 138

GROUP: 3-F

SEX: FEMALE

DOSE: 1.3 (mg base/kg/day)

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

441	130	130	130	130	130	130	130
442	130	130	130	130	130	130	130
443	130	130	130	130	130	130	130
444	130	130	130	130	130	130	130
445	130	130	130	130	130	130	130
446	42	130	130	101	130	130	130
447	130	130	130	130	130	130	130
448	130	130	130	130	130	130	130
449	130	130	130	130	130	130	130
450	130	130	130	130	130	130	130
451	130	130	130	130	130	130	130
452	130	130	130	130	130	130	130
453	130	130	130	130	130	130	--
454	130	130	130	130	130	130	130
455	130	130	130	130	130	130	130
456	130	130	130	130	130	130	130
457	130	130	130	130	130	130	130
458	130	130	130	130	130	130	130
459	130	130	130	130	130	130	130
460	130	130	130	130	130	130	130

MEAN	126	130	130	129	130	130	130
S.D.	19.7	0.0	0.0	6.5	0.0	0.0	0.0
N	20	20	20	20	20	20	19

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 138

GROUP: 4-F

SEX: FEMALE

DOSE: 3.5 (mg base/kg/day)

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

461	130	130	130	130	0	130	130
462	130	130	130	130	130	130	130
463	130	130	130	130	130	130	130
464	--	--	--	--	--	--	--
465	130	130	130	130	130	130	130
466	130	130	130	130	130	130	130
467	130	130	130	130	130	130	130
468	130	130	130	130	130	130	130
469	130	130	130	130	130	130	130
470	130	130	130	130	117	130	130
471	130	130	130	130	130	130	130
472	130	130	130	130	130	130	130
473	130	130	130	130	130	130	130
474	130	130	130	130	130	130	130
475	130	130	130	130	130	130	130
476	130	130	130	130	130	130	130
477	130	130	130	130	130	130	130
478	130	130	66	130	130	130	130
479	130	130	130	130	130	130	130
480	130	130	0	100	0	130	130

MEAN	130	130	120	128	116	130	130
S.D.	0.0	0.0	32.5	6.9	40.9	0.0	0.0
N	19	19	19	19	19	19	19

--: Data Unavailable

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

DRAFT
INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 138

GROUP: 5-F

SEX: FEMALE

DOSE: 300 (mg/kg/day)^a

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

481	130	130	130	130	130	130	130
482	130	130	130	130	130	130	130
483	130	130	130	130	130	130	130
484	130	130	130	130	130	130	130
485	--	--	--	--	--	--	--
486	130	130	130	130	130	130	130
487	130	130	130	130	130	130	130
488	130	130	130	130	130	130	130
489	130	130	130	130	130	d	d
490	--	--	--	--	--	--	--
491	--	--	--	--	--	--	--
492	130	130	130	130	130	130	130
493	130	130	130	130	130	130	130
494	130	130	130	130	130	130	130
495	130	130	130	130	130	130	130
496	130	130	130	130	130	130	130
497	130	130	130	130	130	130	130
498	130	130	130	130	130	130	130
499	130	130	130	130	130	130	130
500	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	17	17	17	17	17	16	16

--: Data Unavailable

d: Sacrificed Moribund

^a Retinol Palmitate given on GD9 and GD10 only

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APPENDIX 5
Teratology Report



Pathology Associates, Inc.

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TERATOLOGY REPORT

FOR

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

UIC/TRL STUDY NUMBER: 138

PREPARED FOR

TOXICOLOGY RESEARCH LABORATORY (TRL)
UNIVERSITY OF ILLINOIS AT CHICAGO (UIC)
DEPARTMENT OF PHARMACOLOGY
1940 W. TAYLOR ST.
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Study No. 138

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I. 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. 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 Teratologist</u>
03/30/95	Skeletal Examination	03/30/95
04/05/95	Individual Animal Data (Raw Data)	04/17/95
04/07/95	Individual Animal Data (Data Entry)	04/17/95
04/14/95	Draft Teratology Report	04/17/95

Patricia L. Bussard
Quality Assurance Auditor

April 17, 1995

Date

TRL STUDY NUMBER: 138
DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

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Study No. 138

Developmental Toxicity (Segment II) Study of WR242511 in Rabbits

II. MATERIALS AND METHODS

A. Cesarean Section

On gestation day 29, all 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 removed from the body. A gross necropsy was then performed. Abnormalities were recorded. Gross findings did not indicate the necessity of retaining any tissue samples containing gross lesions in 10% neutral buffered formalin 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.

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B. 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 and euthanized by intraperitoneal injection of a 40% sodium pentobarbital solution (approximately 0.4 ml/fetus).

2. Visceral Examination

Each fetus was dissected and the abdominal, thoracic and cranial cavities opened and the internal organs 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 retained in 95% alcohol for skeletal examination. These fetuses were macerated in 1% potassium hydroxide, stained with Alizarin Red S and cleared with glycerin (Dawson, 1926). The fetuses were then examined for skeletal formation and ossification.

C. 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 a one-way analysis of variance (ANOVA). If a significant F ratio was obtained ($p \leq 0.05$), Dunnett's test was used for pairwise comparisons of each treatment groups to the 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 pairwise comparisons of each treated group to the control group.

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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 by 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 IBMTM compatible computer with SAS computer programs (SAS/STAT User's Guide, 1989).

III. RESULTS

A. Survival and Pregnancy

Table 1 (Summary Data)

One female each in the 1.3 mg base/kg/day group aborted on gestation day 27 and one female in the 3.5 mg base/kg/day group prematurely delivered on gestation day 29. One female in the positive control group aborted on gestation day 22. The pregnancy rate was 100% in the vehicle control and the 1.3 mg base/kg/day groups, 95% in the 0.5 and 3.5 mg base/kg/day groups and 85% in the positive control group.

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B. Maternal Gross Necropsy

Table 2 (Summary Data)
Appendix A (Individual Data)

No apparent treatment-related changes were observed in the 0.5, 1.3 and 3.5 mg base/kg/day groups or in the positive control group.

C. Cesarean Section Data

Table 3 (Summary Data)
Appendices B and C (Individual Data)

There were no biologically meaningful differences between the vehicle control and the WR242511 treated groups in the cesarean section parameters measured, including the mean numbers of corpora lutea, implantation sites, pre-implantation loss, viable and nonviable fetuses, early and late resorptions, post-implantation loss, total loss/litter, fetal sex ratios, and gravid uterus and fetal weights. In the 3.5 mg base/kg/day group, slight increases were noted in the mean number of early resorptions and percentages of post-implantation loss and total loss/litter. The increases were attributed to one litter with total resorptions and were, therefore, not considered to be related to treatment with WR242511. Treatment-related differences noted in the positive control group included statistically significant increases in the numbers of early resorptions, and the percent post-implantation loss, the percent total loss/litter and a corresponding decrease in the mean number of viable fetuses. In addition, the gravid uterus weight was significantly reduced in the positive control group. The reduction in the uterus weight was attributable to the reduced number of viable fetuses in the group.

D. Fetal Morphological Observations

Tables 4-7 (Summary Data)
Appendix D (Individual Data)

No statistically significant or apparent treatment-related malformations or developmental variations were observed at the 0.5, 1.3 or 3.5 mg base/kg/day levels. 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 cranium, jaws, palate, and pinnae. In

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addition, a significant increase in tail anomalies was noted. The visceral malformations primarily included kidney and/or ureter anomalies. Skeletal malformations included skull, vertebral, caudal vertebrae and hyoid anomalies. The incidences of developmental variations in the positive control group was comparable to the vehicle control group.

IV. DISCUSSION AND CONCLUSIONS

This study was conducted to evaluate the embryo/fetal toxicity and the teratogenic potential of WR242511 in rabbits.

One female each in the 1.3 and 3.5 mg base/kg/day groups prematurely delivered. Premature delivery is not uncommon and the low incidence observed in this study did not indicate any treatment-related effects. Overall pregnancy and maternal gross necropsy findings were not affected by treatment with WR242511. Cesarean section data were comparable between the vehicle control and the 0.5, 1.3 and 3.5 mg base/kg/day groups. Similarly, no biologically meaningful differences were noted in the fetal morphological examination data from the vehicle control vs the WR242511 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 the 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), kidneys and ureters, and vertebral column (including the tail).

In conclusion, no maternal toxicity was observed, as determined by survival and gross necropsy findings. No evidence of embryo/fetal toxicity or teratogenicity was produced at any level tested. The no-effect level for developmental toxicity of WR242511 in rabbits was established at 3.5 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.

Date:

Michael D. Mercieca, B.S.
Teratologist

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V. REFERENCES

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

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

TABLE 1

SUMMARY OF PREGNANCY STATUS

GROUP: DOSE LEVEL (MG BASE/KG/DAY):	1 0	2 0.5	3 1.3	4 3.5	5 300 MG/KG/DAY*
	No.	%	No.	%	No.
FEMALES ON STUDY	20		20		20
FOUND DEAD/EUTHANIZED PREMATURE DELIVERY/ABORTION	0	0.0	0	0.0	0
	0	0.0	1	5.0	1
EXAMINED AT CESAREAN SECTION NONGRAVID	20	100.0	20	100.0	19
	0	0.0	1	5.0	0
GRAVID	20	100.0	19	95.0	18
WITH TOTAL RESORPTIONS	0	0.0	0	0.0	1
WITH LIVE FETUSES	20	100.0	19	100.0	15
TOTAL GRAVID FEMALES	20	100.0	19	95.0	17

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

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TABLE 2

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

SUMMARY OF GROSS NECROPSY OBSERVATIONS

	GROUP: DOSE LEVEL (MG BASE/KG/DAY):				
	1	2	3	4	5
	0	0.5	1.3	3.5	300 MG/KG/DAY ^a
NUMBER OF FEMALES EXAMINED AT THE SCHEDULED GESTATION DAY 29 CESAREAN SECTION	20	20	20 ^b	20 ^b	20 ^b
NO ABNORMALITIES DETECTED	20	20	18 ^c	17 ^c	17 ^c
NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE	0	1	0	1	3
GRAVID - AMMONIUM SULFIDE TEST POSITIVE	0	0	0	0	1
UTERUS					
- GREEN MUCOID MATERIAL	0	0	0	1	0

^a RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10).^b DOES NOT INCLUDE FINDINGS FOR ONE FEMALE IN GROUP 3 AND TWO FEMALES EACH IN GROUPS 4 AND 5 WHICH WERE NOT RECORDED.^c DOES NOT INCLUDE FEMALES WHICH PREMATURELY DELIVERED/ABORTED (SEE APPENDIX A FOR INDIVIDUAL FINDINGS).

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TABLE 3

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS
SUMMARY OF CESAREAN SECTION DATA

GROUP: DOSE LEVEL (MG BASE/KG/DAY):		1	2	3	4	5
		0	0.5	1.3	3.5	300 MG/KG/DAY ^a
NUMBER OF GRAVID FEMALES		20	19	19	18	16
NUMBER OF CORPORA LUTEA	MEAN	9.3 ^b	8.9	8.9	9.1 ^b	9.1 ^{b,c}
	S.D.	1.6	2.2	2.2	1.8	1.9
NUMBER OF IMPLANTATIONS	MEAN	9.1	8.5	8.6	8.3	7.4
	S.D.	1.7	2.5	2.0	2.2	2.6
PERCENT PRE-IMPLANTATION LOSS	MEAN	3.8	5.8	3.1	9.3	17.9
	S.D.	8.6	12.7	4.7	17.9	27.6
NUMBER OF VIABLE FETUSES	MEAN	8.4	8.1	8.1	7.4	5.1*
	S.D.	1.7	2.4	2.0	2.9	2.9
NUMBER OF NONVIABLE FETUSES	MEAN	0.0	0.0	0.0	0.0	0.0
	S.D.	0.0	0.0	0.0	0.0	0.0
NUMBER OF EARLY RESORPTIONS	MEAN	0.5	0.4	0.3	0.8	1.9*
	S.D.	0.7	1.0	0.7	1.9	2.4
NUMBER OF LATE RESORPTIONS	MEAN	0.2	0.0	0.2	0.2	0.3
	S.D.	0.7	0.0	0.7	0.4	0.7
PERCENT POST-IMPLANTATION LOSS	MEAN	7.4	3.6	5.7	11.5	29.5*
	S.D.	8.9	9.4	9.5	23.5	30.0
TOTAL LOSS/LITTER (%)	MEAN	10.9	9.4	8.5	18.5	37.8*
	S.D.	12.2	14.4	11.2	27.2	31.6

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

^b DOES NOT INCLUDE ONE FEMALE FOR WHICH CORPORA LUTEA WERE NOT RECORDED.

^c CORPORA LUTEA FOR ONE FEMALE COULD NOT BE COUNTED DUE TO EARLY EMBRYONIC DEATH SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $p < 0.05$

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

TABLE 3 (CONT.)

SUMMARY OF CESAREAN SECTION DATA

GROUP: DOSE LEVEL (MG BASE/KG/DAY):		1	2	3	4	5
		0	0.5	1.3	3.5	300 MG/KG/DAY*
SEX: MALES / FEMALES		MEAN 4.6 3.8 S.D. 1.8 1.5	3.9 4.2 1.6 1.5	4.1 4.0 1.5 1.8	3.8 4.1 1.8 1.9	2.9 2.6 1.7 1.9
FETAL WEIGHT (g) (LITTER) ^b		MEAN 39.38 S.D. 3.12	41.00 4.11	39.82 4.53	38.20 4.91	41.06 4.52
(MALES) ^b		MEAN 39.53 S.D. 3.22	40.85 4.08	39.83 4.50	38.03 6.29	40.09 5.11
(FEMALES) ^b		MEAN 39.41 S.D. 4.03	41.05 4.36	39.61 4.95	38.15 4.70	40.81 5.03
GRAVID UTERUS WEIGHT (g)		MEAN 462.56 S.D. 70.77	459.45 109.07	451.53 91.39	427.08 104.50	331.00* 125.91

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

^b VALUES FOR EACH GROUP REPRESENTS THE MEAN OF THE TOTAL OF THE LITTER MEANS.
SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P \leq 0.05$

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TABLE 4

SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS
- ABSOLUTE -

GROUP: DOSE LEVEL (MG BASE/KG/DAY):	FETUSES			LITTERS			300 MG/KG/DAY*				
	1	2	3	4	5		1	2	3	4	5
NUMBER EXAMINED EXTERNALLY	167	154	154	126	82		20	19	19	16	15
MICROCEPHALY	0	0	0	0	19		0	0	0	0	5*
CLEFT PALATE	0	0	0	0	6		0	0	0	0	3
EXENCEPHALY	0	0	0	1	0		0	0	0	1	0
MACROSTOMIA	0	0	0	0	11		0	0	0	0	3
FACIAL/NECK - BLEBS	0	0	0	0	36		0	0	0	0	10*
MANDIBLE - MICROGNATHIA	0	0	0	0	1		0	0	0	0	1
MAXILLAE - MICROGNATHIA	0	0	0	0	5		0	0	0	0	3
PINNA ANOMALY	0	0	0	1	25		0	0	0	1	7*
TAIL ANOMALY	0	0	0	0	21		0	0	0	0	8*
FORELIMB - HYPERFLEXURE	0	0	0	0	1		0	0	0	0	1
NUMBER EXAMINED VISCERALLY	167	154	154	132	82		20	19	19	17	15
HEART AND/OR GREAT VESSEL ANOMALY	0	0	2	0	1		0	0	2	0	1
KIDNEY AND/OR URETER ANOMALY	1	1	1	3	8		1	1	1	1	6
NUMBER EXAMINED SKELETALLY	167	154	154	133	82		20	19	19	17	15
VERTEBRAL ANOMALY WITH ASSOCIATED RIB ANOMALY	1	1	0	0	0		1	1	0	0	0
VERTEBRAE ANOMALY	0	0	0	0	5		0	0	0	0	4*
VERTEBRAL CENTRA ANOMALY	0	0	0	0	2		0	0	0	0	2
SKULL ANOMALY	0	1	0	0	22		0	1	0	0	6*
CAUDAL VERTEBRAE ANOMALY	0	1	0	1	22		0	1	0	1	9*
FUSED STERNEBRAE	0	1	0	1	1		0	1	0	1	1
8 CERVICAL VERTEBRAE	1	0	0	0	0		0	0	0	0	0
HYOID ANOMALY	0	0	0	0	34		0	0	0	0	12*
TOTAL MALFORMATIONS											
NUMBER WITH EXTERNAL MALFORMATIONS	0	0	0	1	46		0	0	0	1	13*
NUMBER WITH VISCERAL MALFORMATIONS	1	1	3	3	8		1	1	3	1	6*
NUMBER WITH SKELETAL MALFORMATIONS	2	4	0	2	57		2	3	0	1	13*
TOTAL WITH MALFORMATIONS	3	5	3	6	64		3	4	3	3	14*

* RETINOL PALMITATE (75,000 I.U./KG/DAY ON GESTATION DAYS 9 AND 10).
SIGNIFICANTLY DIFFERENT FROM CONTROL: * = $P \leq 0.05$.

NOTE: FOR GROUP 4, EXTERNAL OBSERVATIONS WERE INADVERTENTLY NOT RECORDED FOR DAM 477 (ALL FETUSES) AND VISCERAL OBSERVATIONS WERE INADVERTENTLY NOT RECORDED FOR DAM 470, FETUS 9; NOT INCLUDED IN CALCULATIONS.

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TABLE 5

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 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	0.5	1.3	3.5	300 MG/KG/DAY*	0	0.5	1.3	3.5	300 MG/KG/DAY*
NUMBER EXAMINED EXTERNALLY	167	154	154	126	82	20	19	19	16	15
NO EXTERNAL VARIATIONS OBSERVED										
NUMBER EXAMINED VISCERALLY	167	154	154	132	82	20	19	19	17	15
MAJOR BLOOD VESSEL VARIATION	24	13	21	27	17	9	5	9	6	9
THYROID VARIATION	1	0	0	0	0	1	0	0	0	0
THYMUS VARIATION	0	1	0	0	0	0	1	0	0	0
GALL BLADDER VARIATION	8	14	15	24	6	6	7	10	9	4
LIVER - ENLARGED	0	0	0	1	0	0	0	0	1	0
LIVER - WHITE AREAS	1	0	0	0	0	1	0	0	0	0
LIVER - CYSTS	0	1	0	0	0	0	1	0	0	0
SPLEEN - SMALL IN SIZE	0	0	1	1	2	0	0	1	1	2
HYDRONEPHROSIS	0	0	1	2	2	0	0	1	1	2
KIDNEY - PALE	0	0	1	0	0	0	0	1	0	0
KIDNEYS - RENAL PAPILLAE NOT DEVELOPED	0	0	1	0	1	0	0	1	0	1
RETROCAVAL URETER	0	0	0	0	2	0	0	0	0	2
IRIS - HEMORRHAGIC RING	2	1	0	1	0	2	1	0	1	0

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

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL.

NOTE: FOR GROUP 4, EXTERNAL OBSERVATIONS WERE INADVERTENTLY NOT RECORDED FOR DAM 477 (ALL FETUSES) AND VISCERAL OBSERVATIONS WERE INADVERTENTLY NOT RECORDED FOR DAM 470, FETUS 9; NOT INCLUDED IN CALCULATIONS.

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TABLE 5 (CONT.)

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

SUMMARY OF FETAL OBSERVATIONS - VARIATIONS

- ABSOLUTE -

GROUP: DOSE LEVEL (MG BASE/KG/DAY):	FETUSES					LITTERS				
	1	2	3	4	5	1	2	3	4	5
	0	0.5	1.3	3.5	300 MG/KG/DAY ^a	0	0.5	1.3	3.5	300 MG/KG/DAY ^a
NUMBER EXAMINED SKELETALLY	167	154	154	133	82	20	19	19	17	15
HYOID UNOSSIFIED	2	2	0	2	0	1	2	0	2	0
ACCESSORY SKULL BONES	1	0	0	0	0	1	0	0	0	0
BENT RIBS	1	0	0	0	0	1	0	0	0	0
7TH CERVICAL RIBS	1	0	0	1	0	1	0	0	1	0
13TH FULL RIBS	78	59	71	49	28	17	15	17	15	13
13TH RUDIMENTARY RIBS	28	24	23	25	8	14	14	13	13	5
12TH RUDIMENTARY RIBS	0	0	0	0	1	0	0	0	0	1
HYOID ARCH(ES) BENT	4	4	8	7	4	4	3	6	3	3
STERNEBRA(E) #5 - #6 UNOSSIFIED	17	11	16	28	8	9	5	8	10	3
STERNEBRA(E) MALALIGNED	6	9	11	4	3	6	6	6	3	2
25 PRESACRAL VERTEBRAE	0	0	0	0	1	0	0	0	0	1
27 PRESACRAL VERTEBRAE	38	26	31	19	19	12	10	10	8	10
TOTAL FETUSES/LITTERS WITH VARIATIONS	133	103	116	108	54	20	19	19	17	13

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

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL.

NOTE: FOR GROUP 4, EXTERNAL OBSERVATIONS WERE INADVERTENTLY NOT RECORDED FOR DAM 477 (ALL FETUSES) AND VISCERAL OBSERVATIONS WERE INADVERTENTLY NOT RECORDED FOR DAM 470, FETUS 9; NOT INCLUDED IN CALCULATIONS.

TABLE 6

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

SUMMARY OF FETAL OBSERVATIONS - MALFORMATIONS
- PERCENT -

GROUP: DOSE LEVEL (MG BASE/KG/DAY):	FETUSES			LITTERS			5		
	1	2	3	4	5	1	2	3	4
	0	0.5	1.3	3.5	300 MG/KG/DAY*	0	0.5	1.3	3.5
NUMBER EXAMINED EXTERNALLY	167	154	154	126	82	20	19	19	16
MICROCEPHALY	0.0	0.0	0.0	0.0	23.2	0.0	0.0	0.0	0.0
CLEFT PALATE	0.0	0.0	0.0	0.0	7.3	0.0	0.0	0.0	0.0
EXENCEPHALY	0.0	0.0	0.0	0.8	0.0	0.0	0.0	0.0	6.3
MACROSTOMIA	0.0	0.0	0.0	0.0	13.4	0.0	0.0	0.0	0.0
FACIAL/NECK - BLEBS	0.0	0.0	0.0	0.0	43.9	0.0	0.0	0.0	0.0
MANDIBLE - MICROGNATHIA	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0
MAXILLAE - MICROGNATHIA	0.0	0.0	0.0	0.0	6.1	0.0	0.0	0.0	0.0
PINNA ANOMALY	0.0	0.0	0.0	0.8	30.5	0.0	0.0	0.0	6.3
TAIL ANOMALY	0.0	0.0	0.0	0.0	25.6	0.0	0.0	0.0	0.0
FORELIMB - HYPERFLEXURE	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0
NUMBER EXAMINED VISCERALLY	167	154	154	132	82	20	19	19	17
HEART AND/OR GREAT VESSEL ANOMALY	0.0	0.0	1.3	0.0	1.2	0.0	0.0	10.5	0.0
KIDNEY AND/OR URETER ANOMALY	0.6	0.6	0.6	2.3	9.8	5.0	5.3	5.3	5.9
NUMBER EXAMINED SKELETALLY	167	154	154	133	82	20	19	19	17
VERTEBRAL ANOMALY WITH ASSOCIATED									
RIB ANOMALY	0.6	0.6	0.0	0.0	0.0	5.0	5.3	0.0	0.0
VERTEBRAE ANOMALY	0.0	0.0	0.0	0.0	6.1	0.0	0.0	0.0	0.0
VERTEBRAL CENTRA ANOMALY	0.0	0.0	0.0	0.0	2.4	0.0	0.0	0.0	0.0
SKULL ANOMALY	0.0	0.6	0.0	0.0	26.8	0.0	5.3	0.0	0.0
CAUDAL VERTEBRAE ANOMALY	0.0	0.6	0.0	0.8	26.8	0.0	5.3	0.0	5.9
FUSED STERNEBRAE	0.6	0.6	0.0	0.8	1.2	0.0	5.3	0.0	5.9
8 CERVICAL VERTEBRAE	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
HYOID ANOMALY	0.0	0.0	0.0	0.0	41.5	0.0	0.0	0.0	0.0
TOTAL MALFORMATIONS									
NUMBER WITH EXTERNAL MALFORMATIONS	0.0	0.0	0.0	0.8	56.1	0.0	0.0	0.0	5.3
NUMBER WITH VISCERAL MALFORMATIONS	0.6	0.6	1.9	2.3	9.8	5.0	5.3	15.8	5.9
NUMBER WITH SKELETAL MALFORMATIONS	1.2	2.6	0.0	1.5	69.5	10.0	15.8	0.0	5.9
TOTAL WITH MALFORMATIONS	1.8	3.2	1.9	4.5	78.0	15.0	21.1	15.8	17.6
									93.3

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

NOTE: FOR GROUP 4, EXTERNAL OBSERVATIONS WERE INADVERTENTLY NOT RECORDED FOR DAM 477 (ALL FETUSES) AND VISCERAL OBSERVATIONS WERE INADVERTENTLY NOT RECORDED FOR DAM 470, FETUS 9; NOT INCLUDED IN CALCULATIONS.

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TABLE 7

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS
SUMMARY OF FETAL OBSERVATIONS - VARIATIONS

- PERCENT -

GROUP: DOSE LEVEL (MG BASE/KG/DAY):	FETUSES					LITTERS					DOSE LEVEL (MG/KG/DAY)*				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
NUMBER EXAMINED EXTERNALLY	167	154	154	126	82	20	19	19	16	15					
NO EXTERNAL VARIATIONS OBSERVED															
NUMBER EXAMINED VISCERALLY	167	154	154	132	82	20	19	19	17	15					
MAJOR BLOOD VESSEL VARIATION	14.4	8.4	13.6	20.3	20.7	45.0	26.3	47.4	35.3	60.0					
THYROID VARIATION	0.6	0.0	0.0	0.0	0.0	5.0	0.0	0.0	0.0	0.0					
THYMUS VARIATION	0.0	0.6	0.0	0.0	0.0	0.0	5.3	0.0	0.0	0.0					
GALL BLADDER VARIATION	4.8	9.1	9.7	18.0	7.3	30.0	36.8	52.6	52.9	26.7					
LIVER - ENLARGED	0.0	0.0	0.0	0.8	0.0	0.0	0.0	0.0	5.9	0.0					
LIVER - WHITE AREAS	0.6	0.0	0.0	0.0	0.0	5.0	0.0	0.0	0.0	0.0					
LIVER - CYSTS	0.0	0.6	0.0	0.0	0.0	0.0	5.3	0.0	0.0	0.0					
SPLEEN - SMALL IN SIZE	0.0	0.0	0.6	0.8	2.4	0.0	0.0	5.3	5.9	13.3					
HYDRONEPHROSIS	0.0	0.0	0.6	1.5	2.4	0.0	0.0	5.3	5.9	13.2					
KIDNEY - PALE	-0.0	0.0	0.6	0.0	0.0	0.0	0.0	5.3	0.0	0.0					
KIDNEYS - RENAL PAPILLAE															
NOT DEVELOPED	0.0	0.0	0.6	0.0	1.2	0.0	0.0	5.3	0.0	6.7					
RETROCAVAL URETER	0.0	0.0	0.0	0.0	2.4	0.0	0.0	0.0	0.0	13.2					
IRIS - HEMORRHAGIC RING	1.2	0.6	0.0	0.8	0.0	10.0	5.3	0.0	5.9	0.0					

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

NOTE: FOR GROUP 4, EXTERNAL OBSERVATIONS WERE INADVERTENTLY NOT RECORDED FOR DAM 477 (ALL FETUSES) AND VISCERAL OBSERVATIONS WERE INADVERTENTLY NOT RECORDED FOR DAM 470, FETUS 9; NOT INCLUDED IN CALCULATIONS.

TABLE 7 (CONT.)

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 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	0.5	1.3	3.5	300 MG/KG/DAY*	0	0.5	1.3	3.5	300 MG/KG/DAY*
NUMBER EXAMINED SKELETALLY	167	154	154	133	82	20	19	19	17	15
HYOID UNOSSIFIED	1.2	1.3	0.0	1.5	0.0	5.0	10.5	0.0	1.8	0.0
ACCESSORY SKULL BONES	0.6	0.0	0.0	0.0	0.0	5.0	0.0	0.0	0.0	0.0
BENT RIBS	0.6	0.0	0.0	0.0	0.0	5.0	0.0	0.0	0.0	0.0
7TH CERVICAL RIBS	0.6	0.0	0.0	0.8	0.0	5.0	0.0	0.0	5.9	0.0
13TH FULL RIBS	46.7	38.3	46.1	36.8	34.1	85.0	78.9	89.5	88.2	86.7
13TH RUDIMENTARY RIBS	16.8	15.6	14.9	18.8	9.8	70.0	73.7	68.4	76.5	33.3
12TH RUDIMENTARY RIBS	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0	6.7
HYOID ARCH(ES) BENT	2.4	2.6	5.2	5.3	4.9	20.0	15.8	31.6	17.6	20.0
STERNEBRA(E) #5 - #6 UNOSSIFIED	10.2	7.1	10.4	21.1	9.8	45.0	26.3	42.1	58.8	20.0
STERNEBRA(E) MALALIGNED	3.6	5.8	7.1	3.0	3.7	30.0	31.6	31.6	17.6	13.3
25 PRESACRAL VERTEBRAE	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0	6.7
27 PRESACRAL VERTEBRAE	23.8	16.9	20.1	14.3	23.2	60.0	52.6	52.6	47.1	66.7
TOTAL FETUSES/LITTERS WITH VARIATIONS	79.6	68.9	75.3	81.2	65.9	100.0	100.0	100.0	100.0	86.7

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

NOTE: FOR GROUP 4, EXTERNAL OBSERVATIONS WERE INADVERTENTLY NOT RECORDED FOR DAM 477 (ALL FETUSES) AND VISCERAL OBSERVATIONS WERE INADVERTENTLY NOT RECORDED FOR DAM 470, FETUS 9; NOT INCLUDED IN CALCULATIONS.

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APPENDIX A

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS
INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 1: 0 MG BASE/KG/DAY

DAM#	ORGAN	OBSERVATION
401		NO ABNORMALITIES DETECTED
402		NO ABNORMALITIES DETECTED
403		NO ABNORMALITIES DETECTED
404		NO ABNORMALITIES DETECTED
405		NO ABNORMALITIES DETECTED
406		NO ABNORMALITIES DETECTED
407		NO ABNORMALITIES DETECTED
408		NO ABNORMALITIES DETECTED
409		NO ABNORMALITIES DETECTED
410		NO ABNORMALITIES DETECTED
411		NO ABNORMALITIES DETECTED
412		NO ABNORMALITIES DETECTED
413		NO ABNORMALITIES DETECTED
414		NO ABNORMALITIES DETECTED
415		NO ABNORMALITIES DETECTED
416		NO ABNORMALITIES DETECTED
417		NO ABNORMALITIES DETECTED
418		NO ABNORMALITIES DETECTED
419		NO ABNORMALITIES DETECTED
420		NO ABNORMALITIES DETECTED

APPENDIX A
 UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS
 INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

DAM#	ORGAN	OBSERVATION
421		NO ABNORMALITIES DETECTED
422		NO ABNORMALITIES DETECTED
423		NO ABNORMALITIES DETECTED
424		NO ABNORMALITIES DETECTED
425		NO ABNORMALITIES DETECTED
		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
426		NO ABNORMALITIES DETECTED
427		NO ABNORMALITIES DETECTED
428		NO ABNORMALITIES DETECTED
429		NO ABNORMALITIES DETECTED
430		NO ABNORMALITIES DETECTED
431		NO ABNORMALITIES DETECTED
432		NO ABNORMALITIES DETECTED
433		NO ABNORMALITIES DETECTED
434		NO ABNORMALITIES DETECTED
435		NO ABNORMALITIES DETECTED
436		NO ABNORMALITIES DETECTED
437		NO ABNORMALITIES DETECTED
438		NO ABNORMALITIES DETECTED
439		NO ABNORMALITIES DETECTED
440		NO ABNORMALITIES DETECTED

APPENDIX A

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

DAM#	ORGAN	OBSERVATION
441		NO ABNORMALITIES DETECTED
442		NO ABNORMALITIES DETECTED
443		^a
444		NO ABNORMALITIES DETECTED
445		NO ABNORMALITIES DETECTED
446		NO ABNORMALITIES DETECTED
447		NO ABNORMALITIES DETECTED
448		NO ABNORMALITIES DETECTED
449		NO ABNORMALITIES DETECTED
450		NO ABNORMALITIES DETECTED
451		NO ABNORMALITIES DETECTED
452		NO ABNORMALITIES DETECTED
453		ABORTED ON GESTATION DAY 27
		ABORTED 10 NORMALLY DEVELOPED FETUSES, FIVE PARTIALLY CANNIBALIZED, FIVE VIABLE AND EUTHANIZED, ALL FETUSES DISCARDED; NO ABNORMALITIES DETECTED AT THE MATERNAL NECROPSY
454		NO ABNORMALITIES DETECTED
455		NO ABNORMALITIES DETECTED
456		NO ABNORMALITIES DETECTED
457		NO ABNORMALITIES DETECTED
458		NO ABNORMALITIES DETECTED
459		NO ABNORMALITIES DETECTED
460		NO ABNORMALITIES DETECTED

a = OBSERVATIONS NOT RECORDED.

APPENDIX A

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

DAM#	ORGAN	OBSERVATION
461		NO ABNORMALITIES DETECTED
462		NO ABNORMALITIES DETECTED
463		^a
464		NO ABNORMALITIES DETECTED
		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
465		NO ABNORMALITIES DETECTED
466		NO ABNORMALITIES DETECTED
		PREMATURE DELIVERY ON GESTATION DAY 29
		ABORTED 9 NORMAL FETUSES, ALL PARTIALLY CANNIBALIZED, ALL FETUSES DISCARDED; NO ABNORMALITIES DETECTED AT THE MATERNAL NECROPSY.
467		NO ABNORMALITIES DETECTED
468		^a
469		NO ABNORMALITIES DETECTED
470		NO ABNORMALITIES DETECTED
471		NO ABNORMALITIES DETECTED
472		NO ABNORMALITIES DETECTED
473		NO ABNORMALITIES DETECTED
474		NO ABNORMALITIES DETECTED
475		NO ABNORMALITIES DETECTED
476		NO ABNORMALITIES DETECTED
477		NO ABNORMALITIES DETECTED
478	UTERUS	GREEN MUCOID MATERIAL IN RIGHT UTERINE HORN
479		NO ABNORMALITIES DETECTED
480		NO ABNORMALITIES DETECTED

^a = OBSERVATIONS NOT RECORDED.

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APPENDIX A

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

INDIVIDUAL MATERNAL GROSS NECROPSY OBSERVATIONS

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

DAM#	ORGAN	OBSERVATION
481		NO ABNORMALITIES DETECTED
482		NO ABNORMALITIES DETECTED
483		NO ABNORMALITIES DETECTED
484		NO ABNORMALITIES DETECTED
485		NO ABNORMALITIES DETECTED
		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
486		NO ABNORMALITIES DETECTED
487		NO ABNORMALITIES DETECTED
488		NO ABNORMALITIES DETECTED
489		ABORTED ON GESTATION DAY 22
		ANIMAL ABORTED 6 FETUSES, 1 FULL FETUS AND 5 HEADS RETAINED IN BOWINS, 2 HEADS WITH MENINGOCOELE, 1 FULL FETUS WITH NO ABNORMALITIES DETECTED, COMPLETE EVALUATION OF THE FETAL HEADS WAS NOT PERFORMED DUE TO APPARENT DISTURBANCE BY THE MOTHER TO THEIR STRUCTURE; NO ABNORMALITIES DETECTED AT THE MATERNAL NECROPSY
490		NO ABNORMALITIES DETECTED
		NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
491		a, NONGRAVID - AMMONIUM SULFIDE TEST NEGATIVE
492		NO ABNORMALITIES DETECTED
493		NO ABNORMALITIES DETECTED
494		NO ABNORMALITIES DETECTED
495		a, GRAVID - AMMONIUM SULFIDE TEST POSITIVE
496		NO ABNORMALITIES DETECTED
497		NO ABNORMALITIES DETECTED
498		NO ABNORMALITIES DETECTED
499		NO ABNORMALITIES DETECTED
500		NO ABNORMALITIES DETECTED

a = OBSERVATIONS NOT RECORDED.

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APPENDIX B

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS
INDIVIDUAL CESAREAN SECTION DATA

GROUP 1: 0 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	
	LEFT	RIGHT	LEFT	RIGHT	TOTAL	TOTAL	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT
401	6	3	9	3	9	5	4	6	3	9	0	0	0	0
402	3	7	10	3	10	6	1	3	0	7	0	0	0	3
403	5	5	10	5	10	7	3	5	0	10	0	0	0	0
404	7	2	9	7	8	3	4	6	0	7	1	0	0	0
405	6	3	9	6	9	4	5	6	0	9	0	0	0	0
406	3	5	8	3	8	2	6	3	0	8	0	0	0	0
407	7	3	10	5	7	3	4	5	0	7	0	0	0	0
408	4	5	9	4	7	4	2	4	0	6	0	1	0	0
409	a	a	a	4	11	6	4	3	0	10	0	0	0	0
410	6	4	10	6	10	6	3	5	0	9	1	0	0	0
411	4	4	8	4	8	3	5	4	0	8	0	0	0	0
412	5	5	10	5	10	3	5	4	0	8	0	1	0	0
413	4	6	10	4	10	3	5	3	0	8	1	1	0	0
414	2	5	7	2	7	4	2	1	0	6	0	1	0	0
415	5	6	11	4	10	3	6	4	0	9	0	1	0	0
416	5	5	10	5	10	5	5	5	0	10	0	0	0	0
417	2	4	6	2	6	5	1	2	0	6	0	0	0	0
418	5	7	12	5	12	8	4	5	0	12	0	0	0	0
419	6	6	12	6	12	8	3	5	0	11	1	0	0	0
420	4	3	7	4	7	3	4	4	0	7	0	0	0	0
TOTAL	177	181	91	76	167	0	0	0	0	10	4	0	0	0
MEAN	9.3	9.1	4.6	3.8	8.4	0.0	0.0	0.0	0.0	0.5	0.2	0.0	0.0	0.0
S.D.	1.6	1.7	1.8	1.5	1.7	0.0	0.0	0.0	0.0	0.7	0.7	0.0	0.0	0.0
N	19	20	20	20	20	20	20	20	20	20	20	20	20	20

a = CORPORA LUTEA NOT RECORDED, NOT INCLUDED IN CALCULATIONS.

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APPENDIX B

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

INDIVIDUAL CESAREAN SECTION DATA

GROUP 2: 0.5 MG BASE/KG/DAY

DAM#	CORPORA LUTEA		TOTAL IMPLANTATIONS		SEX		VIABLE FETUSES		NONVIABLE FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS	
	LEFT RIGHT TOTAL		LEFT RIGHT TOTAL		M F		LEFT RIGHT TOTAL		LEFT RIGHT TOTAL		LEFT RIGHT TOTAL		LEFT RIGHT TOTAL	
	LEFT	RIGHT	LEFT	RIGHT	M	F	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT
421	6	5	11	5	5	6	6	5	0	0	0	0	0	0
422	3	2	5	2	1	3	2	2	0	0	0	0	0	0
423	5	4	9	4	4	4	4	4	0	0	0	0	0	0
424	2	4	6	3	2	1	0	3	0	0	0	0	0	0
425	NONGRAVID													
426	3	6	9	6	4	4	2	6	0	0	1	0	0	0
427	2	6	8	6	2	6	2	6	0	0	0	0	0	0
428	2	7	9	7	5	4	2	7	0	0	0	0	0	0
429	5	3	8	3	5	3	5	3	0	0	0	0	0	0
430	4	5	9	5	4	5	4	5	0	0	0	0	0	0
431	5	5	10	5	3	5	4	4	0	0	0	0	0	0
432	6	6	12	6	5	7	6	6	0	0	1	1	2	0
433	2	6	8	6	4	4	2	6	0	0	0	0	0	0
434	4	3	7	3	4	3	4	3	0	0	0	0	0	0
435	1	5	6	5	3	3	1	5	0	0	0	0	0	0
436	6	8	14	7	7	6	6	7	0	0	0	0	0	0
437	4	5	9	3	4	3	4	3	0	0	0	0	0	0
438	7	4	11	4	1	6	4	3	0	0	0	0	0	0
439	5	4	9	4	6	3	5	4	0	0	3	1	4	0
440	3	6	9	6	6	3	3	6	0	0	0	0	0	0
TOTAL	169	161	75	79					0	0	7	0	0	0
MEAN	8.9	8.5	3.9	4.2					0.0	0.0	0.4	0.0	0.0	0.0
S.D.	2.2	2.5	1.6	1.5					0.0	0.0	1.0	0.0	0.0	0.0
N	19	19	19	19					19	19	19	19	19	19

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APPENDIX B

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

INDIVIDUAL CESAREAN SECTION DATA

GROUP 3: 1.3 MG BASE/KG/DAY

DAM#	CORPORA LUTEA		IMPLANTATIONS		SEX		VIABLE FETUSES		NONVIABLE FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS	
	LEFT	RIGHT	TOTAL	LEFT	RIGHT	TOTAL	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT
441	7	5	12	7	5	12	7	5	0	0	0	0	0	0
442	5	5	10	5	5	10	5	5	0	0	0	0	0	0
443	7	7	14	6	7	13	5	6	0	0	1	1	0	0
444	3	5	8	3	5	8	4	3	0	0	0	0	0	0
445	4	5	9	4	5	9	4	5	0	0	0	0	0	0
446	3	6	9	3	6	9	3	5	0	0	0	0	0	0
447	4	1	5	4	1	5	3	2	0	0	0	1	0	0
448	8	1	9	8	0	8	6	2	0	0	0	0	0	0
449	6	3	9	6	3	9	6	3	0	0	0	0	0	0
450	6	4	10	6	3	9	4	5	0	0	0	0	0	0
451	5	6	11	5	5	10	3	4	0	0	0	0	2	1
452	5	3	8	5	3	8	4	2	0	0	1	1	0	0
453	PREMATURE DELIVERY ON GESTATION DAY 27													
454	4	4	8	3	4	7	2	4	0	0	1	0	0	0
455	4	4	8	4	4	8	4	4	0	0	0	0	0	0
456	5	3	8	5	3	8	5	3	0	0	0	0	0	0
457	3	4	7	3	4	7	4	3	0	0	0	0	0	0
458	3	2	5	3	2	5	3	2	0	0	0	0	0	0
459	3	5	8	3	5	8	5	2	0	0	0	0	1	1
460	8	4	12	8	3	11	4	7	0	0	0	0	0	0
TOTAL	170		164	78	76	154			0		6		4	
MEAN	8.9		8.6	4.1	4.0	8.1			0.0		0.3		0.2	
S.D.	2.2		2.0	1.5	1.8	2.0			0.0		0.7		0.7	
N	19		19	19	19	19			19		19		19	

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APPENDIX B

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

INDIVIDUAL CESAREAN SECTION DATA

GROUP 4: 3.5 MG BASE/KG/DAY

DAM#	TOTAL															
	CORPORA LUTEA		IMPLANTATIONS		SEX		VIABLE FETUSES		NONVIABLE FETUSES		EARLY RESORPTIONS		LATE RESORPTIONS			
	LEFT	RIGHT	TOTAL	LEFT	RIGHT	TOTAL	M	F	LEFT	RIGHT	TOTAL	LEFT	RIGHT	TOTAL		
461	3	4	7	3	4	7	5	1	3	3	6	0	0	0	0	0
462	3	5	8	3	4	7	4	2	3	3	6	0	0	1	1	0
463	1	4	5	1	4	5	2	3	1	4	5	0	0	0	0	0
464	NONGRAVID															
465	5	5	10	5	4	9	5	3	5	3	8	0	0	0	0	1
466	PREMATURE DELIVERY ON GESTATION DAY 29															
467	8	3	11	8	2	10	4	6	8	2	10	0	0	0	0	0
468	5	5	10	5	5	10	3	7	5	5	10	0	0	0	0	0
469	3	4	7	1	1	2	1	1	1	1	2	0	0	0	0	0
470	7	2	9	7	2	9	3	6	7	2	9	0	0	0	0	0
471	4	4	8	4	4	8	4	4	4	4	8	0	0	0	0	0
472	5	3	8	5	3	8	4	3	4	3	7	0	0	1	0	0
473	a	a	a	3	7	10	5	3	2	6	8	0	0	1	2	0
474	7	4	11	7	2	9	2	7	7	2	9	0	0	0	0	0
475	6	5	11	6	5	11	8	3	6	5	11	0	0	0	0	0
476	6	4	10	5	4	9	4	5	4	4	9	0	0	0	0	0
477	5	4	9	5	4	9	3	4	3	4	7	0	0	1	0	1
478	3	5	8	3	5	8	1	6	3	4	7	0	0	0	1	1
479	5	6	11	5	6	11	6	5	5	6	11	0	0	0	0	0
480	9	2	11	6	2	8	b	b	0	0	0	6	2	8	0	0
TOTAL	154	150	304	150	64	69	133	0	0	14	14	3	0	0.8	0.2	3
MEAN	9.1	8.3	8.7	3.8	4.1	7.4	0.0	0.0	0.0	0.0	0.8	0.2	0.0	1.9	0.4	0.2
S.D.	1.8	2.2	2.0	1.8	1.9	2.9	0.0	0.0	0.0	0.0	1.9	0.0	0.0	1.8	0.4	0.4
N	17	18	17	17	17	18	18	18	18	18	18	18	18	18	18	18

a = CORPORA LUTEA NOT RECORDED, NOT INCLUDED IN CALCULATIONS.
b = TOTAL LITTER RESORPTION

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APPENDIX B

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 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 TOTAL		LEFT RIGHT TOTAL		M	F	LEFT RIGHT TOTAL		LEFT RIGHT TOTAL		LEFT RIGHT TOTAL		LEFT RIGHT TOTAL			
481	4	6	10	4	5	9	2	5	3	4	7	0	0	0	0	0
482	8	2	10	0	1	1	0	1	1	1	1	1	2	0	0	0
483	5	5	10	5	5	10	5	0	2	3	5	3	2	5	0	0
484	4	5	9	4	5	9	5	2	4	3	7	0	2	2	0	0
485	NONGRAVID															
486	5	4	9	5	4	9	3	6	5	4	9	0	0	0	0	0
487	3	3	6	3	2	5	2	2	2	2	4	0	0	1	0	0
488	6	1	7	5	0	5	1	0	1	0	1	2	0	2	0	2
489	ABORTION ON GESTATION DAY 22															
490	NONGRAVID															
491	NONGRAVID															
492	4	3	7	4	3	7	3	2	3	2	5	1	1	2	0	0
493	11	0	11	11	0	11	3	6	9	0	9	0	0	2	0	2
494	a	a	a	4	3	7	2	3	2	3	5	2	0	2	0	0
495	b	b	b	5	3	8	c	c	0	0	0	5	3	8	0	0
496	4	9	13	3	6	9	1	2	3	0	3	0	6	6	0	0
497	5	4	9	5	3	8	4	4	5	3	8	0	0	0	0	0
498	5	4	9	5	4	9	6	2	4	4	8	0	0	0	1	0
499	5	2	7	5	2	7	4	3	5	2	7	0	0	0	0	0
500	6	5	11	4	0	4	2	1	3	0	3	1	0	1	0	0

TOTAL	128	118	43	39	82	0	31	5
MEAN	9.1	7.4	2.9	2.6	5.1	0.0	1.9	0.3
S.D.	1.9	2.6	1.7	1.9	2.9	0.0	2.4	0.7
N	14	16	15	15	16	16	16	16

a = CORPORA LUTEA NOT RECORDED, NOT INCLUDED IN CALCULATIONS.
b = CORPORA LUTEA COULD NOT BE COUNTED DUE TO EARLY EMBRYONIC DEATH.
c = TOTAL LITTER RESORPTION

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UIC/TRL STUDY NO.: 138

APPENDIX C

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 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	1	2	3	4	5	6	7	8	9	10	11	12	13
			INDIVIDUAL FETAL WEIGHT												
401	503.11	41.5111	48.52F	36.94M	40.37M	41.14F	36.60M	41.14M	44.19M	40.28F	44.42F	-	-	-	-
402	448.39	34.8471	40.64F	38.46M	34.95M	31.46M	L	L	26.13M	34.64M	37.65M	L	-	-	-
403	538.13	39.2500	44.21M	38.84F	40.04M	34.10M	35.44M	46.03F	44.73M	40.59M	36.35M	32.17F	-	-	-
404	428.15	42.5214	E	43.89F	37.27F	48.19M	41.08M	39.41F	44.07M	43.74F	-	-	-	-	-
405	500.44	39.6644	47.48F	42.56F	32.77M	29.85M	29.90F	39.40F	49.00M	42.43F	43.59M	-	-	-	-
406	478.01	43.4463	50.56F	44.12M	42.83M	51.47F	47.15F	39.26F	32.47F	39.71F	-	-	-	-	-
407	404.25	40.3557	44.34F	39.58M	40.27F	38.01F	36.56M	42.86F	40.87M	-	-	-	-	-	-
408	367.20	41.6167	39.35M	37.03M	47.98F	42.99M	43.68M	E	38.67F	-	-	-	-	-	-
409	475.93	34.9180	E	37.82M	35.82M	33.77M	41.32M	33.47F	30.20F	34.14M	33.26M	34.84F	34.54F	-	-
410	510.15	40.5822	40.71M	41.34M	32.06F	38.94F	39.37M	E	46.34M	43.41F	43.45M	39.62M	-	-	-
411	424.74	38.7875	40.35F	41.39F	39.05M	28.31F	45.38M	40.66F	38.84F	36.32M	-	-	-	-	-
412	451.53	40.9325	E	43.59F	45.77M	40.13F	37.57M	43.02F	E	41.22M	36.21F	39.95F	-	-	-
413	409.38	35.9175	E	41.28M	29.92M	32.42M	34.20F	E	30.71F	33.33F	44.54F	40.94F	-	-	-
414	347.43	38.9283	L	37.22M	41.80F	45.04M	38.13M	34.41F	36.97M	-	-	-	-	-	-
415	483.09	36.9589	38.66F	40.88M	40.63M	36.45F	42.51F	E	32.30F	35.79F	33.71M	31.70F	-	-	-
416	559.95	41.4750	43.34F	41.06M	37.38M	35.41M	42.71M	44.99F	43.63M	42.67F	43.37F	40.19F	-	-	-
417	326.35	37.3883	38.61M	39.57M	41.89F	40.23M	31.15M	32.88M	-	-	-	-	-	-	-
418	587.53	37.1017	41.47M	32.50F	27.66F	33.76M	38.94M	38.89F	35.06F	36.06M	39.52M	33.02M	45.20M	43.14M	-
419	552.20	34.8045	42.82M	37.42M	35.92F	E	20.96F	32.90F	31.36M	47.88M	40.48M	38.80M	30.94M	23.37M	-
420	455.20	46.5371	50.24M	44.66M	46.24M	49.48F	45.75F	43.34F	46.05F	-	-	-	-	-	-

MEAN 462.56 39.3772
S.D. 70.77 3.1239
N 20 20

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

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APPENDIX C

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 2: 0.5 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
421	578.28	37.9391	46.96F	37.64M	37.66M	29.01F	27.47F	34.67M	44.59M	38.28M	43.04F	37.33F	40.68F	-	-
422	260.70	45.0650	49.39F	40.64M	40.95F	49.28F	-	-	-	-	-	-	-	-	-
423	492.81	43.5550	47.42M	38.21M	41.53F	40.66M	47.83F	45.98F	44.58M	42.23F	-	-	-	-	-
424	195.95	42.8000	46.52M	43.58M	38.30F	-	-	-	-	-	-	-	-	-	-
426	505.27	45.2425	E	50.40M	47.08F	53.16F	38.98F	52.26M	46.16F	38.13M	35.77M	-	-	-	-
427	506.16	44.8175	48.03F	43.04F	48.26M	50.22F	43.85F	38.63M	39.44F	47.07F	-	-	-	-	-
428	535.19	42.4789	44.68F	45.52M	44.77M	47.29F	39.78F	36.92M	36.15M	38.31F	48.89M	-	-	-	-
429	488.37	43.1213	46.31M	45.03M	41.54M	38.91F	38.95M	46.38F	41.87M	45.98F	-	-	-	-	-
430	444.75	33.0622	39.34F	39.74M	25.29F	22.39M	41.88M	37.98F	31.34F	27.58M	32.02F	-	-	-	-
431	405.88	35.0738	E	33.07M	34.08F	31.18F	35.80M	40.43M	40.82F	31.08F	34.13F	E	-	-	-
432	629.57	39.3033	47.56M	39.92M	34.34F	36.03F	28.65F	38.39M	37.25M	37.84F	32.97F	44.34F	46.73M	47.62F	-
433	433.39	37.9563	44.10F	26.29M	45.63M	43.25M	41.04F	35.06M	31.61F	36.67F	-	-	-	-	-
434	410.71	42.0671	47.43F	41.63M	43.68M	37.54M	40.53M	40.92F	42.74F	-	-	-	-	-	-
435	344.00	39.8400	35.82M	40.62F	41.19F	40.69M	40.82F	39.90M	-	-	-	-	-	-	-
436	585.31	32.7069	38.96M	36.20F	35.75F	31.00M	31.01F	31.48M	35.20F	31.17F	19.05M	31.84M	33.03F	35.90M	34.60M
437	435.56	46.0614	47.47M	47.15M	39.17F	45.04F	47.23M	48.83F	47.54M	-	-	-	-	-	-
438	413.17	41.3357	E	43.07M	E	36.77F	40.60F	37.09F	E	44.81F	44.09F	E	42.92F	-	-
439	504.33	41.0244	45.57F	44.90M	37.47M	30.40M	40.25M	46.75M	43.97F	40.97M	38.94F	-	-	-	-
440	560.17	45.6122	48.13F	49.52M	50.18M	40.58F	46.40M	42.59M	40.23M	44.33M	48.55F	-	-	-	-
MEAN	459.45	41.0032													
S.D.	109.07	4.1059													
	19	19													

KEY: E= EARLY RESORPTION L= LATE RESORPTION

M=MALE F=FEMALE

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APPENDIX C

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 3: 1.3 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	
441	568.08	34.4925	40.69F	36.04F	33.19M	34.97M	32.39F	33.16F	39.82M	34.29F	39.39M	37.61F	27.25F	25.11M	-	-
442	595.02	44.1530	44.67M	37.65F	42.86M	42.55F	43.76M	49.70M	46.60F	44.03M	43.48F	46.23M	-	-	-	-
443	550.04	35.4164	37.78M	30.50F	E	36.39F	31.47M	33.10F	40.78F	37.03M	35.34M	34.06M	38.14F	E	-	34.99F
444	443.52	38.7575	41.08F	37.83M	38.42M	34.68F	45.85F	41.20M	36.59M	34.41F	-	-	-	-	-	-
445	471.56	36.8789	40.08M	40.84F	30.57M	29.75F	42.91M	43.21M	38.00F	30.37F	36.18F	-	-	-	-	-
446	416.00	35.1013	38.15M	35.38M	33.18F	37.30F	33.14F	29.14F	E	38.83M	35.69F	-	-	-	-	-
447	289.06	38.6640	26.09M	40.30F	40.11F	41.16M	45.66M	-	-	-	-	-	-	-	-	-
448	499.12	44.5813	51.19F	50.99M	45.45M	44.56M	45.62M	44.95F	31.16M	42.73M	-	-	-	-	-	-
449	541.39	43.6933	46.19M	44.06F	46.61M	44.25M	40.74F	40.31M	39.13F	45.74M	46.21M	-	-	-	-	-
450	506.37	42.9733	45.94F	43.31F	42.25M	38.29M	35.82F	47.16F	44.83M	48.87M	40.29F	-	-	-	-	-
451	479.50	39.7257	42.16F	38.66M	40.76F	L	L	28.42F	L	42.96M	41.98M	43.14F	-	-	-	-
452	406.20	48.4600	50.98M	E	43.23M	48.89M	45.28F	51.47M	50.91F	-	-	-	-	-	-	-
454	353.80	41.9583	44.03M	42.88M	E	42.37M	38.01M	40.09M	44.37F	-	-	-	-	-	-	-
455	387.26	35.0425	45.00M	35.83M	28.04M	31.76M	41.90F	35.57M	33.60F	28.64F	-	-	-	-	-	-
456	349.73	32.2438	36.29F	30.58F	25.86M	26.40F	37.79F	31.03F	35.14F	34.86M	-	-	-	-	-	-
457	399.50	42.3571	43.46M	41.59M	45.23M	38.49F	38.31M	44.01F	45.41F	-	-	-	-	-	-	-
458	339.83	46.7300	47.75F	46.70F	45.29F	46.84F	47.07F	-	-	-	-	-	-	-	-	-
459	392.24	37.8314	45.57F	42.42M	40.12M	45.71M	L	35.32M	25.69F	29.99M	-	-	-	-	-	-
460	590.80	37.5818	45.14M	40.37F	34.25F	29.02F	31.74F	33.08F	36.15M	36.36M	45.27F	41.34F	40.68M	-	-	-

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

DRAFT

APPENDIX C

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

GROUP 4: 3.5 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
461	368.56	39.9883	39.38M	40.12F	39.05M	E	40.95M	38.95M	41.48M	-	-	-	-	-	-
462	355.51	42.2833	31.44M	44.42M	41.29M	43.26F	46.50M	46.79F	E	-	-	-	-	-	-
463	280.23	40.5660	43.27F	43.76M	40.31F	38.76F	36.73M	-	-	-	-	-	-	-	-
465	499.42	38.8063	45.80M	41.17M	33.26F	29.79M	39.82M	L	39.72M	42.40F	38.49F	-	-	-	-
467	455.22	30.4830	29.34M	33.35F	20.85F	28.46F	30.83M	33.90F	23.49F	32.41M	36.18F	36.02M	-	-	-
468	564.22	41.3840	43.36M	43.57F	44.82F	37.46F	33.42F	46.10M	45.87F	43.78M	38.92F	36.54F	-	-	-
469	151.30	46.2700	47.26M	45.28F	-	-	-	-	-	-	-	-	-	-	-
470	463.38	38.1211	34.77F	34.25F	37.81F	38.55F	38.39M	41.34M	38.49F	38.49F	41.00M	-	-	-	-
471	534.35	47.7163	46.85M	52.89M	43.88F	48.72M	50.12F	51.32F	46.89M	41.06F	-	-	-	-	-
472	404.00	39.0671	44.18M	39.10M	35.97F	E	31.30F	44.00M	41.86M	37.06F	-	-	-	-	-
473	374.04	31.4750	40.35F	E	29.83M	21.31M	E	27.16F	26.85M	33.44M	34.39F	38.47M	-	-	-
474	462.93	36.7667	35.96F	18.44M	31.75F	44.82F	42.38F	38.29F	36.01F	42.55F	40.70M	-	-	-	-
475	557.58	37.6027	43.19M	41.59F	40.01M	34.79F	33.17M	37.80M	30.01M	29.51M	37.65F	40.78M	45.13M	-	-
476	480.53	39.2767	52.25M	39.47F	34.65F	28.94M	33.77M	45.71F	43.73F	41.06M	33.91F	-	-	-	-
477	412.19	35.7571	48.84F	E	34.51M	L	20.89F	37.98M	39.96M	35.33F	32.79F	-	-	-	-
478	397.33	32.3586	43.78F	37.25F	36.05F	26.70F	L	27.72M	25.43F	29.58F	-	-	-	-	-
479	499.65	31.4455	38.79F	32.14M	27.04M	28.80M	35.05M	34.72F	37.57F	27.30F	29.34F	24.32M	30.83M	-	-

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

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APPENDIX C

DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

INDIVIDUAL GRAVID UTERUS AND FETAL BODY WEIGHT DATA (GRAMS)

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

DAM #	GRAVID UTERUS		INDIVIDUAL FETAL WEIGHT												
	WEIGHT	MEAN FETAL WEIGHT	1	2	3	4	5	6	7	8	9	10	11	12	13
481	428.05	39.1429	40.32F	42.69F	41.61F	E	41.03F	34.02F	32.64M	41.69M	E	-	-	-	-
482	92.41	47.9200	47.92F	-	-	-	-	-	-	-	-	-	-	-	-
483	309.90	39.9760	E	E	36.27M	E	42.52M	E	E	35.01M	41.10M	44.98M	-	-	-
484	417.02	39.2314	43.01M	38.26M	44.14M	38.60M	E	35.82F	E	35.70M	39.09F	-	-	-	-
486	445.04	35.4900	40.24F	36.96M	32.49F	30.32M	29.14F	42.28F	39.60F	36.55M	31.83F	-	-	-	-
487	255.24	41.4525	39.48M	E	35.88F	43.06F	47.39M	-	-	-	-	-	-	-	-
488	145.43	40.4400	E	40.44M	E	L	L	-	-	-	-	-	-	-	-
492	320.05	44.5980	48.70F	48.53M	E	49.26F	E	45.97M	30.53M	-	-	-	-	-	-
493	470.85	33.9633	45.10F	29.11M	L	L	33.73M	34.15F	27.49F	42.80F	27.79F	32.88F	32.62M	-	-
494	332.68	46.7760	51.39F	E	E	49.83F	43.89F	51.59M	37.18M	-	-	-	-	-	-
496	214.97	40.0033	54.99F	27.76F	37.26M	E	E	E	E	E	E	-	-	-	-
497	408.58	34.3275	41.56M	34.85M	32.20F	22.85M	31.24F	39.70F	38.49F	33.73M	-	-	-	-	-
498	544.04	43.6350	25.26F	L	49.01M	43.93M	47.24F	42.26M	48.12M	48.12M	45.14M	-	-	-	-
499	348.32	40.7629	44.59F	41.10M	37.58M	38.78M	45.12M	42.17F	36.00F	-	-	-	-	-	-
500	232.37	48.2067	E	50.50M	50.60M	43.52F	-	-	-	-	-	-	-	-	-

MEAN 331.00 41.0617
 S.D. 125.91 4.5246
 N 15 15

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

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APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 401

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, RUDIMENTARY - VARIATION; BILATERAL	
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; DISTENDED, FLUID COLORLESS	
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; LEFT	
Fetal Position:	Left 06	Unique Fetal Id.: 6
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6 ONLY	
Fetal Position:	Right 01	Unique Fetal Id.: 7
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position:	Right 02	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.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 401 (CONT.)
 Fetal Position: Right 03 Unique Fetal Id.: 9
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Animal: 402
 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), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
 4, SLIGHT

Fetal Position: Left 03 Unique Fetal Id.: 3
 NECK
 (Visceral) THYROID, VARIATION - VARIATION; ENLARGED, RED

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

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

STERNUM
 (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION

Fetal Position: Right 04 Unique Fetal Id.: 7
 STERNUM
 (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 402 (CONT.)
Fetal Position: Right 05 Unique Fetal Id.: 8
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

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

Fetal Position: Right 06 Unique Fetal Id.: 9
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Animal: 403
Fetal Position: Left 01 Unique Fetal Id.: 1
RIBS
(Skeletal) RIB 13, FULL - VARIATION; RIGHT

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

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; LEFT FULL, RIGHT RUDIMENTARY

Fetal Position: Left 05 Unique Fetal Id.: 5
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL (NO
ARTICULATING HEADS)

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 403 (CONT.)

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, RUDIMENTARY - VARIATION; BILATERAL	
Fetal Position:	Right 03	Unique Fetal Id.: 8
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT	
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; LEFT (NO ARTICULATING HEAD)	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Animal: 404		
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	

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APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 404 (CONT.) Unique Fetal Id.: 4

Fetal Position: Left 04

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

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: Left 07 Unique Fetal Id.: 7

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

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 405
 Fetal Position: Left 02 Unique Fetal Id.: 2
 RIBS
 (Skeletal) RIB 13, RUDIMENTARY - 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 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 (NO ARTICULATING HEAD)

Fetal Position: Right 02 Unique Fetal Id.: 8
 RIBS
 (Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT

Fetal Position: Right 03 Unique Fetal Id.: 9
 RIBS
 (Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT

Animal: 406
 Fetal Position: Left 01 Unique Fetal Id.: 1

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

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 406
Fetal Position: Left 02 Unique Fetal Id.: 2
STERNUM
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

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

Fetal Position: Right 05 Unique Fetal Id.: 8
STERNUM
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
2-5, SLIGHT

Animal: 407
Fetal Position: Left 01 Unique Fetal Id.: 1
STERNUM
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
2, 3 AND 4, SLIGHT
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Fetal Position: Right 02 Unique Fetal Id.: 7
STERNUM
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY

Animal: 408
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 (NO ARTICULATING HEAD
ON RIGHT 13TH RIB)

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

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 408 (CONT.)
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: Right 01 Unique Fetal Id.: 5
THORACIC CAVITY
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARTERY 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.: 7
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

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

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS
 INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 409

Fetal Position:	Left 02 *	Unique Fetal Id.: 2
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
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 ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK	
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; LEFT	
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position:	Left 04	Unique Fetal Id.: 4
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
	CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK	
Fetal Position:	Right 01	Unique Fetal Id.: 5
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; RIGHT	
Fetal Position:	Right 02	Unique Fetal Id.: 6
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT	
SKULL		
(Skeletal)	HYOID BODY, UNOSSIFIED - VARIATION	

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 409 (CONT.)	Right 03	Unique Fetal Id.: 7
Fetal Position:		
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
	CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK	
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
SKULL		
(Skeletal)	HYOID ARCH(ES), BENT - VARIATION; LEFT, SLIGHT	
Fetal Position:	Right 04	Unique Fetal Id.: 8
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY	
SKULL		
(Skeletal)	HYOID BODY, UNOSSIFIED - VARIATION	
Fetal Position:	Right 05	Unique Fetal Id.: 9
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT (NO ARTICULATING HEAD / FLOATING)	
Fetal Position:	Right 06	Unique Fetal Id.: 10
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL 7TH CERVICAL RIB, PRESENT - VARIATION; BILATERAL	
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
Fetal Position:	Right 07	Unique Fetal Id.: 11
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 ONLY	
ABDOMEN		
(Visceral)	KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; LEFT KIDNEY MISPLACED CAUDALLY	

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 410		Unique Fetal Id.: 2
Fetal Position: Left 02		
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	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 01		Unique Fetal Id.: 7
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT RUDIMENTARY, RIGHT FULL	
Fetal Position: Right 02		Unique Fetal Id.: 8
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK	
Fetal Position: Right 03		Unique Fetal Id.: 9
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT	

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APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 410 (CONT.)

Fetal Position: Right 04 Unique Fetal Id.: 10
 THORACIC CAVITY
 (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK

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

Animal: 411

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

(Skeletal) HYOID ARCH(ES), BENT - VARIATION; RIGHT, MODERATE

Fetal Position: Left 04 Unique Fetal Id.: 4
 ABDOMEN
 (Visceral) GALL BLADDER, VARIATION - VARIATION; ENLARGED

Fetal Position: Right 01 Unique Fetal Id.: 5
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

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

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 ONLY

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 412		Unique Fetal Id.: 2
Fetal Position: Left 02		
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; RIGHT, WITH SMALL ARTICULATING HEAD	
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY WITH NO ARTICULATING HEAD	
Fetal Position: Left 04		Unique Fetal Id.: 4
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Left 05		Unique Fetal Id.: 5
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 8 CERVICAL VERTEBRAE - MALFORMATION; WITH A 8TH CERVICAL RIB, LEFT	
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE	
Fetal Position: Right 01		Unique Fetal Id.: 6
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; RIGHT	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 412 (CONT.) Unique Fetal Id.: 8

Fetal Position: Right 03

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

VERTEBRAL COLUMN VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

(Skeletal)

ABDOMEN GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE

(Visceral)

Fetal Position: Right 04 Unique Fetal Id.: 9

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

VERTEBRAL COLUMN VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

(Skeletal)

ABDOMEN GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE

(Visceral)

Fetal Position: Right 05 Unique Fetal Id.: 10

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

VERTEBRAL COLUMN VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

(Skeletal)

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 413		Unique Fetal Id.: 2
Fetal Position: Left 02		
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; BILATERAL, WITH SMALL ARTICULATING HEADS	
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS		
(Skeletal)	RIB(S), BENT - VARIATION; 8 AND 9, RIGHT, SLIGHT	
Fetal Position: Right 01		Unique Fetal Id.: 5
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK	
SKULL		
(Skeletal)	HYOID ARCH(ES), BENT - VARIATION; LEFT, SLIGHT	
Fetal Position: Right 03		Unique Fetal Id.: 7
EYES		
(Visceral)	AROUND IRIS, HEMORRHAGIC RING - VARIATION; RIGHT	
Fetal Position: Right 04		Unique Fetal Id.: 8
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; DISTENDED	

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 414
 Fetal Position: Right 02 Unique Fetal Id.: 4
 RIBS
 (Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

Fetal Position: Right 05 Unique Fetal Id.: 7
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; RIGHT, FULL; LEFT RUDIMENTARY
 WITH NO ARTICULATING HEAD

Animal: 415
 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, FULL - VARIATION; BILATERAL

Fetal Position: Left 03 Unique Fetal Id.: 3
 THORACIC CAVITY
 (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK

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

Fetal Position: Right 01 Unique Fetal Id.: 5
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; RIGHT, FULL; LEFT RUDIMENTARY

ABDOMEN
 (Visceral) LIVER, WHITE AREAS - VARIATION; LEFT LOBE, 3 MM IN
 DIAMETER

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 415 (CONT.) Unique Fetal Id.: 7

Fetal Position: Right 03

RIBS (Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT

Fetal Position: Right 04 Unique Fetal Id.: 8

RIBS (Skeletal) RIB 13, FULL - VARIATION; RIGHT, FULL; LEFT, RUDIMENTARY

STERNUM

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

Fetal Position: Right 05 Unique Fetal Id.: 9

THORACIC CAVITY

(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT

CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK

RIBS

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

Fetal Position: Right 06 Unique Fetal Id.: 10

RIBS (Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

Animal: 416 Unique Fetal Id.: 1

Fetal Position: Left 01

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

Fetal Position: Left 02 Unique Fetal Id.: 2

RIBS (Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL, WITH NO ARTICULATING HEADS

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 416 (CONT.)		Unique Fetal Id.: 3
Fetal Position: Left 03		
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
STERNUM		
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 - 5, SLIGHT	
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; RIGHT	
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, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; DISTENDED	

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 416 (CONT.)
 Fetal Position: Right 03 Unique Fetal Id.: 8
 THORACIC CAVITY
 (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK

Fetal Position: Right 04 Unique Fetal Id.: 9
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

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

Fetal Position: Right 05 Unique Fetal Id.: 10
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

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

Animal: 417
 Fetal Position: Left 01 Unique Fetal Id.: 1
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

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

Fetal Position: Left 02 Unique Fetal Id.: 2
 EYES
 (Visceral) AROUND IRIS, HEMORRHAGIC RING - VARIATION; RIGHT

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 417 (CONT.) Unique Fetal Id.: 3
Fetal Position: Right 01
RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
(Skeletal)
SKULL SKULL, ACCESSORY SKULL BONES - VARIATION; TWO, 1 MM X 2 MM
(Skeletal) EACH, ANTERIOR PORTION OF PARIETAL SUTURE, BILATERAL
Fetal Position: Right 02 Unique Fetal Id.: 4
RIBS (Skeletal) RIB 13, FULL - VARIATION; RIGHT, FULL; LEFT, RUDIMENTARY
STERNUM STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY
(Skeletal)
VERTEBRAL COLUMN VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
(Skeletal)
Fetal Position: Right 04 Unique Fetal Id.: 6
RIBS (Skeletal) RIB 13, FULL - VARIATION; LEFT
Animal: 418 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

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 418 (CONT.)		Unique Fetal Id.: 4
Fetal Position:	Left 04	
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
	CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
Fetal Position:	Left 05	Unique Fetal Id.: 5
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position:	Right 01	Unique Fetal Id.: 6
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
	CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
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; RIGHT, FULL; LEFT, RUDIMENTARY	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
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 06	Unique Fetal Id.: 11
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT	

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 419		Unique Fetal Id.: 1
Fetal Position: Left 01		
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE	
Fetal Position: Left 03		Unique Fetal Id.: 3
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; ACCESSORY LEFT SUBCLAVIAN	
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; BILATERAL; LEFT WITH NO ARTICULATING HEAD	
Fetal Position: Left 05		Unique Fetal Id.: 5
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK, ACCESSORY LEFT SUBCLAVIAN	
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; RIGHT, RUDIMENTARY; LEFT, FULL	
STERNUM		
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 - 5, SLIGHT TO MODERATE	

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 419 (CONT.)	Left 06	Unique Fetal Id.: 6
Fetal Position:		
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
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
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; ACCESSORY LEFT SUBCLAVIAN	
SKULL		
(Skeletal)	HYOID ARCH(ES), BENT - VARIATION; RIGHT, SLIGHT	
Fetal Position:	Right 03	Unique Fetal Id.: 9
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; ACCESSORY LEFT SUBCLAVIAN	
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position:	Right 04	Unique Fetal Id.: 10
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 419 (CONT.)
Fetal Position: Right 05 Unique Fetal Id.: 11
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT, WITH NO
ARTICULATING HEAD

Fetal Position: Right 06 Unique Fetal Id.: 12
THORACIC CAVITY
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION;
RETROESOPHAGEAL RIGHT SUBCLAVIAN

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

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

Animal: 420
Fetal Position: Left 01 Unique Fetal Id.: 1
THORACIC CAVITY
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK

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

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

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

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 1: 0 MG/KG/DAY

Animal: 420 (CONT.)
Fetal Position: Right 01 Unique Fetal Id.: 5
THORACIC CAVITY
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK

RIBS
(Skeletal) RIB 13, FULL - VARIATION; RIGHT, FULL; LEFT, RUDIMENTARY

Fetal Position: Right 02 Unique Fetal Id.: 6
THORACIC CAVITY
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK

VERTEBRAL COLUMN
(Skeletal) VERTEBRAL ANOMALY WITH ASSOCIATED RIB ANOMALY -
MALFORMATION; INVOLVING THORACIC VERTEBRAE AND RIBS 9 - 12

Fetal Position: Right 03 Unique Fetal Id.: 7
THORACIC CAVITY
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK

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

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

Animal: 421
 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, RUDIMENTARY - VARIATION; RIGHT, NO ARTICULATING HEAD
 Fetal Position: Left 04 Unique Fetal Id.: 4
 SKULL
 (Skeletal) HYOID BODY, UNOSSIFIED - VARIATION
 Fetal Position: Left 05 Unique Fetal Id.: 5
 STERNUM
 (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
 Fetal Position: Right 05 Unique Fetal Id.: 11
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY
 Animal: 422
 Fetal Position: Right 02 Unique Fetal Id.: 4
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL
 VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
 Animal: 423
 Fetal Position: Right 04 Unique Fetal Id.: 8
 RIBS
 (Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

Animal: 424
 Fetal Position: Right 03 Unique Fetal Id.: 3
 VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Animal: 426
 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, RUDIMENTARY - VARIATION; RIGHT

Fetal Position: Right 01 Unique Fetal Id.: 4
 RIBS
 (Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT, NO ARTICULATING HEAD

Fetal Position: Right 02 Unique Fetal Id.: 5
 STERNUM
 (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
 3 - 5, SLIGHT TO MODERATE

Fetal Position: Right 03 Unique Fetal Id.: 6
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 04 Unique Fetal Id.: 7
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 05 Unique Fetal Id.: 8
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 06 Unique Fetal Id.: 9
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS
 INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

Animal: 427		Unique Fetal Id.: 2
Fetal Position:	Left 02	
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; RIGHT, FULL; LEFT, RUDIMENTARY	
Fetal Position:	Right 03	Unique Fetal Id.: 5
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position:	Right 06	Unique Fetal Id.: 8
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; RIGHT	
Animal: 428		
Fetal Position:	Left 01	Unique Fetal Id.: 1
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; DISTENDED, FLUID--COLORLESS	
Fetal Position:	Left 02	Unique Fetal Id.: 2
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK	
Fetal Position:	Right 02	Unique Fetal Id.: 4
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; RIGHT, FULL; LEFT, RUDIMENTARY	
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; FIVE, ONLY	
Fetal Position:	Right 03	Unique Fetal Id.: 5
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; FIVE, ONLY	

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

Animal: 428 (CONT.) Unique Fetal Id.: 6

Fetal Position: Right 04

STERNUM

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

Fetal Position: Right 05 Unique Fetal Id.: 7

RIBS

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT

STERNUM

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

Fetal Position: Right 07 Unique Fetal Id.: 9

RIBS

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

Animal: 429 Unique Fetal Id.: 2

Fetal Position: Left 02

SKULL

(Skeletal) HYOID ARCH(ES), BENT - VARIATION; RIGHT, SLIGHT

Fetal Position: Left 03 Unique Fetal Id.: 3

RIBS

(Skeletal) RIB 13, FULL - VARIATION; RIGHT

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

Fetal Position: Right 01 Unique Fetal Id.: 6

RIBS

(Skeletal) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

Animal: 429 (CONT.)	Unique Fetal Id.: 8
Fetal Position: Right 03	
RIBS (Skeletal)	RIB 13, FULL - VARIATION; RIGHT, FULL; LEFT, RUDIMENTARY
STERNUM (Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; FIVE, ONLY
Animal: 430	
Fetal Position: Left 01	Unique Fetal Id.: 1
RIBS (Skeletal)	RIB 13, RUDIMENTARY - VARIATION; BILATERAL
STERNUM (Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; FIVE, ONLY
ABDOMEN (Visceral)	KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; LEFT KIDNEY--MISPLACED CAUDALLY
Fetal Position: Left 02	Unique Fetal Id.: 2
RIBS (Skeletal)	RIB 13, RUDIMENTARY - VARIATION; RIGHT, NO ARTICULATING HEAD
STERNUM (Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; FIVE, ONLY
Fetal Position: Left 03	Unique Fetal Id.: 3
NECK (Visceral)	THYMUS, VARIATION - VARIATION; RED, SMALL
THORACIC CAVITY (Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK
RIBS (Skeletal)	RIB 13, FULL - VARIATION; BILATERAL
STERNUM (Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; FIVE, ONLY

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

Animal: 430 (CONT.) Unique Fetal Id.: 4

Fetal Position: Left 04

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

SKULL

(Skeletal) HYOID BODY, UNOSSIFIED - VARIATION

Fetal Position: Right 01 Unique Fetal Id.: 5

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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), 5-6, UNOSSIFIED - VARIATION; FIVE, ONLY

Fetal Position: Right 04 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.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

Animal: 430 (CONT.)
Fetal Position: Right 05 Unique Fetal Id.: 9
RIBS
(Skeletal) RIB 13, FULL - VARIATION; LEFT, NO ARTICULATING HEAD
STERNUM
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; FIVE, ONLY
VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
Animal: 431
Fetal Position: Left 02 Unique Fetal Id.: 2
RIBS
(Skeletal) RIB 13, FULL - VARIATION; RIGHT, RUDIMENTARY; LEFT, FULL
VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
EYES
(Visceral) AROUND IRIS, HEMORRHAGIC RING - VARIATION; RIGHT
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; RIGHT, RUDIMENTARY; LEFT, FULL
Fetal Position: Left 05 Unique Fetal Id.: 5
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT
VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

Animal: 431 (CONT.) Unique Fetal Id.: 6

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.: 7

RIBS

(Skeletal) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 03 Unique Fetal Id.: 8

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 04 Unique Fetal Id.: 9

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Animal: 432

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, RUDIMENTARY - VARIATION; BILATERAL

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

Animal: 432 (CONT.) Unique Fetal Id.: 5
Fetal Position: Left 05
THORACIC CAVITY
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

Fetal Position: Right 02 Unique Fetal Id.: 8
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT, FLOATING

Fetal Position: Right 04 Unique Fetal Id.: 10
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT, FLOATING

Fetal Position: Right 05 Unique Fetal Id.: 11
ABDOMEN
(Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE

Animal: 433 Unique Fetal Id.: 1
Fetal Position: Left 01
STERNUM
(Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; FIVE, ONLY

ABDOMEN
(Visceral) LIVER, CYST(S) - VARIATION; LEFT LATERAL LOBE, 2, PINPOINT

Fetal Position: Right 01 Unique Fetal Id.: 3
STERNUM
(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
FIVE, SLIGHT

Fetal Position: Right 02 Unique Fetal Id.: 4
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT, NO ARTICULATING
HEAD

Fetal Position: Right 04 Unique Fetal Id.: 6
ABDOMEN
(Visceral) GALL BLADDER, VARIATION - VARIATION; DISTENDED

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

Animal: 434 (CONT.)
 Fetal Position: Left 01 Unique Fetal Id.: 1
 RIBS
 (Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT
 VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
 Fetal Position: Left 02 Unique Fetal Id.: 2
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL
 Fetal Position: Left 04 Unique Fetal Id.: 4
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL
 Fetal Position: Right 02 Unique Fetal Id.: 6
 RIBS
 (Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT
 STERNUM
 (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
 3 - 4, SLIGHT
 Animal: 435
 Fetal Position: Left 01 Unique Fetal Id.: 1
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL
 VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
 Fetal Position: Right 01 Unique Fetal Id.: 2
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL
 VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

Animal: 435 (CONT.)		Unique Fetal Id.: 3
Fetal Position:	Right 02	
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; RIGHT, RUDIMENTARY; LEFT, FULL	
Fetal Position:	Right 04	Unique Fetal Id.: 5
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY	
SKULL		
(Skeletal)	HYOID ARCH(ES), BENT - VARIATION; RIGHT, SLIGHT	
Fetal Position:	Right 05	Unique Fetal Id.: 6
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
Animal: 436		
Fetal Position:	Left 01	Unique Fetal Id.: 1
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; RIGHT	
STERNUM		
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 - 5, SLIGHT TO MODERATE	
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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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

Animal: 436 (CONT.) Unique Fetal Id.: 4

Fetal Position: Left 04

THORACIC CAVITY HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT

(Visceral) CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

STERNUM

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

3 - 4, SLIGHT

VERTEBRAL COLUMN

(Skeletal) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE

MALALIGNED AND MALFORMED

ABDOMEN

(Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE

Fetal Position: Left 05 Unique Fetal Id.: 5

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 06 Unique Fetal Id.: 6

THORACIC CAVITY

(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT

CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

ABDOMEN

(Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

Animal: 436 (CONT.) Unique Fetal Id.: 7

Fetal Position: Right 01

RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL; LEFT WITH NO ARTICULATING HEAD

ABDOMEN (Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE

Fetal Position: Right 02 Unique Fetal Id.: 8

THORACIC CAVITY (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

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

ABDOMEN (Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE

Fetal Position: Right 03 Unique Fetal Id.: 9

THORACIC CAVITY (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

VERTEBRAL COLUMN (Skeletal) VERTEBRAL ANOMALY WITH ASSOCIATED RIB ANOMALY - MALFORMATION; INVOLVES THORACIC VERTEBRAE 6 - 12 AND RIGHT RIBS 6 - 7

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; LEFT

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

Animal: 436 (CONT.)	Right 05	Unique Fetal Id.: 11
Fetal Position:		
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	
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE	
Fetal Position: Right 06	Unique Fetal Id.: 12	
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
	CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
Fetal Position: Right 07	Unique Fetal Id.: 13	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Animal: 437		
Fetal Position: Left 01	Unique Fetal Id.: 1	
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; RIGHT, FLOATING RIB	
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; RIGHT, FULL; LEFT RUDIMENTARY AND FLOATING	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

Animal: 437 (CONT.) Unique Fetal Id.: 4

Fetal Position: Left 04

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

ABDOMEN (Visceral) GALL BLADDER, VARIATION - VARIATION; ENLARGED

Fetal Position: Right 01 Unique Fetal Id.: 5

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

VERTEBRAL COLUMN VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

(Skeletal)

Fetal Position: Right 02 Unique Fetal Id.: 6

ABDOMEN (Visceral) GALL BLADDER, VARIATION - VARIATION; DISTENDED

Animal: 438 Unique Fetal Id.: 2

Fetal Position: Left 02

ABDOMEN (Visceral) GALL BLADDER, VARIATION - VARIATION; ENLARGED WITH CLEAR FLUID

Fetal Position: Left 04 Unique Fetal Id.: 4

RIBS (Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT

Fetal Position: Right 01 Unique Fetal Id.: 8

RIBS (Skeletal) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT RUDIMENTARY

ABDOMEN (Visceral) GALL BLADDER, VARIATION - VARIATION; ENLARGED WITH CLEAR FLUID

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

Animal: 438 (CONT.)		Unique Fetal Id.: 9
Fetal Position:	Right 02	
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; ENLARGED	
Animal: 439		
Fetal Position:	Left 03	Unique Fetal Id.: 3
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL; 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	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
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	
STERNUM		
(Skeletal)	STERNEBRA(E), FUSED - MALFORMATION; 2 - 5, MALALIGNED; 3 - 4 FUSED	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

Animal: 439 (CONT.)
 Fetal Position: Right 03 Unique Fetal Id.: 8
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 04 Unique Fetal Id.: 9
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Animal: 440
 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; BILATERAL

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; BILATERAL

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

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

SKULL
 (Skeletal) HYOID ARCH(ES), BENT - VARIATION; BILATERAL, SLIGHT

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 2: 0.5 MG BASE/KG/DAY

Animal: 440 (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, ACCESSORY	
LEFT SUBCLAVIAN	
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL
STERNUM	
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
	3 - 5, SLIGHT
Fetal Position: Right 04	Unique Fetal Id.: 7
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL
SKULL	
(Skeletal)	SKULL, ANOMALY - MALFORMATION; INTERPARIETAL ABSENT
	HYOID ARCH(ES), BENT - VARIATION; BILATERAL, MODERATE
ABDOMEN	
(Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE
Fetal Position: Right 05	Unique Fetal Id.: 8
RIBS	
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; RIGHT
Fetal Position: Right 06	Unique Fetal Id.: 9
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN	
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 441
Fetal Position: Left 01 Unique Fetal Id.: 1
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;
4 - 5, SLIGHT
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
THORACIC CAVITY
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; NO
BRACHIOCEPHALIC TRUNK
RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL
ABDOMEN (Visceral) KIDNEY(S), RENAL PAPILLAE NOT DEVELOPED - VARIATION; WOO
AND HOAR GRADE 1

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 441 (CONT.)		Unique Fetal Id.: 5
Fetal Position: Left 05		
RIBS (Skeletal)	RIB 13, RUDIMENTARY - VARIATION; LEFT, FLOATING RIB	
SKULL (Skeletal)	HYOID ARCH(ES), BENT - VARIATION; RIGHT, SLIGHT	
Fetal Position: Left 06		Unique Fetal Id.: 6
RIBS (Skeletal)	RIB 13, RUDIMENTARY - VARIATION; RIGHT	
STERNUM (Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 - 5, SLIGHT TO MODERATE	
ABDOMEN (Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE	
Fetal Position: Left 07		Unique Fetal Id.: 7
RIBS (Skeletal)	RIB 13, FULL - VARIATION; LEFT	
Fetal Position: Right 01		Unique Fetal Id.: 8
RIBS (Skeletal)	RIB 13, RUDIMENTARY - VARIATION; LEFT, FLOATING RIB	
Fetal Position: Right 02		Unique Fetal Id.: 9
RIBS (Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
STERNUM (Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT	
Fetal Position: Right 05		Unique Fetal Id.: 12
STERNUM (Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 442 (CONT.)
Fetal Position: Left 02 Unique Fetal Id.: 2
RIBS
(Skeletal) RIB 13, FULL - VARIATION; RIGHT
ABDOMEN
(Visceral) KIDNEY(S), PALE - VARIATION; BILATERAL

Animal: 443
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; RIGHT, FULL; LEFT, RUDIMENTARY
AND FLOATING

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;
2 - 5, SLIGHT TO MODERATE

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 443 (CONT.) Unique Fetal Id.: 5

Fetal Position: Left 05

THORACIC CAVITY

(Visceral) HEART, HEART AND/OR GREAT VESSEL, ANOMALY - MALFORMATION;
BULBOUS AORTIC ARCH

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

STERNUM

(Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
2 - 4, SLIGHT TO MODERATE
STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 06 Unique Fetal Id.: 6

RIBS

(Skeletal) RIB 13, FULL - VARIATION; LEFT

Fetal Position: Right 01 Unique Fetal Id.: 7

STERNUM

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

Fetal Position: Right 02 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

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 443 (CONT.)	Unique Fetal Id.: 9
Fetal Position: Right 03	
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL
STERNUM	
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 3 - 4, SLIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
VERTEBRAL COLUMN	
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
Fetal Position: Right 04	Unique Fetal Id.: 10
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; RIGHT
STERNUM	
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
Fetal Position: Right 05	Unique Fetal Id.: 11
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL
Fetal Position: Right 07	Unique Fetal Id.: 13
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; LEFT
STERNUM	
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
Animal: 444	Unique Fetal Id.: 1
Fetal Position: Left 01	
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY; RIGHT, FULL

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 444 (CONT.) Unique Fetal Id.: 2
 Fetal Position: Left 02
 THORACIC CAVITY
 (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

RIBS
 (Skeletal) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY; RIGHT, FULL

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

Fetal Position: Right 01 Unique Fetal Id.: 4
 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

Fetal Position: Right 04 Unique Fetal Id.: 7
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

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

Animal: 445 Unique Fetal Id.: 2
 Fetal Position: Left 02
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; RIGHT, FULL; LEFT, RUDIMENTARY

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 445 (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; LEFT
Fetal Position: Right 01 Unique Fetal Id.: 5
RIBS
(Skeletal) RIB 13, FULL - VARIATION; RIGHT
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
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT
Fetal Position: Right 04 Unique Fetal Id.: 8
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL
VERTEBRAL COLUMN
(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 445 (CONT.)
 Fetal Position: Right 05 Unique Fetal Id.: 9
 RIBS
 (Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL
 VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
 SKULL
 (Skeletal) HYOID ARCH(ES), BENT - VARIATION; LEFT, SEVERE

Animal: 446
 Fetal Position: Right 01 Unique Fetal Id.: 4
 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
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL
 Fetal Position: Right 06 Unique Fetal Id.: 9
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Animal: 447
 Fetal Position: Left 01 Unique Fetal Id.: 1
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY
 STERNUM
 (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY
 ABDOMEN
 (Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 447 (CONT.)

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, 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	

Animal: 448

Fetal Position:	Left 01	Unique Fetal Id.: 1
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION;	LEFT, RUDIMENTARY; RIGHT, FULL
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION;	DISTENDED
Fetal Position:	Left 02	Unique Fetal Id.: 2
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION;	LEFT, FULL; RIGHT, RUDIMENTARY
SKULL		
(Skeletal)	HYOID ARCH(ES), BENT - VARIATION;	BILATERAL, SLIGHT
Fetal Position:	Left 03	Unique Fetal Id.: 3
STERNUM		
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;	
	4 - 5, SLIGHT	
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION;	DISTENDED WITH CLEAR FLUID

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 448 (CONT.)		Unique Fetal Id.: 4
Fetal Position: Left 04		
SKULL		
(Skeletal)	HYOID ARCH(ES), BENT - VARIATION; BILATERAL, SLIGHT	
Fetal Position: Left 05		Unique Fetal Id.: 5
THORACIC CAVITY	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
(Visceral)	CAROTID ARISING FROM BRACHIOCEPHALIC TRUNK	
Fetal Position: Left 07		Unique Fetal Id.: 7
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
ABDOMEN		
(Visceral)	KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; LEFT	
	KIDNEY MISPLACED CAUDALLY	
Fetal Position: Left 08		Unique Fetal Id.: 8
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
	CAROTID ARISING FROM BRACHIOCEPHALIC TRUNK	
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
Animal: 449		Unique Fetal Id.: 1
Fetal Position: Left 01		
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 449 (CONT.)	Left 02	Unique Fetal Id.: 2
Fetal Position:		
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
	CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT RUDIMENTARY AND FLOATING	
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, RUDIMENTARY - VARIATION; LEFT, FLOATING RIB	
Fetal Position:	Left 05	Unique Fetal Id.: 5
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
	CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; RIGHT	
Fetal Position:	Right 01	Unique Fetal Id.: 7
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
Fetal Position:	Right 02	Unique Fetal Id.: 8
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
	CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; RIGHT	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 449 (CONT.) Unique Fetal Id.: 9
 Fetal Position: Right 03
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Animal: 450 Unique Fetal Id.: 2
 Fetal Position: Left 02
 THORACIC CAVITY
 (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 CAROTID ARISING FROM BRACHIOCEPHALIC TRUNK

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

Unique Fetal Id.: 8
 Fetal Position: Right 02
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; LEFT

Unique Fetal Id.: 9
 Fetal Position: Right 03
 RIBS
 (Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT, FLOATING RIB

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

ABDOMEN
 (Visceral) GALL BLADDER, VARIATION - VARIATION; DISTENDED WITH CLEAR
 FLUID

Animal: 451 Unique Fetal Id.: 1
 Fetal Position: Left 01
 RIBS
 (Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT

Unique Fetal Id.: 2
 Fetal Position: Left 02
 RIBS
 (Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 451 (CONT.) Unique Fetal Id.: 9

Fetal Position: Right 04

ABDOMEN

(Visceral) GALL BLADDER, VARIATION - VARIATION; ENLARGED

Fetal Position: Right 05 Unique Fetal Id.: 10

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Animal: 452 Unique Fetal Id.: 1

Fetal Position: Left 01

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

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: Right 01 Unique Fetal Id.: 6

RIBS

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT

STERNUM

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

SKULL

(Skeletal) HYOID ARCH(ES), BENT - VARIATION; RIGHT, SLIGHT

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 452 (CONT.)		Unique Fetal Id.: 7
Fetal Position: Right 02		
THORACIC CAVITY		
(Visceral)	HEART, HEART AND/OR GREAT VESSEL, ANOMALY - MALFORMATION;	
	INTERVENTRICULAR SEPTAL DEFECT, ANTERIOR PORTION OF	
	SEPTUM; BULBOUS PULMONARY TRUNK; VESTIGIAL AORTIC ARCH	
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY	
	WITH NO ARTICULATING HEAD	
Animal: 454		Unique Fetal Id.: 1
Fetal Position: Left 01		
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
	CAROTID ARISING FROM BRACHIOCEPHALIC TRUNK	
Fetal Position: Left 02		Unique Fetal Id.: 2
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; ENLARGED	
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; LEFT, FLOATING RIB	
Fetal Position: Right 04		Unique Fetal Id.: 7
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
Animal: 455		Unique Fetal Id.: 1
Fetal Position: Left 01		
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; DISTENDED	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 455 (CONT.)		Unique Fetal Id.: 2
Fetal Position: Left 02		
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; 5, ONLY	
Fetal Position: Left 04		Unique Fetal Id.: 4
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; DISTENDED	
Fetal Position: Right 01		Unique Fetal Id.: 5
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Fetal Position: Right 03		Unique Fetal Id.: 7
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; LEFT	
Animal: 456		
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 - 5, SLIGHT TO MODERATE	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Left 02		Unique Fetal Id.: 2
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 456 (CONT.)	Left 03	Unique Fetal Id.: 3
Fetal Position:		
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:	Left 04	Unique Fetal Id.: 4
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - 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	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position:	Right 01	Unique Fetal Id.: 6
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; RIGHT, FULL; LEFT, RUDIMENTARY	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 456 (CONT.) Unique Fetal Id.: 7

Fetal Position: Right 02

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

VERTEBRAL COLUMN VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

(Skeletal)

ABDOMEN GALL BLADDER, VARIATION - VARIATION; DISTENDED (Visceral)

Fetal Position: Right 03 Unique Fetal Id.: 8

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

VERTEBRAL COLUMN VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

(Skeletal)

Animal: 457 Unique Fetal Id.: 1

Fetal Position: Left 01

RIBS (Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT

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

Fetal Position: Left 02 Unique Fetal Id.: 2

RIBS (Skeletal) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY; RIGHT, FULL

ABDOMEN KIDNEY(S), HYDRONEPHROSIS - VARIATION; RIGHT, SLIGHT (Visceral)

Fetal Position: Right 01 Unique Fetal Id.: 4

RIBS (Skeletal) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT RUDIMENTARY

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

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 457 (CONT.) Unique Fetal Id.: 6

Fetal Position: Right 03

STERNUM

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

SKULL

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

Fetal Position: Right 04 Unique Fetal Id.: 7

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Animal: 458

Fetal Position: Left 01 Unique Fetal Id.: 1

THORACIC CAVITY

(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT

CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

SKULL

(Skeletal) HYOID ARCH(ES), BENT - VARIATION; LEFT, SEVERE

Fetal Position: Left 02 Unique Fetal Id.: 2

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 01 Unique Fetal Id.: 4

SKULL

(Skeletal) HYOID ARCH(ES), BENT - VARIATION; RIGHT, SEVERE

ABDOMEN

(Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 459

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; RIGHT	
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; BILATERAL; RIGHT WITH NO ARTICULATING HEAD	
Fetal Position:	Right 03	Unique Fetal Id.: 6
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; LEFT, FLOATING RIB	
Fetal Position:	Right 04	Unique Fetal Id.: 7
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position:	Right 05	Unique Fetal Id.: 8
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	

Animal: 460

Fetal Position:	Left 01	Unique Fetal Id.: 1
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 460 (CONT.) Unique Fetal Id.: 2

Fetal Position: Left 02

THORACIC CAVITY (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS (Skeletal) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY WITH NO ARTICULATING HEAD

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 THE BRACHIOCEPHALIC TRUNK

Fetal Position: Left 04 Unique Fetal Id.: 4

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

Fetal Position: Left 05 Unique Fetal Id.: 5

THORACIC CAVITY (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

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

ABDOMEN (Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE SPLEEN, SMALL IN SIZE - VARIATION

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 460 (CONT.) Unique Fetal Id.: 6

Fetal Position: Left 06

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

Fetal Position: Left 07 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

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

ABDOMEN
(Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE

Fetal Position: Left 08 Unique Fetal Id.: 8

THORACIC CAVITY
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS
(Skeletal) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY

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

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 3: 1.3 MG BASE/KG/DAY

Animal: 460 (CONT.)	Unique Fetal Id.: 9
Fetal Position: Right 01	
THORACIC CAVITY	
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION;
	ACCESSORY LEFT SUBCLAVIAN, LEFT CAROTID ARISES FROM THE
	BRACHIOCEPHALIC TRUNK
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN	
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
Fetal Position: Right 02	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
ABDOMEN	
(Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE
Fetal Position: Right 03	Unique Fetal Id.: 11
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN	
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
ABDOMEN	
(Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 461

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		
STERNUM			
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY		
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
RIBS			
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; RIGHT		
STERNUM			
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY		
Fetal Position:	Right 04	Unique Fetal Id.:	7
RIBS			
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; RIGHT		

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 462
 Fetal Position: Left 01 Unique Fetal Id.: 1
 RIBS
 (Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT

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

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, FULL - VARIATION; BILATERAL

Fetal Position: Right 01 Unique Fetal Id.: 4
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

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

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

Fetal Position: Right 04

Animal: 463
 Fetal Position: Right 02 Unique Fetal Id.: 3
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY

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

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 463 (CONT.) Unique Fetal Id.: 4
 Fetal Position: Right 03
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; LEFT

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

Fetal Position: Right 04 Unique Fetal Id.: 5
 RIBS
 (Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT

Animal: 465 Unique Fetal Id.: 1
 Fetal Position: Left 01
 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

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

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

Fetal Position: Right 04 Unique Fetal Id.: 9
 RIBS
 (Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT

Animal: 467 Unique Fetal Id.: 1
 Fetal Position: Left 01
 ABDOMEN
 (Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 467 (CONT.)		Unique Fetal Id.: 2
Fetal Position:	Left 02	
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE	
Fetal Position:	Left 03	Unique Fetal Id.: 3
SKULL		
(Skeletal)	HYOID BODY, UNOSSIFIED - VARIATION	
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE	
Fetal Position:	Left 04	Unique Fetal Id.: 4
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE	
Fetal Position:	Left 05	Unique Fetal Id.: 5
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE	
Fetal Position:	Left 06	Unique Fetal Id.: 6
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE	
Fetal Position:	Left 07	Unique Fetal Id.: 7
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE	
Fetal Position:	Left 08	Unique Fetal Id.: 8
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE	
Fetal Position:	Right 01	Unique Fetal Id.: 9
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE	

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 468
 Fetal Position: Left 01 Unique Fetal Id.: 1
 THORACIC CAVITY
 (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

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 BRACHIOCEPHALIC TRUNK

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

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

RIBS
 (Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT

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, RUDIMENTARY - VARIATION; RIGHT

Fetal Position: Right 01 Unique Fetal Id.: 6
 THORACIC CAVITY
 (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 468 (CONT.) Unique Fetal Id.: 7

Fetal Position: Right 02

THORACIC CAVITY HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT

(Visceral) CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

ABDOMEN

(Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE

Fetal Position: Right 03 Unique Fetal Id.: 8

THORACIC CAVITY HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT

(Visceral) CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

Fetal Position: Right 04 Unique Fetal Id.: 9

THORACIC CAVITY HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT

(Visceral) CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 05 Unique Fetal Id.: 10

RIBS

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

Animal: 469

Fetal Position: Left 01 Unique Fetal Id.: 1

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

ABDOMEN

(Visceral) LIVER, ENLARGED - VARIATION; DIFFUSE

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 469 (CONT.)		Unique Fetal Id.: 2
Fetal Position: Right 01		
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Animal: 470		Unique Fetal Id.: 1
Fetal Position: Left 01		
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
Fetal Position: Left 02		Unique Fetal Id.: 2
THORACIC CAVITY	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
(Visceral)	CAROTID ARISING FROM BRACHIOCEPHALIC TRUNK	
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
THORACIC CAVITY	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
(Visceral)	CAROTID ARISING FROM BRACHIOCEPHALIC TRUNK	
Fetal Position: Left 04		Unique Fetal Id.: 4
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; RIGHT, FULL; LEFT, RUDIMENTARY	
Fetal Position: Left 05		Unique Fetal Id.: 5
THORACIC CAVITY	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
(Visceral)	CAROTID ARISING FROM BRACHIOCEPHALIC TRUNK	
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; DISTENDED WITH CLEAR FLUID	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 470 (CONT.)
Fetal Position: Right 01 Unique Fetal Id.: 8
THORACIC CAVITY
(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISING FROM BRACHIOCEPHALIC TRUNK

Animal: 471
Fetal Position: Left 01 Unique Fetal Id.: 1
RIBS
(Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT

ABDOMEN
(Visceral) GALL BLADDER, VARIATION - VARIATION; DISTENDED

Fetal Position: Left 02 Unique Fetal Id.: 2
ABDOMEN
(Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; LEFT, SLIGHT

Fetal Position: Left 03 Unique Fetal Id.: 3
ABDOMEN
(Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; LEFT, SLIGHT

Animal: 472
Fetal Position: Left 02 Unique Fetal Id.: 2
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

SKULL
(Skeletal) HYOID ARCH(ES), BENT - VARIATION; BILATERAL, MODERATE

ABDOMEN
(Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE

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.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 472 (CONT.) Unique Fetal Id.: 5
 Fetal Position: Left 05
 EYES (Visceral) AROUND IRIS, HEMORRHAGIC RING - VARIATION; RIGHT
 Fetal Position: Right 02 Unique Fetal Id.: 7
 RIBS (Skeletal) RIB 13, FULL - VARIATION; LEFT, RUDIMENTARY, RIGHT, FULL
 Fetal Position: Right 03 Unique Fetal Id.: 8
 RIBS (Skeletal) RIB 13, FULL - VARIATION; BILATERAL
 VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
 Animal: 473 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: Right 01 * Unique Fetal Id.: 4
 RIBS (Skeletal) RIB 13, FULL - VARIATION; RIGHT, FULL; LEFT, RUDIMENTARY
 AND FLOATING
 CONFIRMATIONS OF EXTERNAL FINDINGS -- EXENCEPHALY: SKULL
 BONES MALFORMED AND MALPOSITIONED
 HEAD
 (External) PINNA (E), PINNA (E) ANOMALY - MALFORMATION; BILATERAL,
 SMALL, MALPOSITIONED
 BRAIN, EXENCEPHALY - MALFORMATION

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 473 (CONT.)		Unique Fetal Id.: 6
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.: 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; BILATERAL	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
Fetal Position: Right 06		Unique Fetal Id.: 9
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
Animal: 474		
Fetal Position: Left 01		Unique Fetal Id.: 1
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 474 (CONT.)	Unique Fetal Id.: 2
Fetal Position: Left 02	
THORACIC CAVITY	
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
	CAROTID ARISING FROM BRACHIOCEPHALIC TRUNK
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL
STERNUM	
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY
ABDOMEN	
(Visceral)	GALL BLADDER, VARIATION - VARIATION; RUDIMENTARY
Fetal Position: Left 03	Unique Fetal Id.: 3
THORACIC CAVITY	
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
	CAROTID ARISING FROM BRACHIOCEPHALIC TRUNK
RIBS	
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; LEFT
ABDOMEN	
(Visceral)	GALL BLADDER, VARIATION - VARIATION; ENLARGED
	KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION;
	MISPLACED LEFT KIDNEY
Fetal Position: Left 04	Unique Fetal Id.: 4
THORACIC CAVITY	
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
	CAROTID ARISING FROM BRACHIOCEPHALIC TRUNK
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT, RUDIMENTARY
ABDOMEN	
(Visceral)	KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION;
	MISPLACED LEFT KIDNEY

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 474 (CONT.)	Unique Fetal Id.: 5
Fetal Position: Left 05	
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
ABDOMEN	
(Visceral)	GALL BLADDER, VARIATION - VARIATION; ENLARGED WITH CLEAR FLUID
Fetal Position: Left 07	Unique Fetal Id.: 7
THORACIC CAVITY	
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISING FROM BRACHIOCEPHALIC TRUNK
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN	
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
ABDOMEN	
(Visceral)	GALL BLADDER, VARIATION - VARIATION; ENLARGED KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; MISPLACED LEFT KIDNEY

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 474 (CONT.) Unique Fetal Id.: 8

Fetal Position: Right 01

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Right 02

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Unique Fetal Id.: 9

STERNUM

(Skeletal)

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

ABDOMEN

(Visceral)

GALL BLADDER, VARIATION - VARIATION; ENLARGED

Animal: 475

Fetal Position: Left 01

RIBS

(Skeletal)

RIB 13, RUDIMENTARY.- VARIATION; RIGHT, NO ARTICULATING HEAD

Unique Fetal Id.: 1

STERNUM

(Skeletal)

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

Fetal Position: Left 04

RIBS

(Skeletal)

RIB 13, FULL - VARIATION; BILATERAL

Unique Fetal Id.: 4

STERNUM

(Skeletal)

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

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

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 475 (CONT.)

Fetal Position:	Left 05	Unique Fetal Id.: 5
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; RIGHT	
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 AND 6	
Fetal Position:	Left 06	Unique Fetal Id.: 6
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; RIGHT, FULL; LEFT, RUDIMENTARY WITH NO ARTICULATING HEAD	
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 AND 6	
Fetal Position:	Right 01	Unique Fetal Id.: 7
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 AND 6	
Fetal Position:	Right 02	Unique Fetal Id.: 8
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT, NO ARTICULATING HEAD	
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 AND 6	
Fetal Position:	Right 03	Unique Fetal Id.: 9
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; BILATERAL	
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 6, ONLY	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 475 (CONT.)
 Fetal Position: Right 04 Unique Fetal Id.: 10
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL
 STERNUM
 (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5 AND 6
 Fetal Position: Right 05 Unique Fetal Id.: 11
 RIBS
 (Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT
 Animal: 476
 Fetal Position: Left 01 Unique Fetal Id.: 1
 SKULL
 (Skeletal) HYOID ARCH(ES), BENT - VARIATION; BILATERAL, MODERATE
 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; BILATERAL
 STERNUM
 (Skeletal) STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
 SKULL
 (Skeletal) HYOID ARCH(ES), BENT - VARIATION; BILATERAL, SLIGHT
 ABDOMEN
 (Visceral) GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 476 (CONT.)		Unique Fetal Id.: 3
Fetal Position:	Left 03	
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT	
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 - 4, SLIGHT TO MODERATE STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
Fetal Position:	Left 05	Unique Fetal Id.: 5
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; LEFT	
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
ABDOMEN		
(Visceral)	SPLEEN, SMALL IN SIZE - VARIATION	
Fetal Position:	Right 01	Unique Fetal Id.: 6
SKULL		
(Skeletal)	HYOID ARCH(ES), BENT - VARIATION; BILATERAL, SLIGHT TO MODERATE	
Fetal Position:	Right 02	Unique Fetal Id.: 7
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; RIGHT	
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
SKULL		
(Skeletal)	HYOID ARCH(ES), BENT - VARIATION; BILATERAL, SLIGHT TO MODERATE	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 476 (CONT.) Unique Fetal Id.: 8
 Fetal Position: Right 03
 THORACIC CAVITY
 (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION;
 RETROESOPHAGEAL RIGHT SUBCLAVIAN

RIBS
 (Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL

STERNUM
 (Skeletal) STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION;
 2 - 4, SLIGHT
 STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY

Fetal Position: Right 04 Unique Fetal Id.: 9
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

SKULL
 (Skeletal) HYOID ARCH(ES), BENT - VARIATION; RIGHT, SLIGHT

Animal: 477 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; LEFT

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

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 477 (CONT.) Unique Fetal Id.: 5

Fetal Position: Left 05

STERNUM

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

SKULL

(Skeletal) HYOID BODY, UNOSSIFIED - VARIATION

Fetal Position: Right 01 Unique Fetal Id.: 6

RIBS

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT

STERNUM

(Skeletal) STERNEBRA(E), FUSED - MALFORMATION; 4 - 5

Fetal Position: Right 02 Unique Fetal Id.: 7

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALFORMED, FUSED OR ABSENT

Fetal Position: Right 03 Unique Fetal Id.: 8

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

Fetal Position: Right 04 Unique Fetal Id.: 9

RIBS

(Skeletal) 7TH CERVICAL RIB, PRESENT - VARIATION; BILATERAL, COSTAL CARTILAGE FROM LEFT RIB MERGES WITH COSTAL CARTILAGE FROM LEFT THORACIC RIB 1

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 478		Unique Fetal Id.: 2
Fetal Position: Left 02		
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; ENLARGED	
Fetal Position: Left 03		Unique Fetal Id.: 3
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT	
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; ENLARGED	
Fetal Position: Right 01		Unique Fetal Id.: 4
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISING FROM BRACHIOCEPHALIC TRUNK	
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	
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; ENLARGED WITH CLEAR FLUID	
Fetal Position: Right 05		Unique Fetal Id.: 8
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISING FROM BRACHIOCEPHALIC TRUNK	

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 479

Fetal Position: Left 01 Unique Fetal Id.: 1

THORACIC CAVITY

(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT

CAROTID ARISES FROM BRACHIOCEPHALIC TRUNK

RIBS

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; BILATERAL, WITH NO

ARTICULATING HEADS

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

Fetal Position: Left 03 Unique Fetal Id.: 3

THORACIC CAVITY

(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT

CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK

STERNUM

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

Fetal Position: Left 04 Unique Fetal Id.: 4

THORACIC CAVITY

(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT

CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK

Fetal Position: Left 05 Unique Fetal Id.: 5

THORACIC CAVITY

(Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT

CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK

STERNUM

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

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 479 (CONT.)	Unique Fetal Id.: 6
Fetal Position: Right 01	
STERNUM	
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 5, SLIGHT
ABDOMEN	
(Visceral)	GALL BLADDER, VARIATION - VARIATION; RUDIMENTARY
Fetal Position: Right 03	Unique Fetal Id.: 8
THORACIC CAVITY	
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK
ABDOMEN	
(Visceral)	GALL BLADDER, VARIATION - VARIATION; RUDIMENTARY
Fetal Position: Right 04	Unique Fetal Id.: 9
THORACIC CAVITY	
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK
RIBS	
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; BILATERAL
STERNUM	
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
SKULL	
(Skeletal)	HYOID ARCH(ES), BENT - VARIATION; LEFT, SLIGHT
Fetal Position: Right 05	Unique Fetal Id.: 10
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN	
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

GROUP 4: 3.5 MG BASE/KG/DAY

Animal: 479 (CONT.) Unique Fetal Id.: 11
 Fetal Position: Right 06
 THORACIC CAVITY HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 (Visceral) CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK
 RIBS RIB 13, FULL - VARIATION; LEFT, FULL; RIGHT RUDIMENTARY
 (Skeletal) AND NO ARTICULATING HEAD

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 481
 Fetal Position: Left 01 * Unique Fetal Id.: 1
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; LEFT FULL, RIGHT RUDIMENTARY
 VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
 SKULL
 (Skeletal) HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES
 ABSENT/UNOSSIFIED
 CONFIRMATION OF EXTERNAL FINDINGS--MICROCEPHALY: SKULL
 BONES MALFORMED, MICROGNATHIA - MAXILLAE PREMAXILLAE SMALL
 IN SIZE, BILATERAL; MANDIBLE, SMALL IN SIZE BILATERAL; BENT
 TAIL: CAUDAL VERTEBRAE MALALIGNED OR FUSED
 TAIL
 (External) TAIL, BENT - MALFORMATION
 HEAD
 (External) HEAD, MICROCEPHALY - MALFORMATION
 PINNA (E), PINNA (E) ANOMALY - MALFORMATION; BILATERAL,
 SMALL IN SIZE, MALPOSITIONED
 JAW, MAXILLAE, MICROGNATHIA - MALFORMATION
 FACE, FACIAL BLEBS - MALFORMATION; BILATERAL

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 481 (CONT.) Unique Fetal Id.: 2

Fetal Position: Left 02 *
NECK
(External) NECK, BLEB(S) - MALFORMATION; ONE, VENTRAL

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

SKULL
(Skeletal) HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES UNOSSIFIED/ABSENT
CONFIRMATION OF EXTERNAL FINDINGS--MICROCEPHALY: SKULL BONES MALFORMED; MICROGNATHIA - MAXILLAE: PREMAXILLAE AND MANDIBLE, BILATERAL, SMALL IN SIZE; BENT TAIL CONFIRMED, TAIL APPEARS BENT, VERTEBRAE APPEAR NORMAL

TAIL
(External) TAIL, BENT - MALFORMATION

HEAD
(External) HEAD, MICROCEPHALY - MALFORMATION
PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE AND MALPOSITIONED
JAW, MAXILLAE, MICROGNATHIA - MALFORMATION

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 481 (CONT.)	Left 03 *	Unique Fetal Id.: 3
Fetal Position:		
THORACIC CAVITY	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
(Visceral)	CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
SKULL		
(Skeletal)	HYOID, ANOMALY - MALFORMATION; BODY AND ARCHES MALFORMED	
	CONFIRMATION OF EXTERNAL FINDINGS--MICROCEPHALY: SKULL	
	BONES MALFORMED; BENT TAIL: DISTAL CAUDAL VERTEBRAE	
	MALALIGNED	
TAIL		
(External)	TAIL, BENT - MALFORMATION	
HEAD		
(External)	HEAD, MICROCEPHALY - MALFORMATION	
	PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL,	
	SMALL IN SIZE AND MALPOSITIONED	
	FACE, FACIAL BLEBS - MALFORMATION; BILATERAL	
Fetal Position:	Right 01 *	Unique Fetal Id.: 5
THORACIC CAVITY	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
(Visceral)	CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
SKULL		
(Skeletal)	SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND FUSED	
	HYOID, ANOMALY - MALFORMATION; BODY AND ARCHES MALFORMED	
	CONFIRMATION OF EXTERNAL FINDINGS--BENT TAIL: CAUDAL	
	VERTEBRAE MALALIGNED	
TAIL		
(External)	TAIL, BENT - MALFORMATION	
HEAD		
(External)	PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL,	
	SMALL IN SIZE	
	FACE, FACIAL BLEBS - MALFORMATION; BILATERAL	

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 481 (CONT.)	Unique Fetal Id.: 6
Fetal Position: Right 02 *	
SKULL	
(Skeletal)	HYOID, ANOMALY - MALFORMATION; BODY AND ARCHES MALFORMED CONFIRMATION OF EXTERNAL FINDINGS -- MICROCEPHALY, SKULL BONES MALFORMED AND FUSED; BENT TAIL CONFIRMED, TAIL APPEARS BENT, VERTEBRAE APPEAR NORMAL
TAIL	
(External)	TAIL, BENT - MALFORMATION
HEAD	
(External)	HEAD, MICROCEPHALY - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE FACE, FACIAL BLEBS - MALFORMATION; BILATERAL
Fetal Position: Right 03 *	Unique Fetal Id.: 7
SKULL	
(Skeletal)	SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND FUSED HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES UNOSSIFIED/ABSENT CONFIRMATION OF EXTERNAL FINDINGS--MICROGNATHIA MAXILLAE: PREMAXILLAE SMALL IN SIZE; BENT TAIL: CAUDAL VERTEBRAE MALALIGNED AND FUSED
TAIL	
(External)	TAIL, BENT - MALFORMATION
HEAD	
(External)	PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE JAW, MAXILLAE, MICROGNATHIA - MALFORMATION FACE, FACIAL BLEBS - MALFORMATION; BILATERAL

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 481 (CONT.)

Fetal Position: Right 04 * Unique Fetal Id.: 8

THORACIC CAVITY

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

RIBS

(Skeletal) RIB 13, FULL - VARIATION; RIGHT

VERTEBRAL COLUMN

(Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION

SKULL

(Skeletal)

SKULL, ANOMALY - MALFORMATION; SKULL BONES FUSED AND MALFORMED HYOID, ANOMALY - MALFORMATION; BODY AND ARCHES MALFORMED CONFIRMATION OF EXTERNAL FINDINGS -- BENT TAIL: TAIL APPEARS BENT, VERTEBRAE APPEAR NORMAL

TAIL

(External)

TAIL, BENT - MALFORMATION

HEAD

(External)

PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE FACE, FACIAL BLEBS - MALFORMATION; BILATERAL

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 483	Unique Fetal Id.: 3
Fetal Position: Left 03 *	
SKULL (Skeletal)	HYOID, ANOMALY - MALFORMATION; BODY AND ARCHES MALFORMED CONFIRMATION OF EXTERNAL FINDINGS -- MICROCEPHALY: SKULL BONES MALFORMED AND FUSED; TAIL ABSENT: CAUDAL VERTEBRAE ABSENT
TAIL (External)	TAIL, ABSENT - MALFORMATION
HEAD (External)	HEAD, MICROCEPHALY - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, MALPOSITIONED MOUTH, MACROSTOMIA - MALFORMATION FACE, FACIAL BLEBS - MALFORMATION; BILATERAL, CORNER OF MOUTH
Fetal Position: Left 05 *	Unique Fetal Id.: 5
HEAD (External)	HEAD, MICROCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION FACE, FACIAL BLEBS - MALFORMATION; BILATERAL, CORNER OF MOUTH CONFIRMATION OF EXTERNAL FINDINGS -- MICROCEPHALY AND MACROSTOMIA: SKULL BONES MALFORMED AND FUSED
Fetal Position: Right 03 *	Unique Fetal Id.: 8
TAIL (External)	TAIL, ABSENT - MALFORMATION
HEAD (External)	HEAD, MICROCEPHALY - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALFORMED AND MALPOSITIONED JAW, MANDIBLE, MICROGNATHIA - MALFORMATION FACE, FACIAL BLEBS - MALFORMATION; BILATERAL, CORNER OF MOUTH CONFIRMATION OF EXTERNAL FINDINGS -- MICROCEPHALY: SKULL BONES MALFORMED AND FUSED; MANDIBULAR MICROGNATHIA: MANDIBLE, BILATERAL, SMALL AND MALFORMED; TAIL ABSENT: CAUDAL VERTEBRAE MALFORMED OR ABSENT

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 483 (CONT.)

Fetal Position: Right 04 *

Unique Fetal Id.: 9

TAIL

(External)

TAIL, SHORT - MALFORMATION

HEAD

(External)

MOUTH, MACROSTOMIA - MALFORMATION
FACE, FACIAL BLEBS - MALFORMATION; BILATERAL, CORNER OF MOUTH
CONFIRMATION OF EXTERNAL FINDINGS - MACROSTOMIA: SKULL BONES
MALFORMED AND FUSED; SHORT TAIL: CAUDAL VERTEBRAE MALFORMED
OR ABSENT

Fetal Position:

Right 05 *

Unique Fetal Id.: 10

VERTEBRAL COLUMN

(Skeletal)

CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE
MALFORMED AND FUSED
CONFIRMATION OF EXTERNAL FINDINGS -- MACROSTOMIA: SKULL
BONES MALFORMED AND FUSED

HEAD

(External)

MOUTH, MACROSTOMIA - MALFORMATION
FACE, FACIAL BLEBS - MALFORMATION; (ONE), LEFT, CORNER OF MOUTH

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 484	Left 01 *	Unique Fetal Id.: 1
Fetal Position:		
SKULL (Skeletal)	HYOID, ANOMALY - MALFORMATION; BODY AND ARCHES MALFORMED CONFIRMATION OF EXTERNAL FINDINGS -- MACROSTOMIA AND MICROCEPHALY: SKULL BONES MALFORMED AND FUSED; SHORT AND BENT TAIL: CAUDAL VERTEBRAE FUSED OR ABSENT	
TAIL (External)	TAIL, SHORT AND BENT - MALFORMATION	
ABDOMEN (Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE	
HEAD (External)	HEAD, MICROCEPHALY - MALFORMATION MOUTH, MACROSTOMIA - MALFORMATION FACE, FACIAL BLEBS - MALFORMATION; BILATERAL	
Fetal Position:	Left 02 *	Unique Fetal Id.: 2
STERNUM (Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
SKULL (Skeletal)	HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES UNOSSIFIED/ABSENT CONFIRMATION OF EXTERNAL FINDINGS -- MACROSTOMIA AND MICROCEPHALY: SKULL BONES MALFORMED AND FUSED; BENT TAIL: CAUDAL VERTEBRAE MALFORMED AND FUSED	
TAIL (External)	TAIL, BENT - MALFORMATION	
ABDOMEN (Visceral)	KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; LEFT, UNASCENDED KIDNEY	
HEAD (External)	HEAD, MICROCEPHALY - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; RIGHT, SMALL IN SIZE MOUTH, MACROSTOMIA - MALFORMATION FACE, FACIAL BLEBS - MALFORMATION; BILATERAL	

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 484 (CONT.)	Left 03 *	Unique Fetal Id.: 3
Fetal Position: SKULL (Skeletal)	HYOID, ANOMALY - MALFORMATION; BODY MALFORMED, ARCHES UNOSSIFIED/ABSENT CONFIRMATION OF EXTERNAL FINDINGS -- MICROCEPHALY AND MACROSTOMIA; SKULL BONES MALFORMED AND FUSED; BENT TAIL: CAUDAL VERTEBRAE MALALIGNED	
TAIL (External)	TAIL, BENT - MALFORMATION	
HEAD (External)	HEAD, MICROCEPHALY - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; LEFT, SMALL IN SIZE MOUTH, MACROSTOMIA - MALFORMATION FACE, FACIAL BLEBS - MALFORMATION; BILATERAL	
Fetal Position: RIBS (Skeletal)	Left 04 *	Unique Fetal Id.: 4
STERNUM (Skeletal)	RIB 12, RUDIMENTARY - VARIATION; RIGHT STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
VERTEBRAL COLUMN (Skeletal)	VERTEBRAE, 25 PRESACRAL VERTEBRAE - VARIATION	
SKULL (Skeletal)	HYOID, ANOMALY - MALFORMATION; BODY AND ARCHES MALFORMED CONFIRMATION OF EXTERNAL FINDINGS -- MICROCEPHALY, MACROSTOMIA AND MICROGNATHIA MAXILLAE: SKULL BONES MALFORMED AND/OR FUSED; SHORT AND BENT TAIL: CAUDAL VERTEBRAE MALALIGNED AND FUSED	
TAIL (External)	TAIL, SHORT AND BENT - MALFORMATION	
HEAD (External)	HEAD, MICROCEPHALY - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE MOUTH, MACROSTOMIA - MALFORMATION JAW, MAXILLAE, MICROGNATHIA - MALFORMATION FACE, FACIAL BLEBS - MALFORMATION; BILATERAL	

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 484 (CONT.)	Right 02 *	Unique Fetal Id.: 6
Fetal Position:		
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
VERTEBRAL COLUMN		
(Skeletal)	CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALALIGNED AND FUSED CONFIRMATION OF EXTERNAL FINDINGS - MICROCEPHALY, MACROSTOMIA AND CLEFT PALATE; SKULL BONES MALFORMED AND/OR FUSED	
SKULL		
(Skeletal)	HYOID, ANOMALY - MALFORMATION; BODY AND ARCHES MALFORMED; ADDITIONAL AREAS OF OSSIFICATION PRESENT	
HEAD		
(External)	HEAD, MICROCEPHALY - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE MOUTH, MACROSTOMIA - MALFORMATION MOUTH, PALATE, CLEFT PALATE - MALFORMATION FACE, FACIAL BLEBS - MALFORMATION; BILATERAL	
Fetal Position:	Right 04 *	Unique Fetal Id.: 8
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; RIGHT, RUDIMENTARY; LEFT, FULL	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION CENTRA, ANOMALY - MALFORMATION; LUMBAR CENTRUM NO. 7 AND SACRAL CENTRUM NO. 1 FUSED CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALFORMED AND FUSED CONFIRMATION OF EXTERNAL FINDINGS -- MICROCEPHALY AND MACROSTOMIA; SKULL BONES MALFORMED AND FUSED	
ABDOMEN		
(Visceral)	KIDNEY(S), RENAL PAPILLAE NOT DEVELOPED - VARIATION; WOO AND HOAR GRADE 1, LEFT URETER(S), RETROCAVAL - VARIATION; LEFT GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; KIDNEY MALFORMED, MISSHAPEN AND MALPOSITIONED, RIGHT	
HEAD		
(External)	HEAD, MICROCEPHALY - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, SMALL IN SIZE MOUTH, MACROSTOMIA - MALFORMATION FACE, FACIAL BLEBS - MALFORMATION; BILATERAL	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 484 (CONT.)	Right 05 *	Unique Fetal Id.: 9
Fetal Position:		
NECK		
(External)	NECK, BLEB(S) - MALFORMATION; MULTIPLE, VENTRAL	
RIBS		
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; LEFT	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION VERTEBRAE, ANOMALY - MALFORMATION; INVOLVING SACRAL VERTEBRAE NO. 1 - NO. 4 CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALFORMED AND FUSED CONFIRMATION OF EXTERNAL FINDINGS -- MICROCEPHALY AND CLEFT PALATE: SKULL BONES MALFORMED AND FUSED	
SKULL		
(Skeletal)	HYOID, ANOMALY - MALFORMATION; BODY AND ARCHES MALFORMED OR ABSENT/UNOSSIFIED	
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; SMALL IN SIZE KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; KIDNEY MALFORMED, MISSHAPEN AND MALPOSITIONED, RIGHT	
HEAD		
(External)	HEAD, MICROCEPHALY - MALFORMATION PINNA(E), PINNA(E) ANOMALY - MALFORMATION; MALPOSITIONED AND SMALL IN SIZE MOUTH, PALATE, CLEFT PALATE - MALFORMATION FACE, FACIAL BLEBS - MALFORMATION; BILATERAL	
Animal: 486	Left 01	Unique Fetal Id.: 1
Fetal Position:		
SKULL		
(Skeletal)	HYOID, ANOMALY - MALFORMATION; LEFT ARCH MALPOSITIONED	

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INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 486 (CONT.)

Fetal Position: Left 02

SKULL

(Skeletal) HYOID, ANOMALY - MALFORMATION; BODY AND ARCHES MALFORMED

Unique Fetal Id.: 2

HEAD

(External)

MOUTH, FACIAL BLEBS - MALFORMATION; BILATERAL

Fetal Position: Left 03

RIBS

(Skeletal) RIB 13, RUDIMENTARY - VARIATION; LEFT

Unique Fetal Id.: 3

VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALALIGNED

SKULL

(Skeletal)

SKULL, ANOMALY - MALFORMATION; SKULL BONES FUSED AND MALFORMED

ABDOMEN

(Visceral)

KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; LEFT KIDNEY UNASCENDED

HEAD

(External)

MOUTH, FACIAL BLEBS - MALFORMATION; BILATERAL

Fetal Position: Left 04

SKULL

(Skeletal)

HYOID, ANOMALY - MALFORMATION; BODY AND ARCHES MALPOSITIONED

Unique Fetal Id.: 4

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 486 (CONT.)	Left 05	Unique Fetal Id.: 5
Fetal Position:		
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	
SKULL		
(Skeletal)	SKULL, ANOMALY - MALFORMATION; SKULL BONES FUSED	
	HYOID, ANOMALY - MALFORMATION; BODY MALFORMED; ARCHES MALPOSITIONED	
Fetal Position:	Right 01	Unique Fetal Id.: 6
SKULL		
(Skeletal)	SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND FUSED	
	HYOID, ANOMALY - MALFORMATION; ARCHES MALPOSITIONED	
HEAD		
(External)	MOUTH, FACIAL BLEBS - MALFORMATION; BILATERAL	
Fetal Position:	Right 02	Unique Fetal Id.: 7
STERNUM		
(Skeletal)	STERNEBRA(E), MALALIGNED, SLIGHT TO MODERATE - VARIATION; 2 - 5, SLIGHT	
SKULL		
(Skeletal)	SKULL, ANOMALY - MALFORMATION; SKULL BONES FUSED	
Fetal Position:	Right 04	Unique Fetal Id.: 9
SKULL		
(Skeletal)	SKULL, ANOMALY - MALFORMATION; SKULL BONES FUSED	
	HYOID, ANOMALY - MALFORMATION; ARCHES MALPOSITIONED	

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 487

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

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION
CENTRA, ANOMALY - MALFORMATION; LUMBAR CENTRUM 7 FUSED TO SACRAL CENTRUM 1
CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE
MALALIGNED AND FUSED

SKULL

(Skeletal)

HYOID, ANOMALY - MALFORMATION; BODY MALFORMED; ARCHES MALPOSITIONED
CONFIRMATION OF EXTERNAL FINDINGS -- MICROCEPHALY,
MACROSTOMIA AND CLEFT PALATE: SKULL BONES FUSED AND
MALFORMED

HEAD

(External)

HEAD, MICROCEPHALY - MALFORMATION
PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL AND MALPOSITIONED
MOUTH, MACROSTOMIA - MALFORMATION
MOUTH, PALATE, CLEFT PALATE - MALFORMATION
FACE, FACIAL BLEBS - MALFORMATION; BILATERAL

Fetal Position: Left 03 *

Unique Fetal Id.: 3

RIBS

(Skeletal)

RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal)

VERTEBRAE, ANOMALY - MALFORMATION; INVOLVING LUMBAR VERTEBRAE 1 - 7
CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALFORMED AND MALALIGNED
CONFIRMATION OF EXTERNAL FINDINGS -- MICROCEPHALY: SKULL BONES MALFORMED AND FUSED

SKULL

(Skeletal)

HYOID, ANOMALY - MALFORMATION; BODY MALFORMED; ARCHES ABSENT

HEAD

(External)

HEAD, MICROCEPHALY - MALFORMATION
FACE, FACIAL BLEBS - MALFORMATION; BILATERAL

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 487 (CONT.) Unique Fetal Id.: 4
 Fetal Position: Right 01 *
 THORACIC CAVITY
 (Visceral) HEART, HEART AND/OR GREAT VESSEL, ANOMALY - MALFORMATION;
 INTERRUPTED AORTIC ARCH, LEFT
 SUBCLAVIAN ARISES FROM PULMONARY TRUNK

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

VERTEBRAL COLUMN
 (Skeletal) VERTEBRAE, ANOMALY - MALFORMATION; INVOLVING LUMBAR VERTEBRAE 5 - 7
 CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALALIGNED AND FUSED
 CONFIRMATION OF EXTERNAL FINDINGS -- MICROCEPHALY AND CLEFT
 PALATE: SKULL BONES FUSED AND MALFORMED

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

ABDOMEN
 (Visceral) KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION;
 KIDNEY, RIGHT MALPOSITIONED, LOCATED CLOSER TO VENTRAL
 MIDLINE OF THE BODY THAN NORMAL, ALSO UNASCENDED; KIDNEY MALFORMED

HEAD
 (External) HEAD, MICROCEPHALY - MALFORMATION
 MOUTH, PALATE, CLEFT PALATE - MALFORMATION
 FACE, FACIAL BLEBS - MALFORMATION; BILATERAL
 PINNA(E), PINNA(E) ANOMALY - MALFORMATION; SMALL IN SIZE

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 487 (CONT.)	Right 02 *	Unique Fetal Id.: 5
Fetal Position:		
SKULL		
(Skeletal)	HYOID, ANOMALY - MALFORMATION; ARCHES MALPOSITIONED	
	CONFIRMATION OF EXTERNAL FINDINGS -- MICROCEPHALY AND CLEFT	
	PALATE: SKULL BONES MALFORMED AND FUSED; TAIL SHORT: CAUDAL VERTEBRAE FUSED OR ABSENT	
TAIL		
(External)	TAIL, SHORT - MALFORMATION	
HEAD		
(External)	HEAD, MICROCEPHALY - MALFORMATION	
	MOUTH, PALATE, CLEFT PALATE - MALFORMATION	
	FACE, FACIAL BLEBS - MALFORMATION; BILATERAL	
Animal: 488	Left 02 *	Unique Fetal Id.: 2
Fetal Position:		
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT	
	CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; RIGHT	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
	CONFIRMATION OF EXTERNAL FINDINGS -- MICROCEPHALY AND CLEFT	
	PALATE: SKULL BONES MALFORMED AND FUSED; SHORT TAIL: CAUDAL VERTEBRAE FUSED OR ABSENT	
SKULL		
(Skeletal)	HYOID, ANOMALY - MALFORMATION; BODY MALFORMED; ARCHES ABSENT	
TAIL		
(External)	TAIL, SHORT - MALFORMATION	
HEAD		
(External)	HEAD, MICROCEPHALY - MALFORMATION AND MALPOSITIONED	
	MOUTH, PALATE, CLEFT PALATE - MALFORMATION	
	FACE, FACIAL BLEBS - MALFORMATION; BILATERAL, CORNER OF MOUTH	

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 492 Unique Fetal Id.: 1

Fetal Position: Left 01

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

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION CAUDAL VERTEBRAE MALALIGNED

Fetal Position: Left 02 Unique Fetal Id.: 2

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

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

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

Fetal Position: Left 04 Unique Fetal Id.: 4

RIBS (Skeletal) RIB 13, RUDIMENTARY - VARIATION; RIGHT

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

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

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 492 (CONT.) Unique Fetal Id.: 7

Fetal Position: Right 03

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

VERTEBRAL COLUMN (Skeletal) VERTEBRAE, ANOMALY - MALFORMATION; INVOLVING LUMBAR VERTEBRAE 5 - 7

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

Animal: 493 Unique Fetal Id.: 1

Fetal Position: Left 01

THORACIC CAVITY (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

Fetal Position: Left 02 Unique Fetal Id.: 2

SKULL (Skeletal) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND FUSED

HEAD (External) FACE, FACIAL BLEBS - MALFORMATION; RIGHT CORNER OF MOUTH

Fetal Position: Left 05 Unique Fetal Id.: 5

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 FUSED

HEAD (External) FACE, FACIAL BLEBS - MALFORMATION; SINGLE, LEFT

Fetal Position: Left 06 Unique Fetal Id.: 6

VERTEBRAL COLUMN (Skeletal) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALALIGNED

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 493 (CONT.)		Unique Fetal Id.: 7
Fetal Position: Left 07		
VERTEBRAL COLUMN		
(Skeletal)	CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALALIGNED	
SKULL		
(Skeletal)	HYOID, ANOMALY - MALFORMATION; BODY FORMED IN MULTIPLE PIECES	
Fetal Position: Left 08		Unique Fetal Id.: 8
VERTEBRAL COLUMN		
(Skeletal)	CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALALIGNED	
Fetal Position: Left 09		Unique Fetal Id.: 9
VERTEBRAL COLUMN		
(Skeletal)	CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALFORMED AND MALALIGNED	
SKULL		
(Skeletal)	SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND FUSED	
ABDOMEN		
(Visceral)	URETER(S), RETROCAVAL - VARIATION; RIGHT	
Fetal Position: Left 10		Unique Fetal Id.: 10
THORACIC CAVITY		
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK	
SKULL		
(Skeletal)	HYOID, ANOMALY - MALFORMATION; BODY MALFORMED; ARCHES ABSENT/UNOSSIFIED	

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UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 493 (CONT.) Unique Fetal Id.: 11
 Fetal Position: Left 11
 THORACIC CAVITY
 (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
 CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

RIBS
 (Skeletal) RIB 13, FULL - VARIATION; RIGHT, FULL; LEFT RUDIMENTARY

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

Animal: 494 Unique Fetal Id.: 4
 Fetal Position: Left 04
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; BILATERAL

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

Fetal Position: Right 01 Unique Fetal Id.: 5
 RIBS
 (Skeletal) RIB 13, FULL - VARIATION; LEFT

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

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

SKULL
 (Skeletal) HYOID, ANOMALY - MALFORMATION; ARCHES MALPOSITIONED

ABDOMEN
 (Visceral) KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; RIGHT
 URETER--ABSENT; RIGHT RENAL ARTERY AND VEIN--ABSENT; RIGHT KIDNEY--ABSENT

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 494 (CONT.)

Fetal Position: Right 03 * Unique Fetal Id.: 7

THORACIC CAVITY

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

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

TAIL

(External) TAIL, SHORT - MALFORMATION

CONFIRMATION OF EXTERNAL FINDINGS -- SHORT TAIL: CAUDAL VERTEBRAE MALFORMED AND FUSED OR ABSENT

ABDOMEN

(Visceral) GALL BLADDER, VARIATION - VARIATION; DISTENDED

Animal: 496

Fetal Position: Left 01 Unique Fetal Id.: 1

RIBS

(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

VERTEBRAL COLUMN

(Skeletal) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALFORMED AND MALALIGNED

SKULL

(Skeletal) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND FUSED HYOID, ANOMALY - MALFORMATION; BODY MALFORMED

ABDOMEN

(Visceral) GALL BLADDER, VARIATION - VARIATION; DISTENDED, SLIGHT

HEAD

(External) FACE, FACIAL BLEBS - MALFORMATION; BY MOUTH

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS
INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 496 (CONT.)	Unique Fetal Id.: 2
Fetal Position: Left 02	
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL
VERTEBRAL COLUMN	
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALALIGNED
SKULL	
(Skeletal)	SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND FUSED
ABDOMEN	
(Visceral)	KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; BILATERAL KIDNEYS--SMALL AND MISSHAPEN, MODERATE
HEAD	
(External)	PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED (LOW PLACED) FACE, FACIAL BLEBS - MALFORMATION; BY MOUTH

DRAFT

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 496 (CONT.)	Left 03 *	Unique Fetal Id.: 3
Fetal Position:		
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
VERTEBRAL COLUMN		
(Skeletal)	VERTEBRAE, 27 PRESACRAL VERTEBRAE - VARIATION	
SKULL		
(Skeletal)	SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND FUSED	
	HYOID, ANOMALY - MALFORMATION; BODY MALFORMED; ARCHES ABSENT/UNOSSIFIED	
	CONFIRMATION OF EXTERNAL FINDINGS -- BENT TAIL: CAUDAL VERTEBRAE MALFORMED AND MALALIGNED	
TAIL		
(External)	TAIL, BENT - MALFORMATION	
ABDOMEN		
(Visceral)	KIDNEY(S), HYDRONEPHROSIS - VARIATION; LEFT, SLIGHT	
HEAD		
(External)	FACE, FACIAL BLEBS - MALFORMATION; BY MOUTH	
Animal: 497	Left 01	Unique Fetal Id.: 1
Fetal Position:		
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; LEFT	
Fetal Position:	Left 02	Unique Fetal Id.: 2
RIBS		
(Skeletal)	RIB 13, FULL - VARIATION; BILATERAL	
STERNUM		
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY	
SKULL		
(Skeletal)	HYOID, ANOMALY - MALFORMATION; ARCHES MALPOSITIONED OR ABSENT	
HEAD		
(External)	PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED (LOW)	

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 497 (CONT.) Unique Fetal Id.: 3

Fetal Position: Left 03

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

SKULL HYOID, ANOMALY - MALFORMATION; ARCHES MALPOSITIONED AND BENT, MODERATE TO SEVERE

HEAD PINNA (E), PINNA (E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED (LOW)

(External)

Fetal Position: Left 04 Unique Fetal Id.: 4

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

(Skeletal)

VERTEBRAL COLUMN CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALALIGNED

(Skeletal)

ABDOMEN SPLEEN, SMALL IN SIZE - VARIATION

(Visceral)

HEAD PINNA (E), PINNA (E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED (LOW)

(External)

Fetal Position: Left 05 Unique Fetal Id.: 5

RIBS RIB 13, FULL - VARIATION; BILATERAL

(Skeletal)

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

(Skeletal)

SKULL HYOID, ANOMALY - MALFORMATION; RIGHT ARCH, UNOSSIFIED/ABSENT; LEFT ARCH MALPOSITIONED

(Skeletal)

HEAD PINNA (E), PINNA (E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED (LOW)

(External)

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 497 (CONT.)	Unique Fetal Id.: 6
Fetal Position: Right 01	
RIBS	
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; LEFT
STERNUM	
(Skeletal)	STERNEBRA(E), 5-6, UNOSSIFIED - VARIATION; 5, ONLY
HEAD	
(External)	PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED (LOW)
Fetal Position: Right 02	Unique Fetal Id.: 7
RIBS	
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; RIGHT
VERTEBRAL COLUMN	
(Skeletal)	CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALALIGNED AND FUSED
SKULL	
(Skeletal)	HYOID ARCH(ES), BENT - VARIATION; LEFT, SEVERE
HEAD	
(External)	PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED (LOW)
Fetal Position: Right 03	Unique Fetal Id.: 8
THORACIC CAVITY	
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
	CAROTID ARTERY ARISES FROM BRACHIOCEPHALIC TRUNK
RIBS	
(Skeletal)	RIB 13, RUDIMENTARY - VARIATION; RIGHT
HEAD	
(External)	PINNA(E), PINNA(E) ANOMALY - MALFORMATION; BILATERAL, MALPOSITIONED (LOW)

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APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 498
Fetal Position: Left 01 Unique Fetal Id.: 1
RIBS
(Skeletal) RIB 13, FULL - VARIATION; BILATERAL

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

FORELIMBS
(External) FORELIMB(S), HYPERFLEXURE - MALFORMATION; BILATERAL

ABDOMEN
(Visceral) KIDNEY(S), HYDRONEPHROSIS - VARIATION; BILATERAL, SLIGHT

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.: 6
RIBS
(Skeletal) RIB 13, FULL - VARIATION; LEFT

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

Animal: 499
Fetal Position: Left 01 Unique Fetal Id.: 1
VERTEBRAL COLUMN
(Skeletal) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE
MALALIGNED

SKULL
(Skeletal) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND FUSED
HYOID ARCH(ES), BENT - VARIATION; LEFT, SEVERE

HEAD
(External) FACE, FACIAL BLEBS - MALFORMATION; SINGLE, POSTERIOR TO LEFT EYE

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 499 (CONT.)

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, FULL; RIGHT RUDIMENTARY

VERTEBRAL COLUMN

(Skeletal)

CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALALIGNED

Fetal Position: Left 03

Unique Fetal Id.: 3

THORACIC CAVITY

(Visceral)

HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT
CAROTID ARISES FROM THE BRACHIOCEPHALIC TRUNK

SKULL

(Skeletal)

SKULL, ANOMALY - MALFORMATION; MALFORMED AND FUSED
HYOID ARCH(ES), BENT - VARIATION; RIGHT, MODERATE

Fetal Position: Left 04

Unique Fetal Id.: 4

RIBS

(Skeletal)

RIB 13, FULL - VARIATION; RIGHT, FULL; LEFT RUDIMENTARY

VERTEBRAL COLUMN

(Skeletal)

CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALFORMED AND MALALIGNED

SKULL

(Skeletal)

SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND FUSED

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 499 (CONT.)
 Fetal Position: Left 05 Unique Fetal Id.: 5
 THORACIC CAVITY
 (Visceral) HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION;
 ACCESSORY LEFT SUBCLAVIAN

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

VERTEBRAL COLUMN
 (Skeletal) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALALIGNED

SKULL
 (Skeletal) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND FUSED

Fetal Position: Right 01 Unique Fetal Id.: 6
 VERTEBRAL COLUMN
 (Skeletal) CAUDAL VERTEBRAE, ANOMALY - MALFORMATION; CAUDAL VERTEBRAE MALALIGNED

SKULL
 (Skeletal) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND FUSED
 HYOID, ANOMALY - MALFORMATION; ARCHES ABSENT/UNOSSIFIED

HEAD
 (External) FACE, FACIAL BLEBS - MALFORMATION; BILATERAL, CORNER OF MOUTH

Fetal Position: Right 02 Unique Fetal Id.: 7
 SKULL
 (Skeletal) SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND FUSED

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 500	Left 02 *	Unique Fetal Id.: 2
Fetal Position:		
STERNUM		
(Skeletal)	STERNEBRA(E), FUSED - MALFORMATION; 4 AND 5	
SKULL		
(Skeletal)	SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND FUSED	
	CONFIRMATION OF EXTERNAL FINDINGS -- SHORT TAIL; CAUDAL	
	VERTEBRAE MALFORMED AND FUSED	
TAIL		
(External)	TAIL, SHORT - MALFORMATION	
ABDOMEN		
(Visceral)	GALL BLADDER, VARIATION - VARIATION; ENLARGED	

APPENDIX D

UIC/TRL STUDY NO.: 138 DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

INDIVIDUAL FETAL MORPHOLOGICAL OBSERVATIONS

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

Animal: 500	Unique Fetal Id.: 3
Fetal Position: Left 03 *	
THORACIC CAVITY	
(Visceral)	HEART, MAJOR BLOOD VESSEL, VARIATION - VARIATION; LEFT CAROTID ARTERY ARISING FROM BRACHIOCEPHALIC TRUNK
SKULL	
(Skeletal)	SKULL, ANOMALY - MALFORMATION; SKULL BONES MALFORMED AND FUSED CONFIRMATION OF EXTERNAL FINDINGS -- SHORT AND KINKY TAIL: CAUDAL VERTEBRAE MALALIGNED AND MALFORMED
TAIL	
(External)	TAIL, SHORT AND KINKY - MALFORMATION
Fetal Position: Left 04 *	Unique Fetal Id.: 4
RIBS	
(Skeletal)	RIB 13, FULL - VARIATION; LEFT
VERTEBRAL COLUMN	
(Skeletal)	VERTEBRAE, ANOMALY - MALFORMATION; INVOLVES ALL LUMBAR VERTEBRAE; ALL SACRAL VERTEBRAE ABSENT CONFIRMATION OF EXTERNAL FINDINGS -- RUDIMENTARY TAIL: ALL CAUDAL VERTEBRAE ABSENT; SHORT SNOOT: SKULL BONES MALFORMED AND FUSED
TAIL	
(External)	TAIL, SHORT - MALFORMATION
ABDOMEN	
(Visceral)	SPLEEN, SMALL IN SIZE - VARIATION KIDNEY(S) AND/OR URETER(S), ANOMALY - MALFORMATION; MISSHAPEN, LOW SET LEFT KIDNEY; MALFORMED PELVIS; NO PAPILLAE FORMED--SEVERAL SMALL HOLES
HEAD	
(External)	JAW, MAXILLAE, MICROGNATHIA - MALFORMATION FACE, FACIAL BLEBS - MALFORMATION; BY MOUTH

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APPENDIX 6

Protocol and Amendments

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DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 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 the test article in New Zealand White 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, IL 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 (Day 0): 10/31/94

4.2 Proposed Completion of In-Life Phase: 12/02/94

4.3 Proposed Study Completion Date
(Draft Final Report): 03/02/95

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5.0 TEST ARTICLE

- 5.1 Name or Code No: WR242511 Tartrate
Bottle Number - BM05816
- 5.2 TRL Chemical No: 1720614
- 5.3 Physical Description: Yellow powder
- 5.4 Storage Conditions to Maintain Stability:
- 5.4.1 Temperature: -20 to -15°C.
- 5.4.2 Humidity: Ambient conditions at -20 to -15°C.
- 5.4.3 Light: Protect from light.
- 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.
Teratologist (PAI)	Michael D. Mercieca, B.S.
Reproductive Scientist	Roberto A. Matamoros, D.V.M., Ph.D.
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	Documented in raw data
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, a few days apart in two shipments (day 0 = day of observed mating)
- 7.4 Weight of Animals: 3.0 - 5.0 kg at start of study
- 7.5 Age of Animals: 5 to 8 months at study initiation. The animal supplier will provide birth dates on individual animals.
- 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 study-unique (ear-tag) number by the Supplier and a separate study-unique number (ear-tag) upon arrival at UIC. 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 during the time 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</u> (mg base/kg/day)	<u>Number of</u> <u>Females*</u>
1	Vehicle	0	20
2	WR242511	0.5	20
3	WR242511	1.3	20
4	WR242511	3.5	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.

Dose levels were selected on the basis of a range-finding study (UIC/TRL Study No. 137). 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 Sponso in Task Order UIC-7, Modification 3.

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- 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 for the test article will be prepared daily by diluting a stock formulation (made weekly) to appropriate concentration. Stability data obtained from a previous study (UIC/TRL Study No. 106) indicated that the dosing suspensions are stable for 48 hours at the dosage formulations being tested, and the stock formulation is stable for two weeks. Homogeneity data obtained from UIC/TRL Study No. 107 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 using a mortar and pestle. Stock and dosing suspensions will be stored at 0 - 4°C. Samples of the dosage formulations (including controls and stock suspensions) used at the beginning and at the end of the dosing period will be analyzed for test article concentration prior to use. Only samples within 10% of their intended concentration will be used.
- 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, and in the morning after completion of the dosing period. 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.
- 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 with the left distal uterine horn, 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 site is 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 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 live fetuses will be examined for visceral anomalies and will be sexed internally employing the Staples' fresh tissue dissection techniques (Staples, 1974). All fetuses will be euthanized by I.P. injection of a 40% solution of sodium pentobarbital (0.4 ml/fetus). Fetal examination will include evaluation of the eyes and the brain by a mid-sagittal section. The remaining carcasses will be retained in 95% ethyl alcohol.

8.7.11.3 Skeletal Evaluation: Following completion of the visceral examination, all fetuses will be eviscerated and skinned for 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.

8.7.12 Statistical Analyses

Maternal body weights, weight gains, uterine absolute and relative 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.

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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-Willis 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

Other statistical analyses will be conducted as deemed necessary and will be documented in the raw data.

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 and the responsible individual shall be identified.

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.

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Contract No.: DAMD17-92-C-2001
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Study No.: 138

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.

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 test article samples 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).

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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.

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.

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, J.G. (1965). Methods for administering drugs and detecting malformations in experimental animals. In: Teratology Principles and Techniques (Wilson, J.G. and Warkany, J., eds). Chicago Press, pp. 262-277.

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12.0 PROTOCOL APPROVAL:

STUDY DIRECTOR:

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

11/19/93
Date

QUALITY ASSURANCE:

Ronald Schönbeck
Ronald Schönbeck

11/22/93
Date

SPONSOR APPROVAL:

George J. Schieferstein
George J. Schieferstein, Ph.D.
Contracting Officer's
Representative (COR)

12/13/93.
Date

COMMENTS FROM THE COR:

UIC The University of Illinois
at Chicago

DRAFT

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

November 22, 1993

Barry S. Levine
Med-Pharmacology
312 BGRC, M/C 868

Dear Dr. Levine:

The protocol indicated below has been reviewed in accordance with the Animal Care Policies of the University of Illinois at Chicago and approved on July 20, 1993.

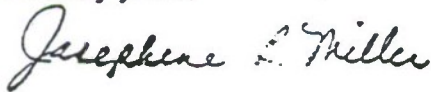
Title of Application: Developmental Toxicity Study of WR242511 In Rabbits

ACC Number: 93-077-9

This institution has Animal Welfare Assurance Number A3460.01 on file with the Office for Protection from Research Risks, NIH. Please transmit this letter of acceptable verification of your research protocol to your sponsor.

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

PROTOCOL AMENDMENT

Study No.: 138

Title: Developmental Toxicity Study of WR242511 in Rabbits

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1. Page 2 Section 5.1

Indicate the Bottle Number of the test article; "BM05816".

Reason: Sponsor requested that the specific bottle number be included in the protocol.

2. Page 4 Section 7

Add the following section:

"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."

Reason: Sponsor requested addition to the protocol.

3. Page 3 Section 7.3

Delete from the text "unconfirmed".

Reason: Time mated females will be provided.

4. Page 3 Section 7.10

Replace the first sentence to read "Animals will be quarantined for at least 3 days during the time of receipt until dosing is initiated on day 6 of gestation."

Reason: Clarification of the period of quarantine.

5. Page 4 Section 7.11

Add the following sentence: "On the days of measured food consumption an exact amount of 130 g will be provided."

Reason: Clarification of the procedure of measuring food consumption.

PROTOCOL AMENDMENT

Study No.: 138

Title: Developmental Toxicity Study of WR242511 in Rabbits

6. Page 4 Section 8.1

- A. Change dosing volume of positive control agent from "5 ml/kg" to "1 ml/kg".
- B. Add the following sentence "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-7, Modification 3."

Reason: Mistake in the protocol (A) and Sponsor requested addition to the protocol (B).

7. Page 5 Section 8.2

Change dosing volume from "5 ml/kg" to "1 ml/kg".

Reason: Mistake in the protocol.

8. Page 5 Section 8.6

Change the text as follows to indicate that stability and homogeneity testing have been performed in previous toxicity studies; "The dosage formulations for the test article will be prepared daily by diluting a stock formulation (made weekly) to appropriate concentration. Stability data obtained from a previous study (UIC/TRL Study No. 106) indicated that the dosing suspensions are stable for 48 hours at the dosage formulations being tested, and the stock formulation is stable for two weeks. Homogeneity data obtained from UIC/TRL Study No. 107 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 using a mortar and pestle. Stock and dosing suspensions will be stored at 0 - 4°C. Samples of the dosage formulations (including controls and stock suspensions) used at the beginning and at the end of the dosing period will be analyzed for test article concentration prior to use. Only samples within 10% of their intended concentration will be used."

Reason: Correction and Sponsor requested addition of the protocol.

9. Page 5 Section 8.7.5

Change the first food consumption day from 6/7 to 7/8.

Reason: To allow for the gradual feeding regimen as described in section 7.12 to be completed.

DRAFT
PROTOCOL AMENDMENT

Study No.: 138

Title: Developmental Toxicity Study of WR242511 in Rabbits

10. Page 6 Section 8.7.6

Add "($\approx$ 50 mg/kg)" after "sodium pentobarbital".

Reason: Clarification of the dose of pentobarbital used for euthanasia.

11. Page 6 Section 8.7.8

Add the following sentence: "If any implantation site is detected, the ovaries will be examined as in 8.7.7".

Reason: If pregnancy evidence is confirmed, ovarian changes should be examined.

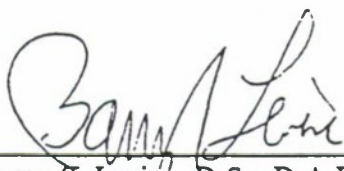
12. Page 7 Section 8.7.10

Change second sentence from "crown-rump length is" to "crown-rump lengths are".

Reason: Mistake in the protocol.

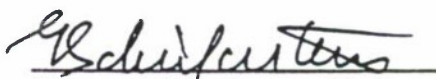
Approvals:

STUDY DIRECTOR:


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

12/10/93
Date

SPONSOR APPROVAL:


George J. Schieferstein, Ph.D.
Contracting Officer's
Representative (COR)

12/13/93
Date

PROTOCOL AMENDMENT
DRAFT

Study No: 138

Title: Developmental Toxicity Study of WR242511 in Rabbits

13. Page 1

Add to the title the phrase (Segment II) to read "Developmental Toxicity (Segment II) Study of WR242511 in Rabbits

Reason: More precision in reflecting the nature of the study as discussed with the Sponsor.

14. Page 1 Section 4.0

Add the following dates:

Proposed Initiation of In-life Phase (Day 0): 10/31/94

Proposed Completion of In-life Phase: 12/02/94

Proposed Study Completion Date
(Draft Final Report): 03/02/95

Reason: Dates were not finalized when the protocol was submitted.

15. Page 2 Section 6.0

Replace Teratologist (PAI) Helen Jamieson, B.S. by Michael D. Mercieca, B.S.

Reason: To reflect changes in personnel.

16. Page 3 Section 7.3

Add the following: "a few days apart in two shipments (day 0 = day of observed mating)"

Reason: To clarify the date for calculating various dates.

17. Page 3 Section 7.6 and Page 4 Section 7.11

Replace Hazelton Research Products, Inc. by HRP, Inc.

Reason: To reflect the correct name.

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18. Page 3 Section 7.8

Replace the first three sentences by the following:

"Each animal will be given a study-unique (ear-tag) number by the Supplier and a separate study-unique number (ear-tag) upon arrival at UIC."

Reason: To clarify the procedure.

19. Page 4 Section 7.11

Change Ralston Purina Company to PMI Feeds, Inc.

Reason: Change in company name.

20. 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	WR242511	0.5
3	WR242511	1.3
4	WR242511	3.5
5	(Retinol Palmitate)	75,000 IU/kg/day (= 300 mg/kg/day)

B. Correct "vitamine" to "vitamin".

C. 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 correct a typographical error.

C. To reflect that the dose-range-finding study has been done, from which dose levels were chosen.

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21. Page 5 Section 8.7.4 and Page 6 Section 8.7.6

Replace "day 30" by "day 29".

Reason: Change in procedures.

22. 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.

23. 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.

24. 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 operationg procedure.

25. Page 7 Section 8.7.10

Delete this phrase from second sentence "and crown-rump lengths are measured".

Reason: Body weight measurement is sufficient to assess fetal toxicity.

26. 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 carcasses will be retained in 95% ethyl alcohol.

Reason: To clarify procedure.

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27. 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.

28. Page 7 Section 8.7.12

Replace the first three paragraphs by the following:

Maternal body weights, weight gains, uterine absolute and relative 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

Other statistical analyses will be conducted as deemed necessary and will be documented in the raw data.

Reason: To represent more appropriately the statistical analysis procedures.

29. Page 9 Section 11.0

Delete "Kimmel" and "Staples" references and add the following references:

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29. Page 9 Section 11.0 (continued)

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, Telford 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.

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.

U.S. Environmental Protection Agency (1991). Guidelines for developmental toxicity

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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.

Reason: Correction and expansion of the reference list as required by the Sponsor.

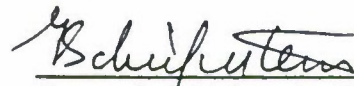
APPROVAL:

STUDY DIRECTOR:


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

11/10/94
Date

SPONSOR APPROVAL:


George J. Schieferstein, Ph.D.
Contracting Officer's
Representative (COR)

11/14/94
Date

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30. 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.

2/21/95
Date

SPONSOR APPROVAL:


George J. Schieferstein, Ph.D.

3/3/95
Date

(end)

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APPENDIX 7
Study Deviations

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Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-7N
Study No.: 138

DEVELOPMENTAL TOXICITY (SEGMENT II)
STUDY OF WR242511 IN RABBITS

Study Deviations*

<u>Deviation Type</u>	<u>Specific Deviation</u>	<u>Effect on Study</u>
Protocol	Temperature was out of range on few occasions.	None, deviation was minimal.
Protocol	Humidity was out of range on one occasion.	None, deviation was minimal.
Protocol	Relative uterine weight (% body weight) was not calculated.	None; mistake in protocol. Statistical analysis should be based on absolute uterine weights.

*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