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Title Page

Volume 1 of 2

Revised Draft Report for Task Order No. UIC-7E

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR242511 IN RATS

Sponsor: US 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

January 14, 1994

Performing Laboratory

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Thirteen Week Oral Toxicity Study of WR242511 in Rats

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This study evaluated the toxicity of WR242511 Tartrate in rats following thirteen weeks of daily oral (gavage) administration. Dose levels studied were 0 (vehicle control), 0.5, 1.5 and 4.5 mg base/kg/day. The primary treatment-related toxic effects of WR242511 were seen in the liver, lungs and RBCs. Males appeared more sensitive than females to the hepatotoxic effects of WR242511 administration. Microscopic liver lesions (hepatocyte degeneration and necrosis), and elevations in serum ALT and/or SDH levels were observed in mid and high dose males. Increased triglyceride and cholesterol levels in high dose females, and increased cholesterol levels in high dose males also suggested potential hepatocellular toxicity. Increases in total bile acids and alkaline phosphatase levels suggested hepatobiliary changes in high dose animals. Pulmonary microscopic lesions (alveolar histiocytosis) were observed in all WR242511-treated groups. These dose-related effects (hepatocyte degeneration and necrosis, and alveolar histiocytosis) probably contributed to the early deaths of seven out of ten high dose males. Treatment-related mild anemia was observed in mid dose and high dose animals. The lesser methemoglobinemic response seen in high dose males than in high dose females may have been secondary to the greater hepatotoxic effect in males, resulting in a reduction in the production of a direct methemoglobin-forming metabolite. Hemosiderosis in the spleen of high dose females was probably secondary to mild hemolytic anemia. Significant methemoglobin production was also observed in mid and high dose animals. Thymic lymphocyte depletion in high dose males was apparently secondary to stress produced by test article administration, but possibly could also be a direct treatment-related effect. Mild leukocytosis possibly secondary to stress and consisting of increased number of lymphocytes, neutrophils, monocytes, and/or eosinophils was seen in high dose animals and mid dose males. Thrombocytopenia was observed in all WR242511-treated groups. Because alveolar histiocytosis, thrombocytopenia, and hematology changes were seen at the low dose level, a no-adverse effect level of WR242511 could not be determined.

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STATEMENT OF COMPLIANCE

To the best of my knowledge, Study No. 107 entitled "Thirteen Week Oral Toxicity Study of WR242511 in Rats" was conducted in compliance with the Good Laboratory Practices regulations as published in 21 CFR 58, 40 CFR 160 and 40 CFR 792 in all material aspects.

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

Signature

Study Director

_____ _____

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

QUALITY ASSURANCE STATEMENT

STUDY TITLE: THIRTEEN WEEK ORAL TOXICITY STUDY OF WR242511 IN RATS

STUDY NUMBER: 107

STUDY DIRECTOR: BARRY S. LEVINE

INITIATION DATE: 12/3/92

This study has been divided into a series of phases. Using a random sampling approach, Quality Assurance personnel monitor 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 12/7/92, TO STUDY DIR 12/7/92, TO MGMT 12/7/92
PHASES: PROTOCOL REVIEW

INSPECT ON 10/13/93, TO STUDY DIR 10/14/93, TO MGMT 10/19/93
PHASES: OPHTHALMOLOGIC EXAMINATION

INSPECT ON 10/14/93, TO STUDY DIR 10/14/93, TO MGMT 10/19/93
PHASES: FOOD CONSUMPTION, BODY WEIGHT, CLINICAL OBSERVATION AND DOSING

INSPECT ON 3/10-11/94, TO STUDY DIR 3/14/94, TO MGMT 3/23/94
PHASES: ANALYTICAL LABORATORY RAW DATA AND DRAFT REPORT

INSPECT ON 3/30-4/1/94, TO STUDY DIR 4/1/94, TO MGMT 4/6/94
PHASES: RAW DATA

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PHASES: DRAFT PATHOLOGY REPORT

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THIRTEEN WEEK ORAL TOXICITY STUDY OF WR242511 IN RATS

Test Article.: WR242511 Tartrate

Sponsor: US Army Medical Materiel
Development Activity
Fort Detrick
Frederick, MD 21702-5009

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Barry S. Levine, D.Sc., D.A.B.T. Date
Study Director

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Clyde W. Wheeler, PhD. Date
Toxicologist

Study Initiation: December 3, 1992
Dosing Initiation: October 14, 1993
In-Life Completion: January 14, 1994

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1. SUMMARY

This study evaluated the toxicity of WR242511 Tartrate in rats following thirteen weeks of daily oral (gavage) administration. Dose levels studied were 0 (vehicle control), 0.5, 1.5 and 4.5 mg base/kg/day. The primary treatment-related toxic effects of WR242511 were seen in the liver, lungs and RBCs. Males appeared more sensitive than females to the hepatotoxic effects of WR242511 administration. Microscopic liver lesions (hepatocyte degeneration and necrosis), and elevations in serum ALT and/or SDH levels were observed in mid and high dose males. Increased triglyceride and cholesterol levels in high dose females, and increased cholesterol levels in high dose males also suggested potential hepatocellular toxicity. Increases in total bile acids and alkaline phosphatase levels suggested hepatobiliary changes in high dose animals. Pulmonary microscopic lesions (alveolar histiocytosis) were observed in all WR242511-treated groups. These dose-related effects (hepatocyte degeneration and necrosis, and alveolar histiocytosis) probably contributed to the early deaths of seven out of ten high dose males. Treatment-related mild anemia was observed in mid dose and high dose animals. Hemosiderosis in the spleen of high dose females was probably secondary to mild hemolytic anemia. Significant methemoglobin production was also observed in mid and high dose animals. The lesser methemoglobinemic response seen in high dose males compared to high dose females may have been secondary to the greater hepatotoxic effect in males, resulting in a reduction in the production of a direct methemoglobin-forming metabolite. Thymic lymphocyte depletion in high dose males was apparently secondary to stress produced by test article administration, but possibly could also be a direct treatment-related effect. Mild leukocytosis possibly secondary to stress and consisting of increased number of lymphocytes, neutrophils, monocytes, and/or eosinophils was seen in high dose animals and mid dose males. Thrombocytopenia was observed in all WR242511-treated groups. Because alveolar histiocytosis, thrombocytopenia, and hematology changes were seen at the low dose level, a no-adverse effect level of WR242511 could not be determined.

2. INTRODUCTION

This study was conducted to determine the specific target organ toxicity, dose-response relationships and determination of a no-adverse effect level of WR242511 tartrate in rats following thirteen weeks of daily oral administration. The study was conducted in accordance with the specifications of the Sponsor. The rats used in the study are a standard and accepted rodent species for regulatory toxicology studies, and was specified by the Sponsor. Oral administration is the intended clinical route and was also specified by the Sponsor. All methods and procedures were conducted in accordance with the Quality Assurance Programs of the Toxicology Research Laboratory, University of Illinois at Chicago and Pathology Associates, Inc., designed to conform with FDA Good Laboratory Practices Regulations. No unforeseen circumstances affected the integrity of the study. Dosing was initiated on October 14, 1993 and the in-life portion was terminated on January 14, 1994.

3. MATERIALS AND METHODS

3.1 Test Article

WR242511 Tartrate (Lot No. DJD-08-235, Batch No. BM05816), a yellow powder, was received on December 15, 1992 and June 16, 1992 from Herner & Co., and was 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 -15 to -20°C and ambient humidity, and protected from light in an amber bottle.

The Analytical Chemistry Report is contained in Appendix 1. The test article was initially identified by GC-MS and the purity was determined to be 99.51% ± 0.02%. The purity was re-determined following the completion of the in-life portion of the study. At that time, the purity was 99.59% ± 0.02%. Thus, the test article was stable under storage conditions.

3.2 Animals

Fifty male and female CD® Virus Antibody Free (VAF) rats were obtained from Charles River Breeding Laboratories (Kingston, NY) on October 6, 1993. The animals were approximately 6 weeks old (date of birth August 30, 1993) upon arrival at the UIC AAALAC-accredited animal facility. Each animal was given a study-unique quarantine/pretest number following placement in cages. Animals were singly housed in polycarbonate cages with Anderson bed-o-cob® bedding (Heinold, Kankakee, IL) in a temperature (65-78°F) and humidity (30-70%) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 840 cm^2 area and 20 cm height, was adequate to house rats 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 with fresh bedding weekly.

Certified Rodent Chow No. 5002 (PMI Feeds Inc., St. Louis, MO) was provided *ad libitum* from arrival until termination, except during an approximate 16 - 20 hour fast prior to blood collection for clinical pathology and/or necropsy. Tap water from an automatic watering system in which the room distribution lines were flushed daily was provided *ad libitum*. The water was not treated with additional chlorine or HCl. There were no known contaminants in the feed or water which were expected to influence the study. The results of the bimonthly comprehensive chemical analyses of Chicago water performed by the City of Chicago are documented in files maintained by Quality Assurance.

3.3 Experimental Design

All animals were examined daily during the eight day quarantine/pretest period, and were approved for use by the Clinical Veterinarian prior to being placed on test. Near the end of the quarantine/pretest period, 40 animals of each sex were randomized by sex into the groups shown in the following table using a computer-generated randomization program, stratified on the basis of body weight.

Treatment Group	Dose Level (mg base/kg/day)	Number of Males	Number of Females
1	0	10	10
2	0.5	10	10
3	1.5	10	10
4	4.5	10	10

During the test animal selection process, each animal was assigned an animal number unique to it within the population making up the study. This number appeared as an ear tag and also appeared on a cage card visible on the front of each cage. The cage card additionally contained the study number, test article identification, sex, treatment group number, and dose level. Cage cards were color-coded as a function of treatment group.

Prior to dosage formulation preparation, the test article was ground to a fine powder using a mortar and pestle. The dosage formulations were prepared fresh daily by diluting a stock formulation (made weekly) with the vehicle (1% methylcellulose/0.2% Tween 80) to appropriate concentrations of the test article. Stability was based on data from a previously conducted study (UIC/TRL Study No. 106) which indicated that the dosing suspensions were stable for 48 hours at the test article concentrations being used and the stock formulation was stable for two weeks. Dosage formulations were also shown to be homogeneous in that previous study. Samples of all dosage formulations used at the onset of Weeks 1, 7 and 13 were analyzed for test article concentration one day prior to their use. The results of these analyses are included in Table 2 and in Appendix 1.

The test article was suspended in the vehicle to result in concentrations necessary to administer the dosage formulations at a volume of 5 ml/kg. The specific volume (ml) administered was calculated on the basis of each animal's most recent body weight. The quantity of the test article was calculated as mg base/kg/day. The test article dosage formulation was administered by gavage once daily for 91 or 92 days beginning on October 14, 1993 (Day 0). The animals were dosed up to and including the day prior to scheduled necropsy. Control animals received the vehicle (1% methylcellulose/0.2% Tween 80). The rats weighed 199 - 248 g (males) and 170 - 205 g (females) on Day 0 and were approximately seven weeks old at initiation of treatment.

Non-fasted body weights were recorded on Day -3, on Day 0 prior to dosing, and weekly thereafter. Fasted body weights were collected at scheduled termination. Clinical signs were observed and recorded for all animals once daily, approximately 1 - 2 hours after dosing. The general behavior, posture, locomotion, breathing pattern and coat were observed for all animals. The animals were also observed immediately prior to dosing and in the afternoon for moribundity/mortality. Physical examinations (clinical observations) which included examination of eyes and all orifices were conducted in Week -1, on Day 0 prior to dosing, and once weekly thereafter. Food consumption was measured for all animals weekly commencing with Week -1. All rats were examined by indirect ophthalmoscopy prior to study initiation (Week -1) and during Week 13. The animals were treated with 1% atropine sulfate eye drops prior to the examination.

Hematology and clinical chemistry parameters were measured for all animals during Weeks 5, 9 and 13. The overnight fasted animals were anesthetized by carbon dioxide inhalation, and approximately 1.5 - 2.0 ml of blood was collected from the orbital sinus to measure the following parameters. The samples were processed in the same random order as collected. Water was available *ad libitum* during all fasting periods. Clinical pathology methodology is contained in Appendix 2.

Hematology

Erythrocyte count and morphology	Mean corpuscular hemoglobin (MCH)
Heinz bodies	Mean corpuscular hemoglobin concentration (MCHC)
Hematocrit	Mean corpuscular volume (MCV)
Hemoglobin	[a]Methemoglobin
Leukocyte count, total and differential	Nucleated RBCs
	Platelet count
	Reticulocyte count

[a]Measured with a Co-oximeter (Instrumentation Laboratory Model 282). The assay was performed within one hour of sample collection. The specimens were kept on wet ice prior to analysis.

Clinical Chemistry

Alanine aminotransferase (ALT)	Glucose
Albumin	Inorganic phosphorus
Albumin/Globulin ratio (calc.)	Potassium
Alkaline phosphatase	Sodium
Calcium	Sorbitol dehydrogenase
Chloride	Total bile acids
Cholesterol	Total protein
Creatinine	Triglycerides
Globulin (calc.)	Urea nitrogen (BUN)

All animals which died on test or were sacrificed if moribund were necropsied on that day. The surviving animals were killed and necropsied in random order over a two consecutive day period (Days 91 and 92). Euthanasia was accomplished by carbon dioxide asphyxiation, and an extensive necropsy was performed under the direction and supervision of the pathologist. Terminal body weights were collected prior to routine sacrifice.

The necropsy procedure was a thorough and systematic examination and dissection of the animal viscera and carcass, and collection and fixation of the following tissues/organs in 10% neutral buffered formalin (NBF). The ear with its identification tag was also saved from each animal with the NBF-fixed tissues.

*Adrenal glands	Pancreas
Aorta	Pituitary
*Brain (fore-, mid-, hind-)	Prostate
Cecum	Rectum
Colon	Salivary gland (submaxillary)
Diaphragm	Sciatic nerve
Duodenum	Seminal vesicles
Esophagus	Skeletal muscle
Eyes with harderian glands	Skin with mammary gland
Femur with marrow	Spinal cord (thoracic)
Gross lesions	*Spleen
*Heart	Stomach
Ileum	*Testes with epididymides
Jejunum	Thymus
*Kidneys	Thyroid gland/Parathyroids
*Liver	Tongue
Lungs/Bronchi	Trachea
Lymph node (mesenteric)	Urinary bladder
*Ovaries	Uterus
	Vagina

*Weighed at scheduled necropsy. Paired organs were weighed as a unit.

All tissues and organs collected at necropsy were examined microscopically for all control and high dose animals. If treatment-related lesions were observed at the high dose, those tissues/organs were examined microscopically within sex for mid and low dose animals sacrificed in Week 14.

3.4 Statistical Analyses

For each sex, Analysis of Variance tests was conducted on body weight, weekly body weight gains, food consumption, hematology, clinical chemistry and organ weight data. Organ weight analysis considered weights relative to brain weight. If a significant F ratio was obtained from an ANOVA test ($p \leq 0.05$), Dunnett's t test was used for pair-wise comparisons with the concurrent control group. The level of significance was $p \leq 0.05$. All statistical analyses procedures compared treated to control animals at each time point. Data were not corrected for baseline values, except that body weight analysis included absolute values, weekly changes and total weight changes. Dose levels for all summary and individual data are expressed on the basis of mg base/kg/day.

Quantitative data were tabulated and are presented in the report. 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 Analyses

The Analytical Chemistry Report is contained in Appendix 1. Dosage formulation analyses are shown in Table 2.

The dosing formulations used on the first day of Week 1 (Day 0) were inadvertently analyzed as the salt, not as the base. The dosing formulations and the stock suspension were therefore adjusted prior to re-analysis resulting in $\pm$ 10% of the target concentration in terms of the salt. Because the dosing suspensions are prepared fresh daily by diluting the stock suspension (made fresh weekly), the dosing formulations used were approximately 25% - 30% lower than their target concentrations in Week 1. This mistake was identified and the stock suspension and the dosing suspensions used in the remainder of the study in Weeks 2 - 13 were prepared in terms of the base, not salt. The dosing suspensions which were tested prior to use on the first day of Weeks 7 and 13 were within 10% of their target concentration in terms of the base.

4.2 Mortality and Clinical Signs/Observations

Summaries of clinical signs and clinical observations are presented in Table 3. Individual clinical signs, daily incidence of clinical signs and summaries of weekly clinical observations are contained in Appendix 3.

Treatment-related deaths included seven high dose males; five animals were moribund sacrificed [Days 19, 21, 28 (two animals), and 63] and two animals were found dead (Days 22 and 24). In Week 13, one low dose male (#328) died as the result of an accident during blood collection. The animal uncontrollably hemorrhaged from the nose and mouth leading to aspiration of blood into the lungs and death by asphyxiation. In Week 13, a mid dose male (#342) demonstrated labored breathing and was subsequently found dead apparently from chronic, active inflammation secondary to a esophageal injury incurred during dosing.

Daily treatment-related clinical signs (1 - 2 hrs post dosing) included rough coat, hunched posture and decreased activity. Beginning in Week 3 and for the remainder of the study, rough coats were periodically seen in all high dose animals. Rough coats were also observed (occasionally) in the majority of the mid dose animals and were seen (infrequently) in a few low dose animals. Hunched posture was limited to high dose males, except for one mid dose male which subsequently died from complications of an esophageal injury, as discussed above, and in one low dose male (#327) in Week

2 which also demonstrated audible breathing secondary to the apparent aspiration of a portion of the dosing suspension. In Week 3, this low dose animal demonstrated a complete recovery. Decreased activity was seen in one high dose male prior to moribund sacrifice. Similar signs of toxicity were seen in the weekly clinical observations (physical examinations; Appendix 3). Clinical signs were not observed in vehicle-treated animals, except for one observation of a rough coat for one female.

4.3 Body Weight

Summaries of body weights and summaries of weight gains are presented in Tables 4 and 5, respectively. Individual body weights and weight gains are contained in Appendix 4. In addition, summaries of body weights are graphically depicted in Figures 1 (males) and 2 (females).

Decreased body weight gains were apparent in high dose males beginning the third study week resulting in significantly decreased body weights as compared to concurrent controls. By the end of the study, an approximate 60% reduction in weight gain was seen for these animals. Although weekly weight gains were not significantly decreased in mid dose males, slight decreases resulted in significantly lower body weights by Day 35 and for the majority of the remainder of the study as compared to controls. Body weights of low dose males were not affected by treatment.

Female body weights did not appear to be affected by treatment. On one occasion (Day 21), a slight decrease in weekly body weight gain was observed for the high dose females (15 g vs. 23 g for control animals), however, this did not have a significant effect on their body weights compared to controls. Although the same mean weight gain (15 g) was noted in mid dose females, it was not statistically significant as the statistical analyses are conducted prior to rounding, i.e. the true mean was 14.8 in mid dose females whereas for the high dose females, it was 14.5.

4.4 Food Consumption

Summaries of food consumption are in Table 6. Individual food consumption data are shown in Appendix 5.

Significantly reduced daily food consumption was observed in high dose males beginning in Week 1 and periodically thereafter. A significant decrease in food intake was noted on two occasions (Weeks 2 and 3) for high dose females, but was not affected thereafter. Food consumption was not affected in mid or low dose animals during the study.

4.5 Clinical Pathology

Summaries of clinical chemistry tests are presented in Table 7. Individual clinical chemistry data are in Appendix 6. Summaries of hematology tests are presented in Table 8. Individual hematology data are in Appendix 7.

Hepatocellular toxicity was suggested as significant increases in serum ALT were seen in mid dose (Weeks 9 and 13) and surviving high dose (Weeks 5, 9 and 13) males (Table 7.1). Sorbitol dehydrogenase (SDH) was also significantly elevated in high dose males throughout the study (Table 7.3). Although not statistically significant, a biologically significant increase in SDH was also observed in mid dose males. In Week 9, a significant decrease in total protein and globulin levels were observed in high dose males (Tables 7.5 and 7.9). A/G ratios, however, were not altered. Possible treatment-related effects occurred on lipoprotein metabolism. Significantly increased levels of serum cholesterol in high dose males and females (Tables 7.17 and 7.18) and of serum triglycerides in high dose females were noted (Table 7.20). None of these apparent WR242511-induced hepatotoxic changes were observed in low dose males or in any female treatment groups, except for the hypercholesterolemia and hypertriglyceridemia seen in high dose females, as previously discussed.

Heptatobiliary changes were suggested by significant elevations in total bile acids in high dose animals (Tables 7.13 and 7.14). In Week 9, serum alkaline phosphatase levels were also increased in high dose males (Table 7.15). These above-mentioned changes were not observed at the lower dose levels.

Significant increases in serum BUN and creatinine levels (Tables 7.21 and 7.23) and significant decreases in serum glucose levels (Table 7.35) were seen in high dose males. These effects were generally seen throughout the study.

Dose-dependent anemia, as indicated by decreased RBC count, hemoglobin, hematocrit, and/or MCHC, was observed in mid and high dose males and in all three female treatment groups (Tables 8.1 - 8.6, 8.11 and 8.12). Hematocrit was only marginally affected, primarily in females, apparently a consequence of compensatory increases in MCV and MCH (Tables 8.7 - 8.10). In Week 9, high dose males paradoxically had an increased RBC count, hemoglobin and hematocrit compared to controls. This hemoconcentration may have reflected a dehydrated state, secondary to significant reductions in weight gain, although clinical signs of dehydration were not observed. Hemoconcentration also probably contributed to an apparent non-effect on RBC count, etc. seen in Weeks 5 and 13. The anemic state was characterized by dose-related increases in polychromasia, poikilocytosis (irregularities in shape) and macrocytosis in the two higher dose levels, especially females, compared to controls. Anisocytosis (irregularities in size) was also seen in high dose females. Reticulocytosis, but not increased nucleated RBCs, was seen as a compensatory response to the mild anemia in

mid and high dose animals (Tables 8.13, 8.14, 8.15 and 8.16). The induction of RBCs with Heinz bodies was also observed in high dose animals and mid dose males, suggesting an oxidant nature of WR242511 (Tables 8.17 and 8.18).

Methemoglobinemia was evident in mid and high dose animals throughout the study (Tables 8.19 and 8.20). Although methemoglobin levels were similar between sex in mid dose animals, methemoglobin levels were approximately 1.6 to 2.0-fold greater in high dose females compared to the surviving high dose males. An approximate two-fold increase in methemoglobin levels, although statistically not significant, was seen in low dose animals of both sexes.

Thrombocytopenia was seen in low, mid and high dose animals throughout the study (Tables 8.21 and 8.22). The maximal reduction in platelet number was ≈ 40% in remaining high dose males, ≈ 13% in mid and low dose males and ≈ 15% in all WR242511-treated female groups. Leukocytosis was also observed throughout the study in high dose animals and in mid dose males (Tables 8.23 and 8.24). This generalized leukocytosis consisted of increased mature and immature neutrophils, lymphocytes and/or monocytes (Tables 8.23 - 8.32). An increase in eosinophils was also seen in Week 9 in high dose males (Table 8.33).

No other clinical pathology changes were related to WR242511 treatment. Sporadic increases and decreases were seen, but were not considered to be biologically significant. The apparent slight, but significant increase in serum sorbitol dehydrogenase levels in low and high dose, but not mid dose females in Week 9 apparently reflects a slight decrease in serum levels in controls rather than an increase in treated animals (Table 7.4). A similar situation was apparent regarding slightly increased serum calcium levels in low and high dose, but not mid dose females in Week 13 (Table 7.32).

4.6 Ophthalmology

The Ophthalmology Report is contained in Appendix 8. WR242511 treatment did not result in treatment-related ophthalmic lesions.

4.7 Organ Weights

Organ weight summaries expressed as % brain weight are presented in Table 9. Individual organ weight data are contained in Appendix 9.

Splenomegaly was seen in mid and high dose animals and in low dose males (Tables 9.1 and 9.2). An increased relative kidney weight was observed in high dose females, but not in corresponding males. The biologic significance of this increased kidney weight is uncertain, because corresponding changes in clinical pathology parameters were not seen in high dose females, only in high dose males which failed to demonstrate elevated kidney weights.

4.8 Pathology

The Pathology Report is contained in Appendix 10. A summary of gross and microscopic lesions is shown in Table 10.

The oral administration of WR242511 in rats was associated with microscopic changes in the liver, lungs, spleen and thymus. Seven apparent treatment-related deaths occurred during the study. The probable cause of death of the seven high dose males included liver (hepatocyte degeneration and necrosis) and lung (alveolar histiocytosis) lesions. Severe thymic lymphocyte depletion was also observed in these animals where the thymus could be identified. Two other early deaths, one low dose and one mid dose male, were not considered to be test article-related. The low dose male (#328) died from an apparent vascular injury incurred during orbital sinus blood collection in Week 13. The animal visibly hemorrhaged uncontrollably from its nose and mouth prior to death, which was related to aspiration of blood resulting in asphyxiation. In Week 13, a mid dose male (#342) died apparently from chronic active inflammation involving the heart and lung (pleura) probably secondary to an esophageal injury. Thymic lymphocyte depletion was also seen in this animal, but it was attributed to the severe and diffuse chronic-active inflammation.

As indicated above, treatment-related histopathologic lesions included hepatocyte degeneration and necrosis, alveolar histiocytosis and thymic lymphocyte depletion. Splenic hemosiderosis was also seen, but was considered secondary to hemolytic anemia. Hepatocyte degeneration was observed in all 10 high dose males (mean group severity score = 2.70; maximum = 4.00) and in 4 mid dose males (mean group severity score = 0.40). Hepatocyte necrosis was also seen in all high dose males (mean group severity score = 1.70) and in one mid dose male (mean group severity score = 0.10). Neither of these lesions was present in low dose males or in any female treatment group. Hepatocyte degeneration was present throughout the affected livers and was characterized by swelling of the hepatocytes resulting in the obstruction of adjacent bile canaliculi. The cytoplasm of these hepatocytes generally had a pale, ground-glass appearance, but some cells were vacuolated. An increase in nuclei in periportal zones suggesting oval cell proliferation was seen in some animals. Hepatocyte necrosis appeared as randomly scattered hepatocytes which had undergone coagulative necrosis and had pyknotic or karyorrhectic nuclei. These microscopic changes were associated with gross lesions in 6 of 7 early death males (4.5 mg base/kg/day) variably described as: mottled lesion; pale, diffuse lesion; irregular linear pigmentation; or irregular, diffuse, dark lesion. Because of the dose-response relationship of the incidence and mean group severity scores, both hepatocyte degeneration and necrosis were interpreted as test article-related changes in males.

Alveolar histiocytosis was seen as a dose-related response in all WR242511-treated groups. This change was characterized by the occurrence of large macrophages throughout the lung containing abundant, finely vacuolated, pale cytoplasm present

individually or in small number in alveoli, or clustered in large numbers in alveoli surrounding terminal bronchioles. Perivascular infiltrates of macrophages and lymphocytes also occurred in association with the alveolar histiocytosis. At necropsy, multiple, irregular, linear, white lesions of the lung in mid and high dose animals correlated with the occurrence of alveolar histiocytosis. Although alveolar histiocytosis was observed in one vehicle control male, this was interpreted as a spontaneous change.

Hemosiderin deposition in the spleen was identified in high dose females, but not males. This change was characterized by golden-brown granular pigment filling the cytoplasm of macrophages in the sinusoids. Splenic hemosiderosis was interpreted as a secondary test article-related change consistent with the pathophysiologic response to a mild hemolytic anemia, which did not result in a detectable increase in hematopoiesis. Although splenic hemosiderosis was observed in the one early death mid dose male, because this change was not observed in high dose males, it was considered an incidental finding. However, increased relative splenic weights (% brain weight) were observed in mid and high dose animals and in low dose males.

Thymic lymphocyte depletion was observed as a test article-related change in high dose males, but not females. This change was observed as a decrease in the number of thymic lymphocytes in the cortical and medullary zones. The microscopic examination of the thymus was not performed for three early death males (#366, #367 and #368) due to an inability to identify the thymus at tissue trimming because of its apparent small size. Although thymic lymphocyte depletion was also observed in the one early death mid dose male (#342), this change was considered to be caused by the chronic, active inflammation which was secondary to an esophageal injury. In high dose males, thymic lymphocyte depletion was interpreted as a test article-related change either secondary to generalized stress or a direct effect of WR242511 treatment.

No other microscopic changes were considered to be related to WR242511 treatment.

5. DISCUSSION/CONCLUSION

This study evaluated the toxicity of WR242511 in CD® rats following thirteen weeks of daily oral (gavage) administration. The results are summarized in Table 1. Seven apparent treatment-related early deaths (found dead or sacrificed moribund) occurred among high dose males during the study. Their probable cause of death included WR242511-induced hepatotoxicity, pulmonary toxicity and hematotoxicity. Thymic lymphocyte depletion was also observed in several of these animals. During the study, a dose-related increase in the incidence of rough coat was observed. Hunched posture was seen in the majority of the high dose males and decreased activity was seen in one high dose male prior to moribund sacrifice. Decreased body weights and/or body weight gains were accompanied by decreased food consumption in high dose males, but not females. In the second and third week of the study, decreased food consumption was seen in high dose females, however this did not result in decreases in body weights. Treatment-related ophthalmic lesions were not observed.

Drug-induced hepatotoxicity was observed in mid and high dose animals. Histologically, WR242511 resulted in hepatocyte degeneration and/or hepatocyte necrosis in all high dose males and several mid dose males, but not in any female treatment groups. The microscopic lesions were accompanied by gross lesions in 6 of the 7 early death high dose males. These lesions were also accompanied by significantly increased serum ALT and/or SDH levels in mid and high dose males. Decreased total protein and globulin levels were also seen in the high dose males. Increased triglyceride and cholesterol levels in high dose females, and increased cholesterol and alkaline phosphatase levels in high dose males also demonstrated potential hepatotoxicity. Although microscopic hepatic changes were not observed for females, increased serum total bile acids were seen in both high dose males and females, suggesting alterations in hepatobiliary function in both groups.

Alveolar histiocytosis was interpreted as another direct WR242511-related change which probably contributed to the deaths of the high dose males. Alveolar histiocytosis was observed in a dose-related response in all WR242511-treated groups. Gross lesions observed on the lungs correlated with the microscopic finding of alveolar histiocytosis.

Treatment-related anemia and methemoglobinemia were observed in mid and high dose animals. However, methemoglobin levels were 1.6 to 2.0-fold greater in high dose females than in high dose males at each time point measured. Rather than reflecting a sex-related difference, the lower methemoglobin levels in high dose males may be secondary to hepatotoxicity in this sex, with a resulting secondary reduction in their metabolic capacity to bioactivate the compound to a direct methemoglobin-forming metabolite. The anemic state was characterized by significantly decreased RBCs, hemoglobin, hematocrit, and/or MCHC and increased MCV and MCH. With increasing dose levels, an increase in the severity and occurrence of poikilocytosis, macrocytosis and polychromasia was observed in mid and high dose animals, most notably in high dose females, which also demonstrated anisocytosis. Compensatory physiologic responses included reticulocytosis, hemosiderosis and the induction of RBCs with Heinz bodies. The induction of Heinz bodies in mid and high dose animals suggested an oxidant nature of WR242511. Splenomegaly was observed in mid and high dose animals and low dose males, but splenic hemosiderosis secondary to hemolytic anemia was only apparent in high dose females.

Mild generalized leukocytosis was seen in high dose animals and mid dose males. The leukocytosis consisted of increased neutrophils (mature and immature), lymphocytes, monocytes, and/or eosinophils. The mild leukocytosis induced was probably an indirect effect of the stress produced by the hemolytic anemia and/or methemoglobinemic state. In addition, high dose males exhibited thymic lymphocyte depletion. This lesion may have been a direct test article-related effect or more possibly a secondary stress-induced change. Thrombocytopenia was observed in all WR242511-treated groups.

In summary, the primary treatment-related toxic effects of WR242511 were seen in the liver, lungs and RBCs. Males appeared more sensitive than females to the hepatotoxic effects of WR242511 administration. Microscopic liver lesions (hepatocyte degeneration and necrosis), and elevations in serum ALT and/or SDH levels were observed in mid and high dose males.

Increased triglyceride and cholesterol levels in high dose females, and increased cholesterol in high dose males also suggested potential hepatocellular toxicity. Increases in total bile acids and alkaline phosphatase levels also suggested hepatobiliary changes in high dose animals. Pulmonary microscopic lesions (alveolar histiocytosis) were observed in all WR242511-treated groups. These dose-related effects (hepatocyte degeneration and necrosis, and alveolar histiocytosis) probably contributed to the early deaths of seven out of ten high dose males. Treatment-related mild anemia was observed in mid dose and high dose animals. Hemosiderosis in the spleen of high dose females was probably secondary to mild hemolytic anemia. Significant methemoglobin production was also observed in mid and high dose animals. The lesser methemoglobinemic response seen in high dose males compared to high dose females may have been secondary to the greater hepatotoxic effect in males, resulting in a reduction in the production of a direct methemoglobin-forming metabolite. Thymic lymphocyte depletion in high dose males was apparently secondary to stress produced by test article administration, but possibly could also be a direct treatment-related effect. Mild leukocytosis possibly secondary to stress and consisting of increased number of lymphocytes, neutrophils, monocytes, and/or eosinophils was seen in high dose animals and mid dose males. Thrombocytopenia was observed in all WR242511-treated groups. Because alveolar histiocytosis, thrombocytopenia, and hematology changes were seen at the low dose level, a no-adverse effect level of WR242511 could not be determined in the present investigation.

6. PERSONNEL

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
Toxicologist	Clyde W. Wheeler, PhD.
Pathologist	Michael J. Tomlinson, D.V.M., Ph.D., D.A.C.V.P.
Analytical Chemist	Adam Negrusz, Ph.D.
Clinical Veterinarian	James E. Artwohl, D.V.M., Ph.D., D.A.C.L.A.M.
Ophthalmologist	Samuel J. Vainisi, D.V.M., D.A.C.V.O.
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Nancy Dinger, B.S.
Clinical Pathology	Maria Lang, A.T., C.V.T.
Chemistry Specialist	Thomas Tolhurst, B.S.
Quality Assurance	Ronald C. Schoenbeck

7. ARCHIVES

The raw data, specimens, test article reserves, and final report are archived at the Toxicology Research Laboratory (TRL), University of Illinois at Chicago (UIC), Department of Pharmacology, 1940 W. Taylor St., Chicago, IL 60612-7353.

Table 1

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR242511 IN RATS

Summary of Toxic Responses

Dose (mg base/kg/day)	0	0.5	1.5	4.5
Rats/Sex	10	10	10	10
Deaths[a]	-	1 (M-AC)	1 (M-AC)	7(M)
Body Weights/Gains	-	NE	↓ (M)	↓ (M)
Food Consumption	-	NE	NE	↓ (M) (F?)
Clinical Observations (Signs)	-	Rough coat (3M/2F) Hunched posture (1M)	Rough coat (8M/9F) Hunched posture (1M)	Rough coat (10M/10F) Hunched posture (9M) Decreased Activity (1M)
Clinical Chemistry[b]	-	NE	↑ ALT (M) ↑ SDH (M?)	↑ ALT (M) ↑ SDH (M) ↓ TP (M) ↓ GLOB (M) ↑ TBA ↑ CHOL ↑ ALKP (M) ↑ TRIG (F) ↑ BUN (M) ↑ CREAT (M) ↓ GLUC (M)
Hematology[c]	-	↓ RBC (F) ↓ HGB (F) ↓ MCV (M) ↓ PLT	↓ RBC ↓ HGB ↓ HCT (F) ↓ MCV ↑ MCH ↓ MCHC ↑ RETIC ↑ HEINZ (M) ↑ METHGB ↓ PLT ↑ LEUK (M) ↑ MNEUT (M) ↑ INEUT (M) ↑ LYMPH (M)	↓ RBC (F) ↓ HGB (F) ↓ HCT (F) ↑ MCV (F) ↑ MCH (F) ↓ MCHC ↑ RETIC ↑ HEINZ ↑ METHGB ↓ PLT ↑ LEUK ↑ MNEUT ↑ INEUT (F) ↑ LYMPH ↑ MONO ↑ EOSIN (M)
Ophthalmology	-	NE	NE	NE
Organ Weights	-	↑ Spleen (M)	↑ Spleen	↑ Spleen ↑ Kidneys (F?)
Histopathology	Lungs - alveolar histiocytosis (1M)	Lungs - alveolar histiocytosis (4M/1F)	Liver - hepatocyte degeneration (4M) hepatocyte necrosis (1M) Lungs - alveolar histiocytosis (8M/9F) Spleen - hemosiderin pigment (1M) Thymus - lymphocyte depletion (1M)	Liver - hepatocyte degeneration (10M) hepatocyte necrosis (10M) Lungs - alveolar histiocytosis (10M/10F) Spleen - hemosiderin pigment (9F) Thymus - lymphocyte depletion (4M)
CONCLUSIONS	The primary treatment-related toxic effects of WR242511 were seen in the liver, lungs and RBCs. Males appeared more sensitive than females to the hepatotoxic effects of WR242511 administration. Microscopic liver lesions (hepatocyte degeneration and necrosis), and elevations in serum ALT and/or SDH levels were observed in mid and high dose males. Increased triglyceride and cholesterol levels in high dose females, and increased cholesterol levels in high dose males also suggested potential hepatocellular toxicity. Increases in total bile acids and alkaline phosphatase levels suggested hepatobiliary changes in high dose animals. Pulmonary microscopic lesions (alveolar histiocytosis) were observed in all WR242511-treated groups. These dose-related effects (hepatocyte degeneration and necrosis, and alveolar histiocytosis) probably contributed to the early deaths of seven out of ten high dose males. Treatment-related mild anemia was observed in mid dose and high dose animals. Hemosiderosis in the spleen of high dose females was probably secondary to mild hemolytic anemia. Significant methemoglobin production was also observed in mid and high dose animals. The lesser methemoglobinemic response seen in high dose males compared to high dose females may have been secondary to the greater hepatotoxic effect in males, resulting in a reduction in the production of a direct methemoglobin-forming metabolite. Thymic lymphocyte depletion in high dose males was apparently secondary to stress produced by test article administration, but possibly could also be a direct treatment-related effect. Mild leukocytosis possibly secondary to stress and consisting of increased number of lymphocytes, neutrophils, monocytes, and/or eosinophils was seen in high dose animals and mid dose males. Thrombocytopenia was observed in all WR242511-treated groups. Because alveolar histiocytosis, thrombocytopenia, and hematology changes were seen at the low dose level, a no-adverse effect level of WR242511 could not be determined in the present investigation.			

[a]AC = accidental death

[b]ALT = alanine aminotransferase, SDH = sorbitol dehydrogenase, TP = total protein, GLOB = globulin, TBA = total bile acids, CHOL = cholesterol, TRIG = triglycerides, BUN = blood urea nitrogen, CREA = creatinine, GLUC = glucose, ALKP = alkaline phosphatase.

[c]RBC = red blood cell counts, HGB = hemoglobin, HCT = hematocrit, MCV = mean corpuscular volume, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, RETIC = reticulocytes, HEINZ = Heinz bodies, METHGB = methemoglobin, PLT = platelet, LEUK = leukocytes, MNEUT = mature neutrophils, INEUT = immature neutrophils, LYMPH = lymphocytes, MONO = monocytes, EOSIN = eosinophils.

? = Possible or marginal effect NE = No effect

M = Male, F = Female

Table 2

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR242511 IN RATS

Dosage Formulation Analyses[a]

Target Concentration (mg base/ml)	Day 0 (mg/ml)	Day 0 (mg base/ml)	Day 0 % Target	Day 42 (mg base/ml)	Day 42 % Target	Day 84 (mg base/ml)	Day 84 % Target
0	0.00	0.00	----	0.00	----	----	----
0.1	0.0963 ± 0.0030	0.0684 ± 0.0021	68.40	0.1077 ± 0.0014	107.7	0.0939 ± 0.0002	93.9
0.3	0.3208 ± 0.0019	0.2278 ± 0.0013	75.93	0.3101 ± 0.0024	103.4	0.2986 ± 0.0008	99.5
0.9	0.9058 ± 0.0562	0.6431 ± 0.0399	71.46	0.9655 ± 0.0017	107.3	0.8901 ± 0.0042	98.9

[a]Mean ± standard deviation for triplicate runs.

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR242511 IN RATS

DRAFT

SUMMARY OF CLINICAL SIGNS

STUDY: 107 SEX: MALE

DOSE:(mg/kg)	0	0.5	1.5	4.5 (mg base/kg/day)
GROUP:	1-M	2-M	3-M	4-M
Accidental Death	0	1	1	0
Scheduled Sacrifice	10	9	9	3
Animal Found Dead	0	0	0	2
Sacrificed Moribund	0	0	0	5
Decreased Activity	0	0	0	1
Hunched Posture	0	1	1	9
Rough Coat	0	3	8	10
Total Number of Animals	10	10	10	10

STUDY: 107 SEX: FEMALE

DOSE:(mg/kg)	0	0.5	1.5	4.5 (mg base/kg/day)
GROUP:	1-F	2-F	3-F	4-F
Scheduled Sacrifice	10	10	10	10
Rough Coat	1	2	9	10
Total Number of Animals	10	10	10	10

Table 4.1

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR242511 IN RATS

DRAFT

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 107 SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1-M	0.5 2-M	1.5 3-M	4.5 4-M	mg base/kg/day
DAY -3	MEAN	196	196	196	196	
	S.D.	8.2	9.7	10.6	9.8	
	N	10	10	10	10	
DAY 0	MEAN	231	227	225	223	
	S.D.	8.7	9.5	13.0	10.0	
	N	10	10	10	10	
DAY 7	MEAN	303	291	292	287	
	S.D.	11.3	17.9	14.6	17.0	
	N	10	10	10	10	
DAY 14	MEAN	361	342	344	333	
	S.D.	19.0	33.0	16.6	41.5	
	N	10	10	10	10	
DAY 21	MEAN	415	396	384	329*	
	S.D.	22.0	25.7	22.7	79.0	
	N	10	10	10	9	
DAY 28	MEAN	457	440	4D8	324*	
	S.D.	25.7	25.1	51.6	90.2	
	N	10	10	10	6	
DAY 35	MEAN	484	464	439*	374*	
	S.D.	31.1	22.8	31.7	69.7	
	N	10	10	10	4	
DAY 43	MEAN	524	509	476*	432*	
	S.D.	34.9	23.2	32.5	52.3	
	N	10	10	10	4	
DAY 49	MEAN	554	539	500*	427*	
	S.D.	34.2	27.1	33.1	70.1	
	N	10	10	10	4	
DAY 56	MEAN	579	564	522*	364*	
	S.D.	36.7	26.9	34.7	107.5	
	N	10	10	10	4	
DAY 63	MEAN	586	569	530*	379*	
	S.D.	40.7	30.0	36.3	108.1	
	N	10	10	10	4	
DAY 70	MEAN	614	601	553*	475*	
	S.D.	42.0	26.8	35.7	74.7	
	N	10	10	10	3	
DAY 77	MEAN	628	619	571*	513*	
	S.D.	49.0	28.4	41.1	67.9	
	N	10	10	10	3	
DAY 84	MEAN	646	643	586*	500*	
	S.D.	53.5	27.6	49.3	84.7	
	N	10	10	10	3	
DAY 90	MEAN	650	652	599	482*	
	S.D.	49.6	22.8	45.5	101.9	
	N	10	9	9	3	

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

Table 4.2

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 107 SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1-F	0.5 2-F	1.5 3-F	4.5 4-F
					(mg base/kg/day)
DAY -3	MEAN	174	174	175	174
	S.D.	6.9	8.4	8.6	8.5
	N	10	10	10	10
DAY 0	MEAN	189	190	189	188
	S.D.	5.6	10.9	8.2	8.9
	N	10	10	10	10
DAY 7	MEAN	220	220	220	217
	S.D.	8.4	16.3	13.4	16.7
	N	10	10	10	10
DAY 14	MEAN	241	248	245	234
	S.D.	10.6	21.2	16.9	19.5
	N	10	10	10	10
DAY 21	MEAN	265	269	260	249
	S.D.	13.4	25.9	15.5	22.1
	N	10	10	10	10
DAY 28	MEAN	278	285	280	263
	S.D.	14.4	30.5	20.7	24.3
	N	10	10	10	10
DAY 35	MEAN	282	291	286	270
	S.D.	15.7	30.4	23.7	27.5
	N	10	10	10	10
DAY 43	MEAN	301	308	304	288
	S.D.	13.0	35.5	26.2	31.3
	N	10	10	10	10
DAY 49	MEAN	313	322	307	298
	S.D.	16.8	45.1	33.3	34.6
	N	10	10	10	10
DAY 56	MEAN	315	330	319	300
	S.D.	17.3	46.4	29.6	30.4
	N	10	10	10	10
DAY 63	MEAN	318	334	328	304
	S.D.	16.3	41.7	30.4	31.4
	N	10	10	10	10
DAY 70	MEAN	329	344	339	316
	S.D.	18.4	47.0	33.3	31.0
	N	10	10	10	10
DAY 77	MEAN	331	352	344	319
	S.D.	14.5	49.3	41.0	35.3
	N	10	10	10	10
DAY 84	MEAN	338	358	350	321
	S.D.	20.9	48.4	42.6	32.9
	N	10	10	10	10
DAY 90	MEAN	341	361	351	324
	S.D.	28.1	52.4	43.8	33.3
	N	10	10	10	10

Analysis of Variance using DUNNETT'S Procedure

Table 5.1

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 107 SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1-M	0.5 2-M	1.5 3-M	4.5 4-M (mg base/kg/day)
DAY 7	MEAN	73	64	67	63
	S.D.	6.6	15.7	5.9	9.0
	N	10	10	10	10
DAY 14	MEAN	57	51	52	46
	S.D.	8.2	17.2	7.1	31.2
	N	10	10	10	10
DAY 21	MEAN	54	54	40	-6*
	S.D.	7.5	13.6	15.2	48.2
	N	10	10	10	9
DAY 28	MEAN	43	45	24	-40*
	S.D.	5.2	10.4	36.5	59.8
	N	10	10	10	6
DAY 35	MEAN	27	24	30	20
	S.D.	7.7	8.2	29.4	30.5
	N	10	10	10	4
DAY 43	MEAN	40	45	37	58*
	S.D.	8.0	8.2	13.0	22.3
	N	10	10	10	4
DAY 49	MEAN	29	30	24	-5*
	S.D.	5.7	13.9	6.5	56.3
	N	10	10	10	4
DAY 56	MEAN	26	25	22	-63*
	S.D.	6.5	6.6	7.5	56.3
	N	10	10	10	4
DAY 63	MEAN	6	5	8	15
	S.D.	6.5	8.9	6.9	67.2
	N	10	10	10	4
DAY 70	MEAN	28	32	24	59*
	S.D.	6.5	8.6	8.4	38.2
	N	10	10	10	3
DAY 77	MEAN	14	17	17	37*
	S.D.	10.4	9.3	6.5	19.0
	N	10	10	10	3
DAY 84	MEAN	18	25	15	-13*
	S.D.	9.8	12.2	10.4	33.7
	N	10	10	10	3
DAY 90	MEAN	4	3	5	-18*
	S.D.	7.2	5.9	9.7	31.4
	N	10	9	9	3
TOTAL GAIN	MEAN	420	425	374	258*
	S.D.	47.7	25.0	40.0	96.4
	N	10	9	9	3

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 107 SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1-F	0.5 2-F	1.5 3-F	4.5 4-F
					(mg base/kg/day)
DAY 7	MEAN	30	31	31	29
	S.D.	5.0	7.2	8.4	9.1
	N	10	10	10	10
DAY 14	MEAN	22	27	25	17
	S.D.	7.9	8.2	8.0	9.3
	N	10	10	10	10
DAY 21	MEAN	23	21	15	15*
	S.D.	7.4	8.6	6.9	8.4
	N	10	10	10	10
DAY 28	MEAN	13	17	20	15
	S.D.	3.0	7.3	9.2	6.2
	N	10	10	10	10
DAY 35	MEAN	4	6	6	7
	S.D.	4.7	2.9	6.6	9.1
	N	10	10	10	10
DAY 43	MEAN	19	17	18	18
	S.D.	3.5	7.9	7.1	16.7
	N	10	10	10	10
DAY 49	MEAN	12	14	3	9
	S.D.	8.4	11.5	14.0	7.4
	N	10	10	10	10
DAY 56	MEAN	2	7	12	2
	S.D.	7.2	9.4	12.3	10.5
	N	10	10	10	10
DAY 63	MEAN	4	4	9	4
	S.D.	6.9	9.6	11.2	8.2
	N	10	10	10	10
DAY 70	MEAN	10	10	12	12
	S.D.	6.8	10.0	6.3	6.5
	N	10	10	10	10
DAY 77	MEAN	2	9	5	3
	S.D.	8.1	5.5	9.1	6.6
	N	10	10	10	10
DAY 84	MEAN	7	5	6	3
	S.D.	8.1	5.2	6.4	6.5
	N	10	10	10	10
DAY 90	MEAN	3	4	1	3
	S.D.	8.9	6.7	6.3	6.9
	N	10	10	10	10
TOTAL GAIN	MEAN	151	172	162	137
	S.D.	26.8	44.9	39.8	28.6
	N	10	10	10	10

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

Table 6.1

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

DRAFT

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 107 SEX: MALE

PERIOD	DDSE:(mg/kg) GROUP:	0 1-M	0.5 2-M	1.5 3-M	4.5 4-M
DAY 0	INTAKE (g)	24	23	23	23
	S.D.	1.2	1.5	1.4	1.8
	N	10	10	10	10
DAY 7	INTAKE (g)	28	26	27	25*
	S.D.	1.8	1.5	1.6	1.8
	N	10	10	10	10
DAY 14	INTAKE (g)	30	28	28	26
	S.D.	2.9	5.5	2.1	4.9
	N	10	10	10	10
DAY 21	INTAKE (g)	30	30	28	21*
	S.D.	2.6	2.3	2.6	7.9
	N	10	10	10	9
DAY 28	INTAKE (g)	31	31	26	15*
	S.D.	2.1	3.2	7.3	11.1
	N	10	10	10	6
DAY 31	INTAKE (g)	34	32	30	23*
	S.D.	2.5	2.9	2.8	9.5
	N	10	10	10	4
DAY 43	INTAKE (g)	32	32	30	31
	S.D.	3.1	2.2	3.0	2.4
	N	10	10	10	4
DAY 49	INTAKE (g)	32	31	29	22*
	S.D.	2.8	4.7	2.7	9.0
	N	10	10	10	4
DAY 56	INTAKE (g)	32	33	30	12
	S.D.	2.8	2.7	2.3	10.7
	N	10	10	10	4
DAY 59	INTAKE (g)	34	36	33	16*
	S.D.	3.2	2.8	3.1	11.9
	N	10	10	10	4
DAY 70	INTAKE (g)	32	32	30	33
	S.D.	3.0	1.8	2.6	3.8
	N	10	10	10	3
DAY 77	INTAKE (g)	33	33	30	31
	S.D.	3.7	2.3	2.7	5.6
	N	10	10	10	3
DAY 84	INTAKE (g)	32	35	29	26
	S.D.	5.0	3.1	3.8	5.0
	N	10	10	10	3
DAY 87	INTAKE (g)	35	34	31	22*
	S.D.	3.0	2.3	5.1	11.1
	N	10	10	10	3

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 107 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.5 2-F	1.5 3-F	4.5 4-F
DAY 0	INTAKE (g)	19	20	19	19
	S.D.	0.9	1.2	1.4	1.4
	N	10	10	10	10
DAY 7	INTAKE (g)	19	21	20	20
	S.D.	1.5	2.3	2.0	1.5
	N	10	10	10	10
DAY 14	INTAKE (g)	22	22	22	19*
	S.D.	1.9	2.2	1.2	2.1
	N	10	10	10	10
DAY 21	INTAKE (g)	20	21	21	18*
	S.D.	1.9	2.2	1.8	1.8
	N	10	10	10	10
DAY 28	INTAKE (g)	21	23	22	19
	S.D.	1.8	3.3	1.9	2.0
	N	10	10	10	10
DAY 31	INTAKE (g)	22	25	24	24
	S.D.	2.2	3.0	3.0	4.4
	N	10	10	10	10
DAY 43	INTAKE (g)	23	23	22	21
	S.D.	2.0	2.3	2.5	2.4
	N	10	10	10	10
DAY 49	INTAKE (g)	21	23	20	20
	S.D.	2.1	3.5	2.9	3.0
	N	10	10	10	10
DAY 56	INTAKE (g)	22	24	22	20
	S.D.	2.1	2.5	2.0	1.9
	N	10	10	10	10
DAY 59	INTAKE (g)	24	26	27	23
	S.D.	3.9	2.5	4.7	4.3
	N	10	10	10	10
DAY 70	INTAKE (g)	20	21	22	20
	S.D.	2.4	1.9	2.2	2.5
	N	10	10	10	10
DAY 77	INTAKE (g)	21	22	22	22
	S.D.	2.0	2.4	3.4	2.5
	N	10	10	10	10
DAY 84	INTAKE (g)	21	22	23	23
	S.D.	2.2	2.4	3.1	4.0
	N	10	10	10	10
DAY 87	INTAKE (g)	24	24	22	20
	S.D.	3.8	3.2	3.1	2.9
	N	10	10	10	10

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

Table 7.1

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Alanine Aminotransferase

STUOY IO: 107
STUOY NO: 107
ABBR: ALT

SEX: MALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEOURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	62	58	52
SD	6.9	8.5	6.8
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	62	57	54
SD	5.6	7.3	6.2
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	71	74*	68*
SD	13.3	8.5	10.2
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	179*	199*	185*
SD	30.9	36.0	25.3
N	4	4	3

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Alanine Aminotransferase

STUDY ID: 107
STUDY NO: 107
ABBR: ALT

SEX: FEMALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	67	60	56
SD	14.5	19.6	18.4
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	62	57	68
SD	10.8	9.8	22.8
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	66	53	62
SD	14.9	8.2	20.5
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	74	64	57
SD	14.4	15.7	6.3
N	10	10	10

Table 7.3

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Sorbitol Dehydrogenase

STUDY ID: 107
STUDY NO: 107
ABBR: SDH

SEX: MALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	15.4	13.8	14.7
SD	3.04	4.84	3.19
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	13.8	12.5	15.3
SD	4.42	2.72	4.20
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	18.0	16.8	18.4
SD	6.20	2.90	5.49
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	30.2*	21.8*	39.5*
SD	7.99	8.77	13.62
N	3	4	3

*-Significant Difference from Control P < .05

Table 7.4

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Sorbitol Dehydrogenase

STUDY ID: 107
STUDY NO: 107
ABBR: SDH

SEX: FEMALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	13.7	11.3	14.4
SD	5.42	6.36	5.17
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	17.3	17.6*	16.9
SD	5.73	5.65	5.72
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	17.7	15.3	17.0
SD	5.70	6.09	5.87
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	21.2	17.7*	19.2
SD	6.28	2.60	4.16
N	10	10	9

*-Significant Difference from Control P < .05

Table 7.5

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Total Protein

STUDY ID: 107
STUDY NO: 107
ABBR: TP

SEX: MALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	7.9	7.9	7.9
SD	0.37	0.48	0.51
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	7.6	7.6	7.8
SD	0.40	0.45	0.31
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	7.5	8.1	7.7
SD	0.52	0.38	0.47
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	7.8	6.7*	7.2
SD	0.87	0.47	1.10
N	4	4	3

*-Significant Difference from Control P < .05

Table 7.6

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Total Protein

STUDY ID: 107
STUDY NO: 107
ABBR: TP

SEX: FEMALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	8.1	8.2	8.4
SD	0.52	0.76	0.42
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	8.1	8.2	8.7
SD	0.53	0.72	0.78
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	8.5	8.2	8.6
SD	0.47	0.64	0.46
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	8.5	8.4	9.0
SD	0.49	0.47	0.39
N	10	10	10

Table 7.7

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Albumin

STUDY ID: 107
STUDY NO: 107
ABBR: ALB

SEX: MALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	4.4	4.3	4.2
SD	0.32	0.24	0.24
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	4.3	4.2	4.2
SD	0.60	0.34	0.19
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	4.3	4.5	4.2
SD	0.54	0.39	0.30
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	4.6	3.8	4.0
SD	0.22	0.69	0.55
N	4	4	3

Table 7.8

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Albumin

STUDY ID: 107
STUDY NO: 107
ABBR: ALB

SEX: FEMALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	4.6	4.8	4.7
SD	0.50	0.73	0.29
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	4.5	4.8	5.0
SD	0.56	0.43	0.56
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	4.8	4.8	4.8
SD	0.41	0.36	0.34
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	4.7	5.0	5.2
SD	0.33	0.39	0.36
N	10	10	10

Table 7.9

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Globulin

STUDY ID: 107
STUDY NO: 107
ABBR: GLOB

SEX: MALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	3.4	3.7	3.7
SD	0.25	0.39	0.33
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	3.3	3.4	3.6
SD	0.44	0.34	0.29
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	3.3	3.6	3.6
SD	0.28	0.50	0.34
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	3.2	2.9*	3.1
SD	0.75	0.25	0.55
N	4	4	3

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Globulin

STUDY ID: 107
STUDY NO: 107
ABBR: GLOB

SEX: FEMALE

UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	3.5	3.4	3.7
SD	0.33	0.42	0.32
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	3.6	3.3	3.8
SD	0.37	0.60	0.32
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	3.7	3.4	3.8
SD	0.31	0.46	0.33
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	3.7	3.4	3.9
SD	0.42	0.58	0.37
N	10	10	10

Table 7.11

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: A/G Ratio

STUDY ID: 107
STUDY NO: 107
ABBR: A/G

SEX: MALE

UNITS: -

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	1.30	1.18	1.14
SD	0.145	0.135	0.082
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	1.38	1.24	1.18
SD	0.470	0.169	0.113
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	1.32	1.27	1.18
SD	0.244	0.332	0.134
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	1.49	1.31	1.29
SD	0.359	0.368	0.058
N	4	4	3

Table 7.12

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: A/G Ratio

STUDY ID: 107
STUDY NO: 107
ABBR: A/G

SEX: FEMALE

UNITS: -

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	1.33	1.44	1.26
SD	0.231	0.325	0.139
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	1.28	1.52	1.33
SD	0.241	0.369	0.131
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	1.31	1.42	1.30
SD	0.173	0.214	0.157
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	1.29	1.51	1.36
SD	D.196	D.381	D.2D9
N	10	10	10

Table 7.13

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Total Bile Acids

STUDY ID: 107
STUDY NO: 107
ABBR: TBA

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	43.6	48.8	45.2
SD	16.93	17.31	22.15
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	43.6	34.6	43.1
SD	17.90	12.19	27.59
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	40.1	59.5	59.9
SD	20.16	30.06	35.54
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	252.8*	218.1*	225.4*
SD	146.06	151.61	137.04
N	4	4	3

*-Significant Difference from Control P < .05

Table 7.14

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Total Bile Acids

STUDY ID: 107
STUDY NO: 107
ABBR: TBA

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	34.9	29.2	30.3
SD	16.44	21.10	16.10
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	47.8	34.1	33.4
SD	38.39	16.57	10.79
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	46.9	30.7	41.2
SD	37.64	15.80	25.22
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	86.6	88.9*	74.0*
SD	80.37	75.95	38.72
N	10	10	10

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Alkaline Phosphatase

STUDY ID: 107
STUDY NO: 107
ABBR: ALKP

SEX: MALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	240	176	141
SD	38.4	43.6	30.7
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	259	204	157
SD	78.3	87.8	42.6
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	240	199	161
SD	37.7	43.0	30.4
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	299	293*	212
SD	45.4	77.3	71.9
N	4	4	3

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Alkaline Phosphatase

STUDY ID: 107
STUDY NO: 107
ABBR: ALKP

SEX: FEMALE

UNITS: U/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	161	112	101
SD	40.0	35.2	49.3
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	172	126	75
SD	55.4	50.1	25.8
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	162	110	76
SD	50.3	36.2	21.6
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	201	112	86
SD	45.5	26.9	23.5
N	10	10	10

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Cholesterol

STUDY ID: 107
STUDY NO: 107
ABBR: CHOL

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	51	48	58
SD	10.0	13.4	13.5
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	57	52	57
SD	16.1	21.2	11.6
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	56	57	61
SD	8.9	7.4	7.8
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	88*	100*	108*
SD	13.7	21.7	32.6
N	4	4	3

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Cholesterol

STUDY ID: 107
STUDY NO: 107
ABBR: CHOL

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	58	55	58
SD	10.9	7.4	16.3
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	56	54	62
SD	12.3	11.3	16.2
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	67	62	68
SD	14.7	11.9	12.8
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	83*	80*	89*
SD	11.6	13.0	13.9
N	10	10	10

*-Significant Difference from Control P < .05

Table 7.19

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THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Triglycerides

STUDY ID: 107
STUDY NO: 107
ABBR: TRY

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	93	117	154
SD	55.2	45.1	94.6
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	90	118	141
SD	45.0	52.0	59.4
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	58	90	91
SD	20.7	19.4	20.9
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	72	106	85
SD	23.1	30.2	26.7
N	4	4	3

Table 7.20

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Triglycerides

STUDY ID: 107
STUDY NO: 107
ABBR: TRY

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	57	62	78
SD	18.6	20.5	46.8
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	53	72	87
SD	14.7	22.8	32.4
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	67	70	103
SD	23.1	26.7	37.1
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	87*	124*	140*
SD	33.2	44.0	67.7
N	10	10	10

*-Significant Difference from Control P < .05

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Table 7.21

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Blood Urea Nitrogen

STUDY ID: 107
STUDY NO: 107
ABBR: BUN

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	14.7	17.4	16.8
SD	3.85	3.25	2.79
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	14.7	15.1	16.9
SD	3.21	2.31	2.94
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	15.8	17.2	17.1
SD	2.79	2.14	2.93
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	21.7*	22.3*	22.6*
SD	4.79	5.33	3.25
N	4	4	3

*-Significant Difference from Control P < .05

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THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Blood Urea Nitrogen

STUDY ID: 107
STUDY NO: 107
ABBR: BUN

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	18.8	18.9	16.7
SD	3.06	3.04	5.22
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	18.0	18.2	17.3
SD	3.28	3.34	2.29
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	18.8	18.3	18.9
SD	2.69	3.17	2.21
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	17.8	17.7	17.5
SD	4.76	2.57	3.95
N	10	10	10

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THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Creatinine

STUDY ID: 107
STUDY NO: 107
ABBR: CREA

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	0.53	0.54	0.54
SD	0.031	0.034	0.046
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	0.52	0.56	D.55
SD	0.047	0.067	0.054
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	0.56	0.59	0.59
SD	0.046	0.047	0.056
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	0.62*	0.60	0.73*
SD	0.131	0.105	0.075
N	4	4	3

*-Significant Difference from Control P < .05

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THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Creatinine

STUDY ID: 107
STUDY NO: 107
ABBR: CREA

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	0.58	0.62	0.64
SD	0.063	0.074	0.082
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	0.59	0.65	0.64
SD	0.066	0.062	0.039
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	0.57	0.61	0.64
SD	0.045	0.056	0.074
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	0.55	0.60	0.65
SD	0.055	0.039	0.072
N	10	10	10

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THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Sodium

STUDY ID: 107
STUDY NO: 107
ABBR: NA

SEX: MALE

UNITS: mmol/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	145	144	145
SD	1.1	1.5	1.9
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	143	144	145
SD	1.3	2.2	2.7
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	144	144	145
SD	1.9	1.1	1.1
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	146	142	146
SD	2.5	1.3	3.0
N	4	4	3

Table 7.26

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Sodium

STUDY ID: 107
STUDY NO: 107
ABBR: NA

SEX: FEMALE

UNITS: mmol/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	142	143	144
SD	1.5	1.5	1.4
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	143	144	144
SD	1.3	2.3	2.8
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	144*	143	145
SD	1.2	1.6	1.7
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	144	143	145
SD	1.6	1.7	1.1
N	10	10	10

*-Significant Difference from Control P < .05

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THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Potassium

STUDY ID: 107
STUDY NO: 107
ABBR: K

SEX: MALE

UNITS: mmol/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	5.63	5.94	5.68
SD	0.305	0.433	0.605
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	5.66	5.65	5.98
SD	0.494	0.522	0.682
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	5.54	5.75	5.42
SD	0.353	0.508	0.352
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	6.26	5.68	6.49
SD	0.824	0.436	0.865
N	4	4	3

Table 7.28

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Potassium

STUDY ID: 107
STUDY NO: 107
ABBR: K

SEX: FEMALE

UNITS: mmol/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	5.81	5.68	5.37
SD	0.467	0.437	0.450
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	5.52	5.46	5.57
SD	0.347	0.329	0.440
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	5.67	5.41	5.65
SD	0.334	0.354	0.325
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	5.61	5.38	5.55
SD	0.347	0.245	0.237
N	10	10	10

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THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Chloride

STUDY ID: 107
STUDY NO: 107
ABBR: CL

SEX: MALE

UNITS: mEq/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	117	116	116
SD	6.2	2.5	2.2
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	111	112	115
SD	3.7	2.5	4.8
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	115	117	116
SD	6.7	6.7	4.6
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	115	118	116
SD	4.6	6.6	11.0
N	4	4	3

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THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Chloride

STUDY ID: 107
STUDY NO: 107
ABBR: CL

SEX: FEMALE

UNITS: mEq/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	118	115	116
SD	5.2	3.9	3.2
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	119	116	117
SD	4.8	4.0	3.9
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	117	115	115
SD	2.9	4.8	4.9
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	114	116	115
SD	4.1	5.7	3.0
N	10	10	10

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THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Calcium

STUDY ID: 107
STUDY NO: 107
ABBR: CA

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	11.3	11.1	10.9
SD	0.95	0.70	0.72
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	10.9	11.0	11.1
SD	0.39	0.60	0.79
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	11.0	10.6	11.2
SD	0.37	0.49	0.39
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	11.8	11.1	11.5
SD	0.72	0.13	0.21
N	4	4	3

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Calcium

STUDY ID: 107
STUDY NO: 107
ABBR: CA

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	11.6	11.4	11.3
SD	0.37	0.48	0.57
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	11.4	11.3	12.1*
SD	0.49	0.57	0.65
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	11.6	11.5	11.9
SD	0.45	0.27	0.45
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	11.8	11.8	12.1*
SD	0.37	0.48	0.54
N	10	10	10

*-Significant Difference from Control P < .05

Table 7.33

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THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Inorganic Phosphorus

STUDY ID: 107
STUDY NO: 107
ABBR: IP

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	10.3	9.5	9.1
SD	0.76	1.03	0.65
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	9.8	8.9	9.6
SD	1.10	0.80	2.40
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	10.0	9.3	8.6
SD	1.01	0.96	1.11
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	10.7	9.1	8.9
SD	1.22	1.68	1.76
N	4	4	3

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THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Inorganic Phosphorus

STUDY ID: 107
STUDY NO: 107
ABBR: IP

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	8.5	7.7	7.1
SD	1.21	1.00	1.05
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	9.1	8.0	7.7
SD	1.21	1.38	0.89
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	8.9	7.8	7.6
SD	1.53	1.06	0.96
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	9.2	8.5	7.5
SD	0.40	0.86	0.64
N	10	10	10

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THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Glucose

STUDY ID: 107
STUDY NO: 107
ABBR: GLU

SEX: MALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	153	159	164
SD	26.7	34.2	35.3
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	147	142	162
SD	25.0	26.8	33.2
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	144	139	148
SD	21.0	15.8	16.4
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	124	112*	110*
SD	14.6	13.8	22.7
N	4	4	3

*-Significant Difference from Control P < .05

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THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
TEST: Glucose

STUDY ID: 107
STUDY NO: 107
ABBR: GLU

SEX: FEMALE

UNITS: mg/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	156	135	157
SD	27.3	19.3	40.8
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	174	159	159
SD	35.6	27.1	28.3
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	155	147	142
SD	28.7	23.7	12.0
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	146	129	132
SD	19.6	17.1	16.0
N	10	10	10

Table 8.1

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THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Erythrocytes

STUDY ID: 107 SEX: MALE
ABBR: RBC UNITS: 10^6/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	7.62	8.36	8.61
SD	0.315	0.354	0.376
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	7.62	8.11	8.31
SD	0.151	0.471	0.408
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	6.80*	7.71*	7.69*
SD	0.233	0.261	0.380
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	7.79	9.51*	8.57
SD	0.849	1.285	0.488
N	4	4	3

*-Significant Difference from Control P < .05

Table 8.2

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Erythrocytes

STUDY ID: 107
ABBR: RBC

SEX: FEMALE
UNITS: 10^6/cmm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	7.47	7.91	8.08
SD	0.353	0.290	0.280
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	7.16	7.73	7.68*
SD	0.362	0.332	D.511
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	7.13	7.18*	7.35*
SD	0.223	0.340	D.339
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	6.49*	6.51*	6.58*
SD	0.310	0.199	0.228
N	1D	1D	1D

*-Significant Difference from Control P < .05

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THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Hemoglobin

STUDY ID: 107 SEX: MALE
ABBR: HGB UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	16.0	16.1	16.0
SD	0.71	0.85	0.73
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	15.9	16.2	15.9
SD	0.52	1.02	0.84
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	14.8*	15.4	14.8*
SD	0.55	0.58	0.62
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	15.7	17.9*	16.3
SD	1.60	2.06	1.30
N	4	4	3

*-Significant Difference from Control P < .05

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THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Hemoglobin

STUDY ID: 107 SEX: FEMALE
ABBR: HGB UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	16.1	16.4	16.1
SD	0.66	0.50	0.50
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	15.4*	16.2	15.5*
SD	0.65	0.28	0.60
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	15.4*	15.0*	15.3*
SD	0.55	0.60	0.53
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	14.5*	14.2*	14.0*
SD	0.59	0.40	0.55
N	10	10	10

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Hematocrit

STUDY ID: 107
ABBR: HCT

SEX: MALE
UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	44.4	45.5	45.2
SD	2.06	2.51	2.16
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	44.8	46.2	45.2
SD	1.67	3.39	2.78
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	42.4	44.8	43.0
SD	1.40	1.30	1.95
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	45.1	52.2*	47.5
SD	4.07	5.83	3.04
N	4	4	3

*-Significant Difference from Control P < .05

Table 8.6

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
TEST: Hematocrit

STUDY ID: 107
ABBR: HCT

SEX: FEMALE
UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	42.7	44.9	44.8
SD	1.76	1.59	1.68
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	41.5	44.7	43.4
SD	1.35	0.93	1.64
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	42.1	41.9*	42.4*
SD	1.12	1.59	1.44
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	40.8	40.1*	40.2*
SD	1.89	1.16	1.88
N	10	10	10

**-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Mean Corpuscular Volume

STUDY ID: 107
ABBR: MCV

SEX: MALE
UNITS: fL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	58.2	54.4	52.5
SD	1.59	1.71	1.72
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	58.8	56.9*	54.4
SD	1.76	2.09	2.21
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	62.3*	58.2*	55.9*
SD	1.30	1.43	1.46
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	58.0	55.0	55.4
SD	2.57	2.23	1.03
N	4	4	3

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Mean Corpuscular Volume

STUDY ID: 107
ABBR: MCV

SEX: FEMALE
UNITS: fL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	57.1	56.8	55.4
SD	1.20	1.19	1.61
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	58.0	57.9	56.7
SD	1.93	1.89	1.98
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	59.1*	58.4	57.7*
SD	1.60	1.80	1.88
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	62.9*	61.7*	61.2*
SD	1.69	2.41	2.28
N	10	10	10

*-Significant Difference from Control P < .05

Table 8.9

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Mean Corpuscular Hemoglobin

STUDY ID: 107
ABBR: MCH

SEX: MALE
UNITS: pg

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	21.0	19.2	18.6
SD	0.59	0.80	0.64
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	20.9	20.1	19.1
SD	0.51	0.64	0.76
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	21.8*	20.0	19.3
SD	0.57	0.64	0.46
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	20.2	18.9	19.0
SD	0.85	1.08	0.47
N	4	4	3

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Mean Corpuscular Hemoglobin

STUDY IO: 107 SEX: FEMALE
ABBR: MCH UNITS: pg

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	21.5	20.8	20.0
SD	0.58	0.45	0.67
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	21.5	20.9	20.3
SD	1.04	0.72	0.69
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	21.5	21.0	20.8*
SD	0.61	0.78	0.82
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	22.4*	21.8*	21.3*
SD	0.49	0.63	0.64
N	10	10	10

*-Significant Difference from Control P < .05

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THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Mean Corpus. Hemo. Conc.

STUDY ID: 107
ABBR: MCHC

SEX: MALE
UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	36.0	35.4	35.3
SD	0.69	0.65	0.63
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	35.5	35.2	35.2
SD	0.45	0.63	0.48
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	34.9*	34.4*	34.5*
SD	0.49	0.50	0.44
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	34.9*	34.4*	34.2*
SD	0.74	0.67	0.61
N	4	4	3

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Mean Corpus. Hemo. Conc.

STUDY ID: 107
ABBR: MCHC

SEX: FEMALE
UNITS: g/dL

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	37.7	36.6	36.1
SD	0.45	0.61	0.70
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	37.1	36.2	35.8
SD	0.96	0.73	0.36
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	36.5*	35.9	36.1
SD	0.77	0.68	0.66
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	35.5*	35.3*	34.9*
SD	0.66	1.03	0.79
N	10	10	10

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Reticulocyte Count

STUDY ID: 107
ABBR: RETICS

SEX: MALE
UNITS: %RBCs

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	0.6	0.7	0.6
SD	0.49	0.46	0.53
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	1.2	0.7	0.8
SD	0.72	0.43	0.47
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	2.4*	1.1	1.0
SD	1.36	0.45	0.49
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	2.1	1.8*	1.2
SD	1.80	1.05	0.40
N	4	4	3

**-Significant Difference from Control P < .05

Table 8.14

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
TEST: Reticulocyte Count

STUDY ID: 107
ABBR: RETICS

SEX: FEMALE
UNITS: %RBCs

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	0.3	0.3	0.7
SD	0.28	0.21	0.30
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	0.4	0.3	0.7
SD	0.33	0.27	0.38
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	1.1*	1.3*	0.7
SD	0.82	0.83	0.33
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	2.5*	3.6*	3.5*
SD	0.93	1.33	0.79
N	10	10	10

*-Significant Difference from Control P < .05

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Nucleated Red Cells

STUDY ID: 107
ABBR: NRBC

SEX: MALE
UNITS: COUNT

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	0	0	0
SD	0.0	0.0	0.0
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	0	0	0
SD	0.0	0.0	0.0
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	0	0	0
SD	0.0	0.0	0.0
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	0	0	0
SD	0.0	0.0	0.0
N	4	4	3

WBC corrected for NRBC = or > 10

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Nucleated Red Cells

STUOY ID: 107
ABBR: NRBC

SEX: FEMALE
UNITS: COUNT

ANALYSIS OF VARIANCE FOLLOWEO BY OUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	0	0	0
SD	0.0	0.0	0.0
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	0	0	0
SD	0.0	0.0	0.0
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	0	0	0
SD	0.0	0.0	0.0
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	0	0	0
SD	0.0	0.0	0.0
N	10	10	10

WBC corrected for NRBC = or > 10

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Heinz Bodies

STUDY ID: 107
ABBR: HB

SEX: MALE
UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	0.0	0.0	0.1
SD	0.00	0.06	0.16
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	0.0	0.0	0.1
SD	0.00	0.09	0.10
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	0.3*	0.4*	0.3
SD	0.24	0.25	0.35
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	0.3*	0.2	0.6*
SD	0.13	0.24	0.44
N	4	4	3

*-Significant Difference from Control P < .05

Table 8.18

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Heinz Bodies

STUDY ID: 107
ABBR: HB

SEX: FEMALE
UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	0.0	0.0	0.1
SD	0.00	0.03	0.07
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	0.0	0.0	0.1
SD	0.00	0.00	0.28
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	0.1	0.2	0.1
SD	0.13	0.25	0.16
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	1.0*	1.2*	1.2*
SD	0.74	0.63	0.69
N	10	10	10

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: % Methemoglobin

STUDY ID: 107
ABBR: %METHGB

SEX: MALE
UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	0.7	0.9	0.8
SD	0.20	0.27	0.21
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	1.7	1.8	1.8
SD	0.31	0.35	0.40
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	4.7*	5.6*	5.8*
SD	1.09	1.41	1.16
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	6.9*	6.8*	8.6*
SD	2.70	2.77	3.08
N	4	4	3

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: % Methemoglobin

STUDY ID: 107
ABBR: %METHGB

SEX: FEMALE
UNITS: %

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	0.8	0.9	0.7
SD	0.23	0.30	0.18
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	1.7	1.8	1.5
SD	0.36	1.01	0.28
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	4.2*	5.8*	6.5*
SD	0.91	1.20	0.91
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	11.6*	13.9*	13.7*
SD	2.13	2.38	2.66
N	10	10	10

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Platelets

STUDY ID: 107
ABBR: PLT

SEX: MALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	1102	1092	1066
SD	83.4	95.8	90.0
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	1037	954*	958
SD	112.0	90.9	79.1
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	1055	984	932*
SD	100.3	109.0	148.3
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	909	640*	831*
SD	242.0	176.0	176.0
N	4	4	3

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Platelets

STUDY ID: 107
ABBR: PLT

SEX: FEMALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	1259	1173	1157
SD	115.1	99.1	74.7
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	1076*	1027*	1004*
SD	118.7	121.6	161.9
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	1081*	1067	964*
SD	141.5	129.1	83.6
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	1044*	997*	983*
SD	109.2	82.9	79.2
N	10	10	10

*-Significant Difference from Control P < .05

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THIRTEEN WEEK ORAL TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Leukocytes

STUDY ID: 107
ABBR: WBC

SEX: MALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	18.5	17.7	15.8
SD	4.66	3.09	2.47
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	20.3	17.6	17.4
SD	3.56	3.79	2.57
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	24.8*	24.7*	22.8*
SD	1.87	3.57	5.42
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	29.0*	25.5*	30.1*
SD	5.58	9.02	7.57
N	4	4	3

WBC corrected for NRBC = or > 10
*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Leukocytes

STUDY ID: 107
ABBR: WBC

SEX: FEMALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	14.8	13.1	10.7
SD	2.16	4.08	2.66
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	14.3	11.8	10.4
SD	4.91	4.23	3.92
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	17.9	14.5	14.4
SD	3.91	3.36	5.04
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	27.5*	24.4*	23.3*
SD	4.20	5.60	7.10
N	10	10	10

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

Table 8.25

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: M. Neutrophils

STUDY ID: 107
ABBR: M. Neutrop

SEX: MALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	2.6	2.5	2.1
SD	1.09	1.28	1.05
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	3.2	2.0	2.5
SD	0.71	0.90	1.35
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	4.6*	3.9	3.9*
SD	1.73	1.38	1.37
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	5.6*	5.0*	7.5*
SD	1.45	2.56	2.85
N	4	4	3

WBC corrected for NRBC = or > 10
*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: M. Neutrophils

STUDY ID: 107
ABBR: M. Neutrop

SEX: FEMALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	1.6	2.7	1.7
SD	0.59	2.54	0.72
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	3.3	2.0	1.6
SD	3.06	1.09	1.43
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	2.9	2.1	2.5
SD	0.53	0.49	1.02
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	3.6	3.3	3.4*
SD	1.29	1.17	0.92
N	10	10	10

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: I. Neutrophils

STUDY ID: 107
ABBR: I. Neutrop

SEX: MALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	0.1	0.1	0.3
SD	0.09	0.23	0.21
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	0.2	0.3	0.6
SD	0.30	0.24	0.39
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	0.6*	0.5	0.9
SD	0.40	0.38	0.71
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	0.5	0.5	0.6
SD	0.39	0.37	0.15
N	4	4	3

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: I. Neutrophils

STUDY ID: 107
ABBR: I. Neutrop

SEX: FEMALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	0.1	0.1	0.2
SD	0.12	0.16	0.14
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	0.2	0.2	0.2
SD	0.19	0.17	0.16
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	0.1	0.2	0.5
SD	0.12	0.21	0.38
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	0.6*	0.3	0.8*
SD	0.73	0.33	0.65
N	10	10	10

WBC corrected for NRBC = or > 10
*-Significant Difference from Control P < .05

Table 8.29

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Lymphocytes

STUDY ID: 107
ABBR: Lymphocyte

SEX: MALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	15.0	14.3	12.7
SD	4.30	2.87	2.40
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	16.0	14.6	13.4
SD	2.68	2.59	1.31
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	18.6	19.3*	16.8*
SD	2.23	3.81	4.89
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	20.6*	16.2	20.0*
SD	4.42	6.01	4.88
N	4	4	3

WBC corrected for NRBC = or > 10
*-Significant Difference from Control P < .05

Table 8.30

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Lymphocytes

STUDY ID: 107
ABBR: Lymphocyte

SEX: FEMALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	12.5	10.0	8.5
SD	2.48	3.12	2.46
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	10.1	9.3	8.0
SD	5.03	3.20	2.53
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	14.3	11.7	10.9
SD	3.70	2.90	3.84
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	21.9*	19.9*	18.1*
SD	4.55	4.07	6.32
N	10	10	10

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

Table 8.31

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Monocytes

STUDY ID: 107
ABBR: Monocytes

SEX: MALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	0.7	0.5	0.6
SD	0.40	0.34	0.21
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	0.8	0.7	0.7
SD	0.51	0.51	0.74
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	1.0	0.9	0.9
SD	0.64	0.82	0.77
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	2.0*	3.5*	1.8
SD	1.04	1.01	0.85
N	4	4	3

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

Table 8.32

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Monocytes

STUDY ID: 107
ABBR: Monocytes

SEX: FEMALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	0.5	0.3	0.3
SD	0.16	0.28	0.30
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	0.6	0.2	0.4
SD	0.41	0.28	0.28
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	0.5	0.4	0.4
SD	0.31	0.39	0.57
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	1.2*	0.8*	0.9*
SD	0.66	0.35	0.62
N	10	10	10

WBC corrected for NRBC = or > 10
*-Significant Difference from Control P < .05

Table 8.33

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Eosinophils

STUDY ID: 107
ABBR: Eosinophil

SEX: MALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	0.2	0.2	0.2
SD	0.21	0.16	0.22
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	0.1	0.1	0.1
SD	0.12	0.10	0.10
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	0.2	0.1	0.3
SD	0.18	0.12	0.34
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	0.4	0.4*	0.2
SD	0.52	0.32	0.15
N	4	4	3

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Eosinophils

STUDY ID: 107
ABBR: Eosinophil

SEX: FEMALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	0.1	0.1	0.1
SD	0.20	0.16	0.12
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	0.2	0.1	0.2
SD	0.16	0.11	0.19
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	0.1	0.2	0.1
SD	0.14	0.13	0.16
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	0.2	0.2	0.1
SD	0.27	0.34	0.11
N	10	10	10

WBC corrected for NRBC = or > 10

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Basophils

STUDY ID: 107
ABBR: Basophils

SEX: MALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	0.0	0.0	0.0
SD	0.00	0.00	0.06
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	0.0	0.0	0.0
SD	0.06	D.DD	D.D6
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	0.0	0.0	0.0
SD	0.00	0.00	0.00
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	0.1	0.0	0.0
SD	0.15	0.00	0.00
N	4	4	3

WBC corrected for NRBC = or > 10

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Basophils

STUDY ID: 107
ABBR: Basophils

SEX: FEMALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	0.0	0.0	0.0
SD	0.00	0.06	0.00
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	0.0	0.0	0.0
SD	0.06	0.00	0.00
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	0.0	0.0	0.0
SD	0.00	0.00	0.00
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	0.0	0.0	0.0
SD	0.00	0.00	0.00
N	10	10	10

WBC corrected for NRBC = or > 10

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Atypical Lymphocytes

STUDY ID: 107
ABBR: Atypical L

SEX: MALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-M : 0 mg base/kg/day			
MEAN	0.0	0.0	0.0
SD	0.00	0.00	0.00
N	10	10	10
Group: 2-M : 0.5 mg base/kg/day			
MEAN	0.0	0.0	0.0
SD	0.00	0.00	0.00
N	10	10	10
Group: 3-M : 1.5 mg base/kg/day			
MEAN	0.0	0.0	0.0
SD	0.00	0.00	0.00
N	10	10	10
Group: 4-M : 4.5 mg base/kg/day			
MEAN	0.0	0.0	0.0
SD	0.00	0.00	0.00
N	4	4	3

WBC corrected for NRBC = or > 10

DRAFT

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
TEST: Atypical Lymphocytes

STUDY ID: 107
ABBR: Atypical L

SEX: FEMALE
UNITS: 10^3/ccm

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

PERIOD(s):	WEEK 5	WEEK 9	WEEK 13
Group: 1-F : 0 mg base/kg/day			
MEAN	0.0	0.0	0.0
SD	0.00	0.00	0.00
N	10	10	10
Group: 2-F : 0.5 mg base/kg/day			
MEAN	0.0	0.0	0.0
SD	0.00	0.00	0.00
N	10	10	10
Group: 3-F : 1.5 mg base/kg/day			
MEAN	0.0	0.0	0.0
SD	0.00	0.00	0.00
N	10	10	10
Group: 4-F : 4.5 mg base/kg/day			
MEAN	0.0	0.0	0.0
SD	0.00	0.00	0.00
N	10	10	10

WBC corrected for NRBC = or > 10

Table 9.1

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR242511 IN RATS

ORGAN WEIGHT SUMMARY (% BRAIN WEIGHT)

STUDY: 107
SEX: MALE

ALL FATES DAYS: BEGINNING-92 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

GROUP:	(1) 1-M	(2) 2-M	(3) 3-M	(4) 4-M
ADRENAL GLANDS (% BRAIN WEIGHT)				
MEAN	2.91	3.07	2.95	2.81
SD	0.429	0.601	0.831	0.276
N	10	9	9	3
HEART (% BRAIN WEIGHT)				
MEAN	89.53	92.39	84.15	90.90
SD	9.643	9.768	11.658	13.593
N	10	9	9	3
KIDNEYS (% BRAIN WEIGHT)				
MEAN	210.83	219.96	209.37	204.43
SD	22.680	14.507	20.219	19.541
N	10	9	9	3
LIVER (% BRAIN WEIGHT)				
MEAN	944.85	1057.61	931.58	998.24
SD	84.685	101.946	115.071	125.185
N	10	9	9	3
SPLEEN (% BRAIN WEIGHT)				
MEAN	43.44	64.17*	80.42*	78.85*
SD	4.874	8.836	6.160	19.471
N	10	9	9	3
TESTES WITH EPIDIDYMIDES (% BRAIN WEIGHT)				
MEAN	246.13	239.38	239.01	226.52
SD	14.349	10.622	17.891	29.954
N	10	9	9	3

(1)-0 mg base/kg/day
(2)-0.5 mg base/kg/day
(3)-1.5 mg base/kg/day
(4)-4.5 mg base/kg/day
* - Significant difference P < .05

Table 9.2

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR242511 IN RATS

ORGAN WEIGHT SUMMARY (% BRAIN WEIGHT)

STUDY: 107
SEX: FEMALE

ALL FATES DAYS: BEGINNING-92 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

GROUP:	(5) 1-F	(6) 2-F	(7) 3-F	(8) 4-F
ADRENAL GLANDS (% BRAIN WEIGHT)				
MEAN	4.57	4.48	4.13	4.27
SD	1.035	0.961	1.413	0.653
N	10	10	10	10
HEART (% BRAIN WEIGHT)				
MEAN	60.22	62.02	62.30	58.72
SD	9.009	7.959	6.858	7.293
N	10	10	10	10
KIDNEYS (% BRAIN WEIGHT)				
MEAN	126.21	129.16	139.77	146.05*
SD	7.755	11.448	10.955	19.000
N	10	10	10	10
LIVER (% BRAIN WEIGHT)				
MEAN	575.42	571.52	611.90	626.01
SD	49.900	92.261	77.609	65.644
N	10	10	10	10
OVARIES (% BRAIN WEIGHT)				
MEAN	8.16	6.96	6.52	7.52
SD	2.143	2.008	2.604	2.181
N	10	10	10	10
SPLEEN (% BRAIN WEIGHT)				
MEAN	35.11	36.46	48.13*	77.40*
SD	6.409	8.053	7.926	10.341
N	10	10	10	10

(5)-0 mg base/kg/day
(6)-0.5 mg base/kg/day
(7)-1.5 mg base/kg/day
(8)-4.5 mg base/kg/day
* - Significant difference P < .05

Table 10

THIRTEEN WEEK ORAL TOXICITY STUDY OF WR242511
WITH A THIRTEEN WEEK RECOVERY PERIOD IN RATS

Summary of Gross and Microscopic Lesions

GROSS LESIONS		Dose (mg base/kg/day)			
ORGAN - lesion	Sex	0	0.5	1.5	4.5
LIVER - Mottled, pale diffuse, irregular linear pigmentation or irregular, diffuse, dark lesion	M	0/10	0/10	0/10	6/10
	F	0/10	0/10	0/10	0/10
LUNGS - Bilateral, multiple, irregular, linear and white	M	0/10	0/10	5/10	3/10
	F	0/10	0/10	8/10	10/10

MICROSCOPIC LESIONS[a,b]		Dose (mg base/kg/day)			
ORGAN - lesion	Sex	0	0.5	1.5	4.5
LIVER - Hepatocyte degeneration	M	0/10 (0.00)	0/10 (0.00)	4/10 (0.40)	10/10 (2.70)
	F	0/10 (0.00)	-	-	0/10 (0.00)
- Hepatocyte necrosis	M	0/10 (0.00)	0/10 (0.00)	1/10 (0.10)	10/10 (1.70)
	F	0/10 (0.00)	-	-	0/10 (0.00)
LUNGS - Alveolar histiocytosis	M	1/10 (0.10)	4/10 (0.40)	8/10 (1.40)	10/10 (1.50)
	F	0/10 (0.00)	1/10 (0.10)	9/10 (1.40)	10/10 (2.00)
SPLEEN - Hemosiderin pigment	M	0/10 (0.00)	0/10 (0.00)	1/10 (0.20)	0/10 (0.00)
	F	0/10 (0.00)	0/10 (0.00)	0/10 (0.00)	9/10 (1.20)
THYMUS - Lymphocyte depletion	M	0/10 (0.00)	0/10 (0.00)	1/10 (0.40)	4/7 (1.57)
	F	0/10 (0.00)	-	-	0/10 (0.00)

[a]Incidences (mean group severity) - Group mean severity was calculated by dividing the sum of all severity scores for a finding by the number of tissues examined.

[b]Lesion severity was scored as follows:

1 = Minimal 3 = Moderate
2 = Mild 4 = Marked

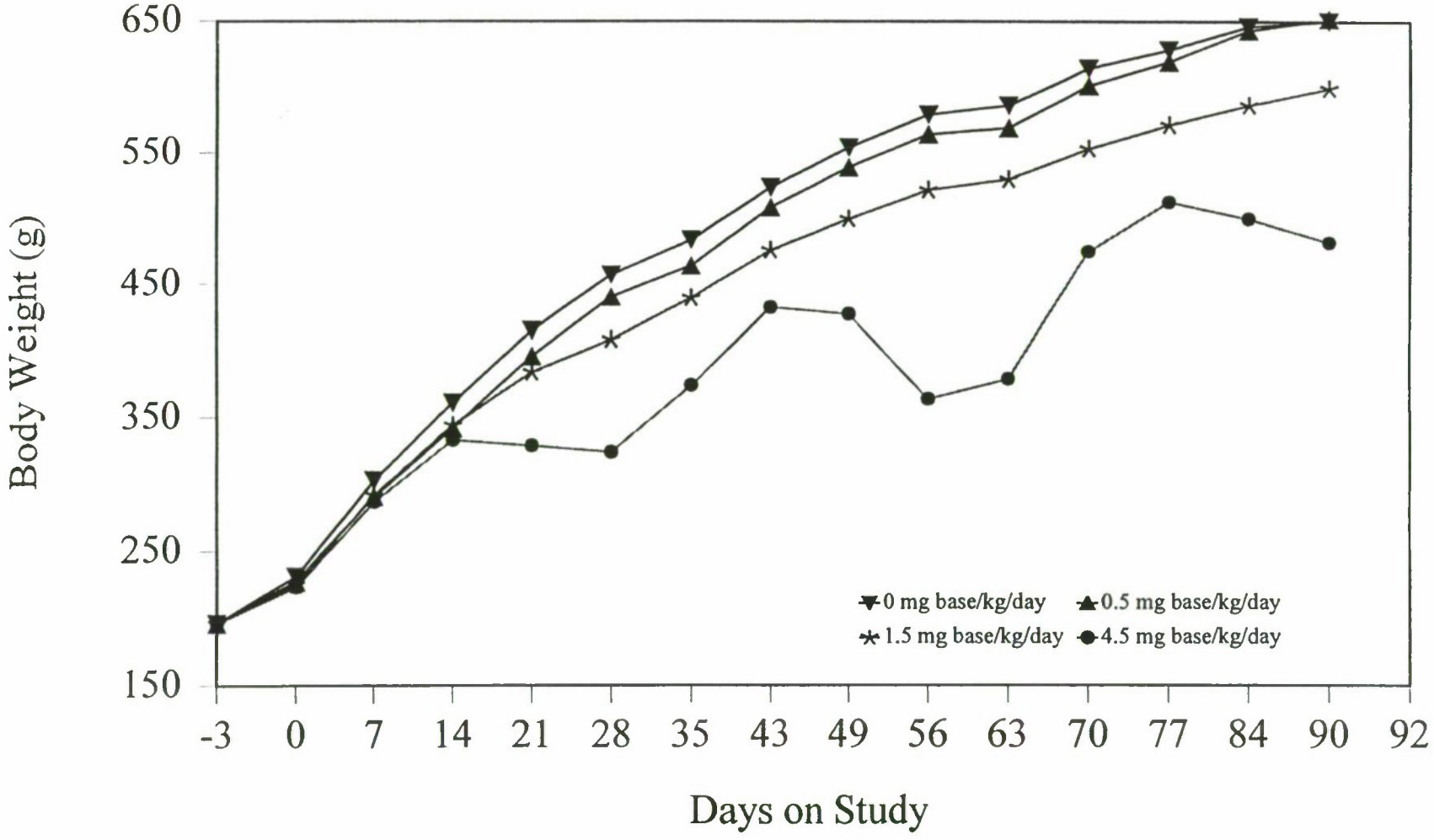
- = Animals were not microscopically examined because treatment-related lesions were not observed in the high dose within the sex.

For additional information see Pathology Report in Appendix 10.

FIGURE 1

Thirteen Week Oral Toxicity Study of WR242511 in Rats

SUMMARY OF MALE BODY WEIGHTS

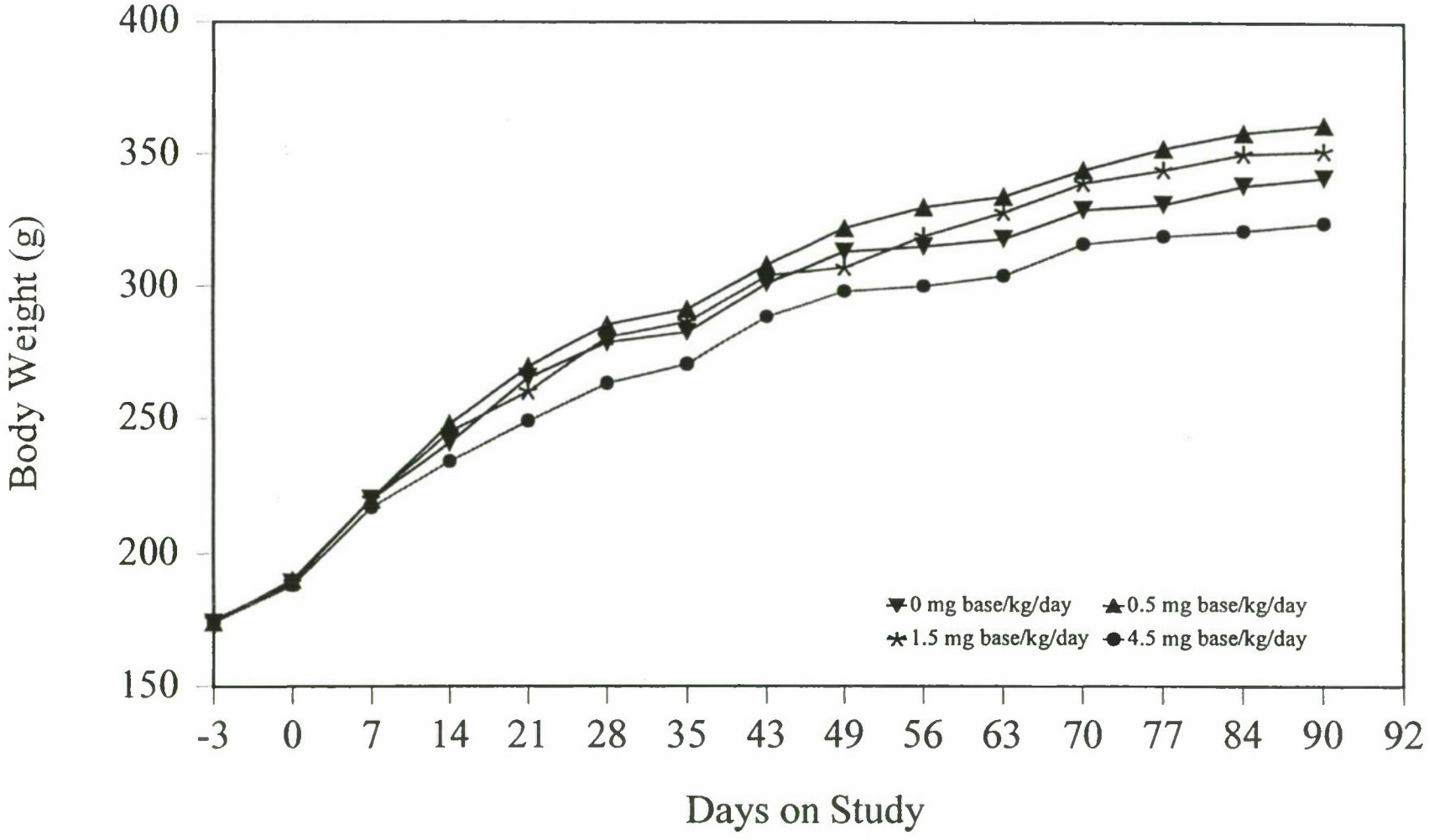


Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-7E
UIC/TRL Study No.: 107

FIGURE 2

Thirteen Week Oral Toxicity Study of WR242511 in Rats

SUMMARY OF FEMALE BODY WEIGHTS



Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-7E
UIC/TRL Study No.: 107

DRAFT

APPENDIX 1

Analytical Chemistry Report

DRAFT

THIRTEEN WEEK ORAL TOXICITY STUDY OF 8-[(4-AMINO-1-METHYLBUTYL)AMINO]-5-(1-HEXYLOXY-6-METHOXY-4-METHYLQUINOLINE DL-TARTRATE (WR242511) IN RATS
STUDY NUMBER 107

Part I: **Identity and Purity Study of WR242511**

Part II: **Assay Precision and Accuracy for the Quantitation of WR242511**

Part III: **Stability and Homogeneity of WR242511 in 1% Methylcellulose/0.2% Tween 80 Suspensions**

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

Analysts: Adam Negrusz
A. Karl Larsen, Jr.
Thomas Tolhurst

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: Adam Negrusz, Ph.D.

Report Prepared: February 21, 1994

Approved: February 21, 1994
Dr. Eugene F. Woods, Ph.D.
Laboratory Director E Woods

Part I: Identity and Purity of WR242511

Objective

The objective of this study was to confirm the identity and establish the purity 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 from 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 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 sample was weighed into a 25 ml volumetric flask. The sample was dissolved in and the volume brought to mark with mobile phase. A 50 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:

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

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 99.51%, standard deviation - 0.02%, terminal 99.59% $\pm$ 0.02%. The assay results are presented in Tables 1 and 2.

FIGURE 1

MASS SPECTRUM OF WR242511 SAMPLE

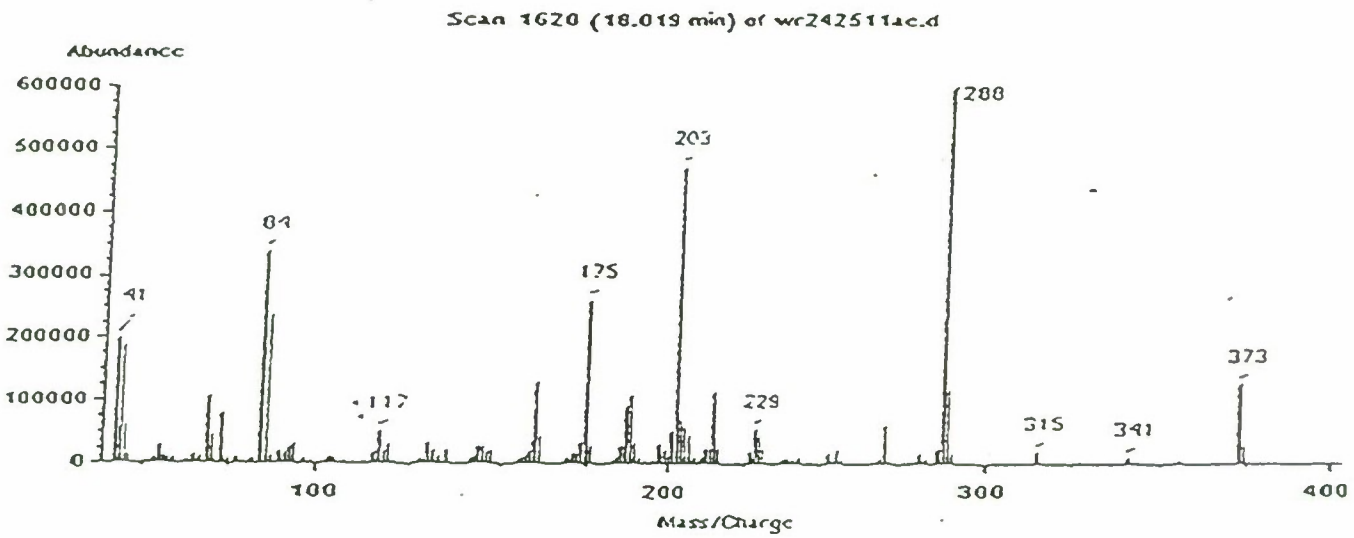


FIGURE 2

ULTRAVIOLET SPECTRUM OF WR242511

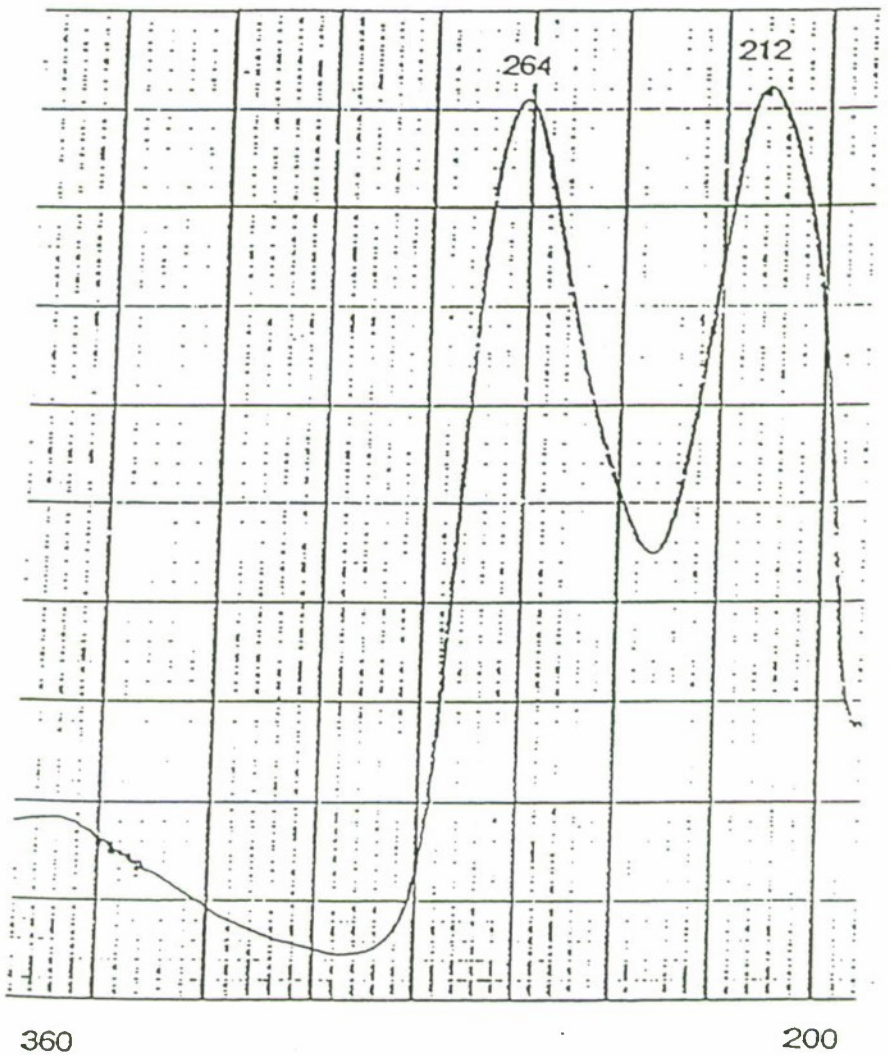
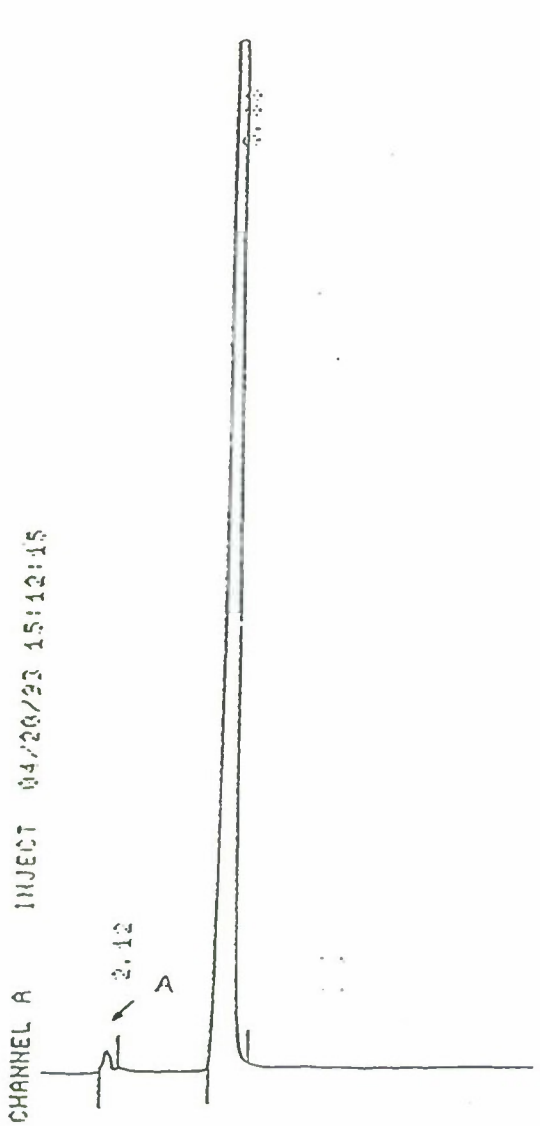


FIGURE 3

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



A

B

Table 1

Purity Data for WR242511
Initial Sample

Solutions

Peak Identity	1	2	3	4	5	6
A	4370	4354	4307	4414	3925	4509
WR242511	871097	863423	869317	869227	872867	862653
% Purity	99.501	99.498	99.507	99.495	99.552	99.480

Mean ± S.D. - 99.505 ± 0.024

Table 2

Purity Data for WR242511
Terminal Sample

Solutions

Peak Identity	1	2	3	2	5	6
A	2472	2588	2528	2688	2604	2690
WR242511	629694	641818	626102	622993	626183	632866
% Purity	99.592	99.598	99.598	99.558	99.586	99.577

Mean ± S.D. - 99.585 ± 0.015

Part II: Assay Precision and Accuracy for the Quantitation of WR242511

Introduction

The concentrations of WR242511 in 1% methylcellulose/0.2% Tween 80 suspensions were determined by high performance liquid chromatography (HPLC) using a cyano column for separation and UV detection at 230 nm. A standard curve was analyzed at the beginning and end of each assay run and replicate analysis of controls was used to determine intra-day and inter-day variability.

Analytical Method

Reagents

Subject sample (WR242511 tartrate) was supplied by Toxicology Research Laboratory. HPLC grade methanol, acetonitrile, ammonium formate and formic acid were purchased from Fisher Scientific. HPLC grade water was supplied through a Millipore, MILLI-Q Reagent Water System which was fed with distilled water.

Standards

All WR242511 concentrations reflect free base value. A 0.71 mg base/ml WR242511 stock solution was prepared by weighing 100 mg of DL-tartrate salt (mole fraction = 0.71) into a 100 ml volumetric flask. The content was dissolved in and the volume brought to mark with mobile phase. Calibration standard solutions were prepared in mobile phase using 0.71 mg base/ml WR242511 stock solution as follows.

Volume Transferred (ml)	Flask Volume (ml)	Final Concentration (μg base/ml)
1.0	100	7.1
2.0	100	14.2
4.0	100	28.4
6.0	100	42.6
8.0	100	56.8
10.0	100	71.0

Aliquots of 0.5 ml from each calibration standard solution were transferred to individually labelled crimp-top vials, sealed and stored at -20°C until analyzed.

Controls

Control A (0.639 mg base/ml), control B (3.55 mg base/ml) and control C (7.81 mg base/ml) were prepared by weighing 90 mg, 500 mg and 1100 mg respectively of WR242511 DL-tartrate salt into three 100 ml volumetric flasks, dissolved in and diluted to mark with mobile phase. Aliquots of 1.5 ml of each control were transferred to individually labelled screw-capped vials, sealed and stored at -20°C until analyzed.

Analytical Procedure

One set of WR242511 calibration standards and three vials of each stock control solution were removed from a -20°C freezer to warm up prior to samples analysis. Working control solutions were prepared as follows. Control A - 1 ml of stock solution was transferred to a 25 ml volumetric flask and diluted to

mark with mobile phase. Control B - 1 ml of stock solution was transferred to a 25 ml volumetric flask and diluted to mark with mobile phase. Five ml were then transferred to another 25 ml volumetric flask and diluted to mark with mobile phase. Control C was prepared the same way as control B. The standard curve was run at the beginning and at the end of the day. Controls were analyzed in a random order. Representative chromatograms of the working control solutions are shown in Figure 4.

HPLC System

See Part I, Purity section, WR242511 was monitored at 230 nm.

Calculations

A standard curve was run at the beginning and the end of the day. Final concentration for controls and samples were determined using a composite standard curve. The composite standard curve was determined by linear least squared regression analysis of the peak areas for WR242511 as a function of concentration. WR242511 concentrations (mg base/ml) for controls and samples were determined using the following equation:

$$\text{WR242511 conc.} = (Y-B)/M \times (d.f./1000)$$

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

Results

Standard Curve

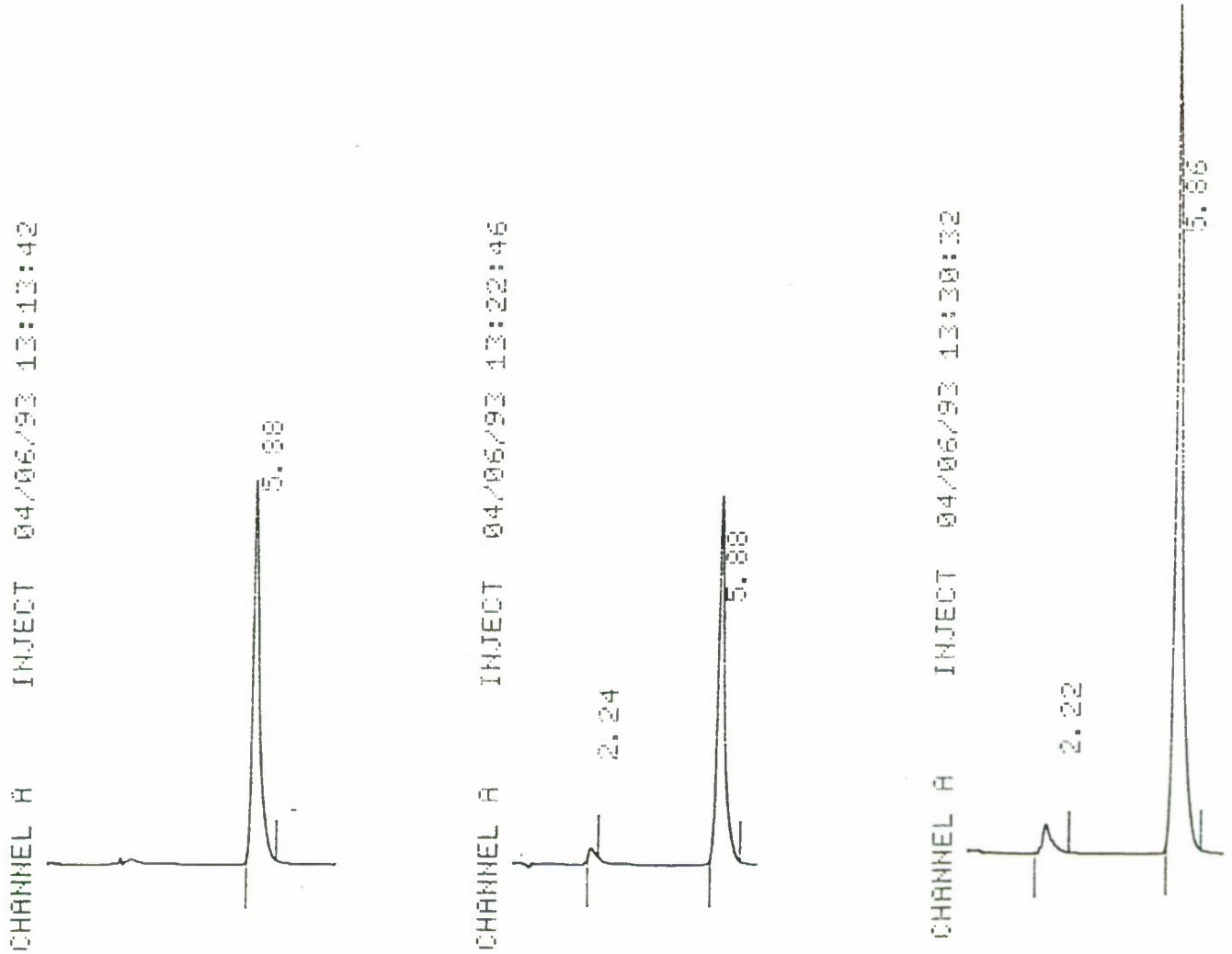
The standard curves were linear over the range of WR242511 assayed (7.1 μg base/ml - 71 μg base/ml) and had a mean for the regression coefficient of 0.9996 ($\pm$ 0.0003). A representative standard curve is shown in Figure 5.

Precision and Accuracy

Precision and accuracy were determined using controls at three different concentrations (0.639 mg base/ml, 3.55 mg base/ml and 7.81 mg base/ml). Intra-day variability was determined using six replicates of each control analyzed on a single assay. Inter-day variability was determined over a twenty one day period analyzing replicates of each solution. The results are summarized in Table 3.

FIGURE 4

WR242511 REPRESENTATIVE CHROMATOGRAMS



CONTROL A **CONTROL B** **CONTROL C**

FIGURE 5

STANDARD CURVE FOR WR242511

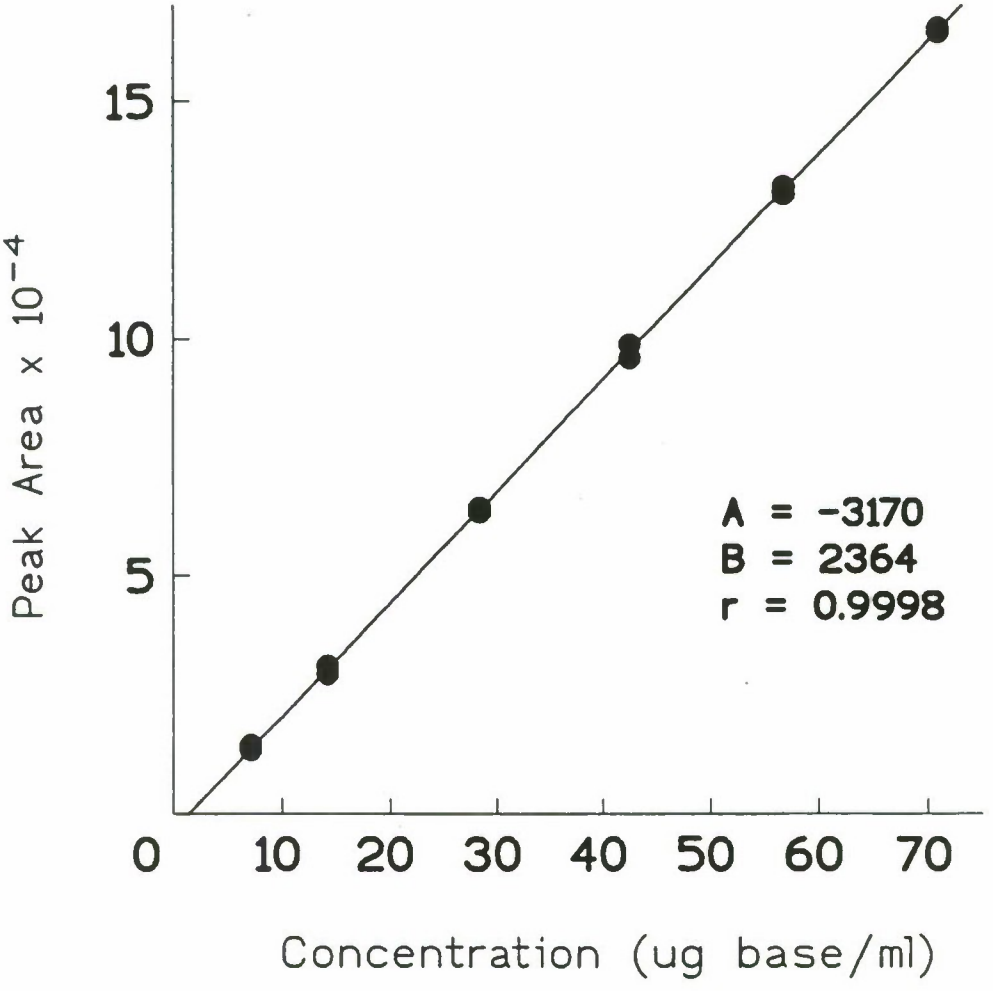


Table 3

Accuracy and Precision of WR242511 Control Concentrations (mg base/ml)

	Control A	Control B	Control C
Theoretical concentration	0.639	3.550	7.810
INTRA-DAY (N=6)			
Mean measured conc. (± S.D.)	0.656 (± 0.011)	3.608 (± 0.023)	7.874 (± 0.104)
% coefficient of variation	1.68	0.64	1.32
% relative accuracy	2.66	1.63	0.82
INTER-DAY (N=27)			
Mean measured conc. (± S.D.)	0.659 (± 0.014)	3.389 (± 0.187)	7.432 (± 0.278)
% coefficient of variation	2.12	5.52	3.74
% relative accuracy	3.13	-4.54	-4.84

Part III: Stability and Homogeneity of WR242511 in 1% Methylcellulose/0.2% Tween 80 Suspensions

Introduction

Two suspensions of WR242511 in 1% methylcellulose/0.2% Tween 80 were submitted by the Toxicology Research Laboratory for stability and homogeneity study. The suspensions were stored at 4°C (± 2°C) and sample aliquots were analyzed over a twenty one day period. Homogeneity was shown by comparing the mean (± S.D.) sample concentration at the three levels, within a single suspension, from which the dilution aliquots were taken.

Methodology

Reagents

See Part II, Analytical Method: Reagents.

Standard

See Part II, Analytical Method: Standards.

Controls

See Part II, Analytical Method: Controls.

Sample Preparation

Two suspension samples of WR242511, submitted by the Toxicology Research Laboratory and stored under refrigeration, were allowed to warm to room temperature and mixed prior to diluting. A 1 ml aliquot was withdrawn from each sample (low concentration suspension and high concentration suspension) using a 1 ml syringe and transferred to two 25 ml volumetric flasks, respectively. Each 1 ml aliquot was withdrawn from a different level within the individual sample suspension (top, middle and bottom third). The content of each volumetric flask was then thoroughly mixed and diluted to mark with the mobile phase. A 5 ml aliquot from high concentration suspension dilution was transferred to a 25 ml volumetric flask and diluted to mark with the mobile phase. The final dilutions for low and high concentration suspensions were 1 : 25 and 1 : 125, respectively.

Nine 1 ml aliquots were diluted, as previously described, and analyzed immediately to determine baseline levels of WR242511 (three from the top, three from the middle and three from the bottom third). Triplicate dilutions were prepared and analyzed at all subsequent intervals.

HPLC System

See Part II, Analytical Method: HPLC System.

Calculations

See Part II, Analytical Method: Calculations.

Data Analysis

The stability of WR242511 in 1% methylcellulose/0.2% Tween 80, stored at 4°C was assessed by examining the percentage change from baseline concentration at each time interval. A change from the baseline concentration of greater than 10% was considered to represent a significant loss of potency. Homogeneity was shown by comparing the mean (± S.D.) sample concentration at three levels, within a single suspension, from which the dilution aliquots were taken.

Results

The results of the stability testing of WR242511 in 1% methylcellulose/0.2% Tween 80 are summarized in Table 4 and Figure 6. There was a greater than 10% loss of potency of the low concentration WR242511 suspension by 96 hours, but less than 10% at the 48 hour time point. There was no loss of potency observed as defined by a decrease from baseline concentration of greater than 10% over the time interval studied of the high concentration WR242511 suspension. Three samples were drawn from each stability suspension. The samples were drawn after mixing and from the different levels (top, middle and bottom third of each suspension). Table 5 shows the mean (± S.D.) concentrations of WR242511 in samples drawn from the top, middle and bottom third of the suspensions in each stability sample. The homogeneity of the low concentration WR242511 suspension was studied over the time period during which the compound was determined to be stable (0 to 2 days). The homogeneity of high WR242511 concentration suspension was observed over the time period of 21 days. These results demonstrate the suspensions to be homogeneous.

Table 4

Stability of WR242511 Suspensions
(storage at 4°C)

Time (days)

	0	4	0	4	8	11	14	21
Mean WR242511 Conc. (mg base/ml)	0.69	0.59	0.64	0.59	0.48	0.42	0.40	0.39
Standard Deviation	0.01	0.004	0.08	0.02	0.01	0.0002	0.02	0.02
Percentage of Baseline Concentration	100.00	95.65	92.75	85.51	69.57	60.87	57.97	56.52
Mean WR242511 Conc. (mg base/ml)	8.37	8.37	8.38	8.46	8.21	8.27	8.18	8.06
Standard Deviation	0.09	0.04	0.08	0.08	0.03	0.15	0.10	0.18
Percentage of Baseline Concentration	100.00	100.00	100.12	101.08	98.09	98.81	97.73	96.30

FIGURE 6

STABILITY OF WR242511 IN SUSPENSIONS STORED AT 4°C

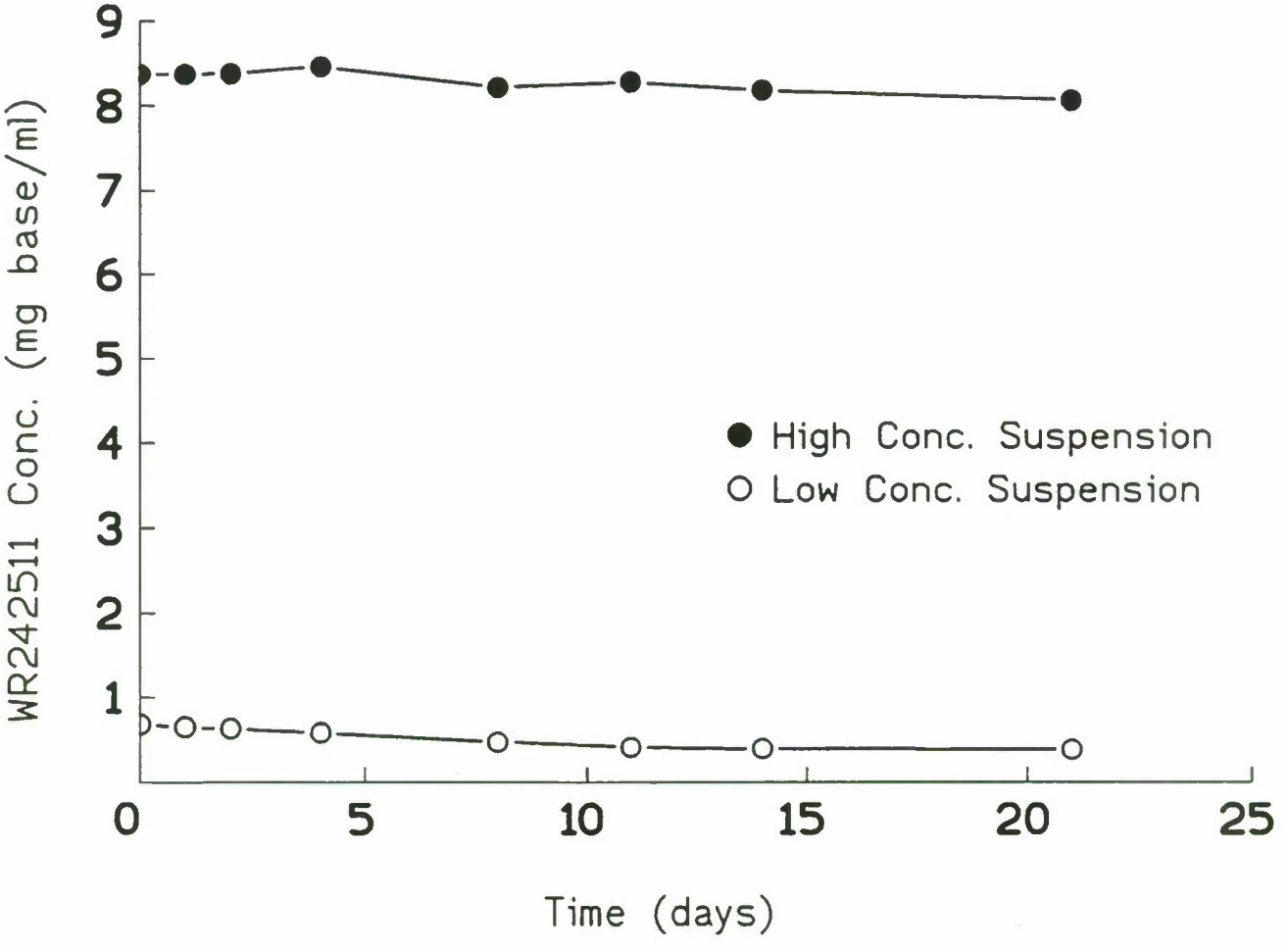


Table 5

WR242511 Concentrations (mg base/ml) in Samples Drawn From The Upper, Middle and Bottom Thirds of Stability Solutions Stored at 4°C Over a 21 Day Period

	Suspension # 1	Suspension # 2
TOP-THIRD (mg base/ml ± S.D.)	0.68 (± 0.04)	8.34 (± 0.09)
MIDDLE-THIRD (mg base/ml ± S.D.)	0.66 (± 0.03)	8.29 (± 0.18)
BOTTOM-THIRD (mg base/ml ± S.D.)	0.67 (± 0.03)	8.28 (± 0.16)

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

Introduction

Samples from Study No. 107 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 October 13, 1993, November 24, 1993 and January 5, 1994. All samples submitted were analyzed by high performance liquid chromatography by an existing analytical method (SOP No. 01MA05-01).

Analytical Method

Reagents

See Part II: Analytical Method.

Standards

See Part II: Analytical Method.

Controls

Controls were prepared using WR242511 tartrate. The first set of dosing formulations for Study No. 107 was analyzed using controls of which concentrations were expressed as mg/ml of salt. Base concentrations for WR242511 were determined using a molar fraction of 0.71. WR242511 free base concentration for the 1 mg/ml of salt control stock solution was 0.71 mg base/ml and 2.13 mg base/ml for the 3 mg/ml of salt. Control A (0.71 mg base/ml) and control B (2.13 mg base/ml) were prepared by weighing 25 mg and 75 mg, respectively, of WR242511 DL-tartrate salt into two 25 ml volumetric flasks, dissolved in and diluted to mark with mobile phase. A 1 ml volume was then transferred from control A solution to another 25 ml volumetric flask and diluted to mark with the mobile phase. A 1 ml volume from control B solution was transferred to another 25 ml volumetric flask and diluted to mark with the mobile phase. A 10 ml volume was next transferred to another 25 ml volumetric flask and diluted to mark with the mobile phase. The concentrations of the working control solutions were 40 μg/ml of salt (28.4 μg base/ml) and 48 μg/ml of WR242511 tartrate (34.08 μg base/ml), respectively. Control A and control B were made up fresh every day of analysis.

HPLC System

See Part I: HPLC System.

Results

Results of dosing formulations analysis for Study No. 107 are presented in Table 6. For the first set of dosing formulations (October 13, 1993) the FTL Sample Submission Form did not indicate that target concentrations reflected free base. As a result samples were inadvertently analyzed based on salt concentration.

Table 6

Results of Dosing Formulations Analysis for Study No. 107

October 13, 1993

Sample Identification	Target Conc. (mg/ml)	Mean Measured Conc. (± S.D) (mg/ml)	Mean Measured Conc. (± S.D.) (mg base/ml)
ORANGE	0.1	0.0963 (± 0.0030)	0.0684 (± 0.0021)
BLUE WITH WHITE DOT	0.3	0.3208 (± 0.0019)	0.2278 (± 0.0013)
BLACK	0.9	0.9058 (± 0.0562)	0.6431 (± 0.0399)

November 24, 1993

Sample Identification	Target Concentration (mg base/ml)	Mean Measured Conc. (± S.D.) (mg base/ml)
ORANGE	0.1	0.1077 (± 0.0014)
BLUE WITH WHITE DOT	0.3	0.3101 (± 0.0024)
BLACK	0.9	0.9655 (± 0.0017)

January 05, 1994

Sample Identification	Target Concentration (mg base/ml)	Mean Measured Conc. (± S.D.) (mg base/ml)
ORANGE	0.1	0.0939 (± 0.0002)
BLUE WITH WHITE DOT	0.3	0.2986 (± 0.0008)
BLACK	0.9	0.8901 (± 0.0042)

APPENDIX 2

Clinical Pathology Methodology

CLINICAL CHEMISTRY

Alanine Aminotransferase (ALT/GPT)
Based on the methodology of the IFCC
Ciba-Corning 550 Express Clinical Chemistry System
Clin. Chim. Acta 105 147-154F (1980)

Sorbitol Dehydrogenase (SDH)
Fructose → Sorbitol oxidase reaction
Ciba-Corning 550 Express Clinical Chemistry System
Asada, M. and Galanbos J.T.
Gastroenterology 44, 578, 1963.
Wiesner, I.S. *et al.*
Am. J. Dig. Dis. 10, 147, 1965.

Total Protein
Biuret technique
Ciba-Corning 550 Express Clinical Chemistry System
Kingsley, G.J.
Lab. Clin. Med. 27, 840, 1942.

Albumin
Bromocresol green method
Ciba-Corning 550 Express Clinical Chemistry System
Doumas, B.T. and Biggs, H.G.
Standard Methods of Clinical Chemistry, 7, 175, 1972.

Total Bile Acids (TBA)
3α- Hydroxy bile acid oxidation procedure (Sigma Diagnostic kit)
Ciba-Corning 550 Express Clinical Chemistry System
Mashige, F. et. al.
Clin. Chem. 27, 1352-1356, 1981.

Alkaline Phosphatase (ALP)
Based on the kinetic procedure by Bowers & McComb as recommended by the IFCC (1983)
Ciba-Corning 550 Express Clinical Chemistry System
Bowers, G.N. Jr., McComb, R.B.
Clin. Chem. 12 70, 1966
IFCC Methods
J. Clin. Chem. Clin. Biochem., 21, 731, 1983

Cholesterol (CHOL)
Cholesterol esterase-oxidase method
Ciba-Corning 550 Express Clinical Chemistry System
Allain, C. C., *et al.*
Clin. Chem. 20, 470, 1974.

Triglycerides (TRY)
Methodology of Nagele, *et al,* & a final Trinder reaction.
Ciba-Corning 550 Express Clinical Chemistry System
Nagele, U., Hagele, E.O., *et al.*
J. clin. Chem. Clin Biochem 22, 165, 1984.

Urea Nitrogen (BUN)
Modified urease technique
Ciba-Corning 550 Express Clinical Chemistry System
Talke, H. and Schubert, G.E.
Klin. Wchnschr. 43, 174, 1965.

CLINICAL CHEMISTRY (Continued)

Creatinine (CREA)
Jaffe method
Ciba-Corning 550 Express Clinical Chemistry System
Larsen. K.
Clin. Chem. Acta, 41, 209, 1972

Na+, K+
Ion specific electrodes
Model 614 ISE Na+/K+ Analyzer (Ciba Corning)

Chloride (CL)
Mercuric thiocyanate procedure
Ciba-Corning 550 Express Clinical Chemistry System
Frankel S., Reitman S., Sonnenwirth, A.C.,
Gradwohl's Clinical Lab Method & Diagnosis
C. V. Mosby Co. (1970) 144.

Calcium (CA)
Modified alizarin procedure
Ciba-Corning 550 Express Clinical Chemistry System
Richterich R., Clinical Chemistry: Theory and Practice,
Translated from 2nd German Edition by S. Raymond and J. H.
Wilkinson. New York, Acad. Press (1969) 304.

Phosphorus, Inorganic (IP)
Ammonium molybdate method
Ciba-Corning 550 Express Clinical Chemistry System
Daly. J.A., et al.
Clin. Chem. 18, 263, 1972.

Glucose (GLU)
Hexokinase method
Ciba-Corning 550 Express Clinical Chemistry System
Neese, J. W., et al.
U. S. Dept. of HEW No. (CDC) 77-8330, 1, 1976.

Test Directory

STUDY: 107

NO.	ABBR. / UNITS	DESCRIPTION / PRECISION	CALCULATED	OPERAND A	OPERAND B	---LOWER LIMIT--- MALE	---LOWER LIMIT--- FEMALE	---UPPER LIMIT--- MALE	---UPPER LIMIT--- FEMALE
1.	ALT U/L	Alanine Aminotransferase Integer	NO			30	30	70	70
2.	SDH U/L	Sorbitol Dehydrogenase 0.0	NO			20	20	60	60
3.	TP g/dL	Total Protein 0.0	NO			5.3	5.3	8.5	8.5
4.	ALB g/dL	Albumin 0.0	NO			3.4	3.4	5.6	5.6
5.	TBA mg/dL	Total Bile Acids 0.0	NO			0.0	0.0	100.0	100.0
6.	ALKP U/L	Alkaline Phosphatase Integer	NO			60	60	300	300
7.	CHOL mg/dL	Cholesterol Integer	NO			50	50	300	300
8.	TRY mg/dL	Triglycerides Integer	NO			0	0	300	300
9.	BUN mg/dL	Blood Urea Nitrogen 0.0	NO			7.0	7.0	22.0	22.0
10.	CREA mg/dL	Creatinine 0.00	NO			0.40	0.40	0.80	0.80
11.	NA mmol/L	Sodium Integer	NO			140	140	148	148
12.	K mmol/L	Potassium 0.00	NO			5.00	5.00	7.00	7.00
13.	CL mEq/L	Chloride Integer	NO			95.0	95.0	112.0	112.0
14.	CA mg/dL	Calcium 0.0	NO			8.5	8.5	12.0	12.0
15.	IP mg/dL	Inorganic Phosphorus 0.0	NO			6.5	6.5	11.0	11.0

Test Directory

STUDY: 107

NO.	ABBR. / UNITS	DESCRIPTION / PRECISION	CALCULATED	OPERAND A	OPERAND B	---LOWER LIMIT--- MALE	---LOWER LIMIT--- FEMALE	---UPPER LIMIT--- MALE	---UPPER LIMIT--- FEMALE
16.	GLU mg/dL	Glucose Integer	NO			80	80	150	150
17.	GLOB g/dL	Globulin 0.0	Operand A - Operand B	TP	ALB	2.0	2.0	4.5	4.5
18.	A/G -	A/G Ratio 0.00	Operand A / Operand B	ALB	GLOB	1.00	1.00	4.00	4.00

(END OF REPORT) 30-MAR-1994

HEMATOLOGY

Erythrocyte Count (RBC)
Electronic counting procedure
Sysmex 180A Hematology Analyzer

Hemoglobin (HGB)
Cyanomethemoglobin method
Sysmex 180A Hematology Analyzer

Hematocrit (HCT)
Indirect method; calculated value based on volume of red cells and volume of blood

Mean Corpuscular Volume (MCV)
Indirect method; calculated value based on hematocrit and red blood cell count

Mean Corpuscular Hemoglobin (MCH)
Indirect method; calculated value based on erythrocyte count and hemoglobin

Mean Corpuscular Hemoglobin Concentration (MCHC)
Indirect method; calculated value based on hematocrit and hemoglobin

Heinz Bodies (HB)
Methyl violet staining technique

Methemoglobin (% METHGB)
Co-oximeter (Instrumentation Laboratory Model 282)

Leukocyte Count (WBC)
Electronic counting procedure
Sysmex 180A Hematology Analyzer

Platelet Count (PLT)
Electronic counting procedure
Sysmex 180A Hematology Analyzer

Reticulocyte Count (RETICS)
New methylene blue staining procedure
Brecher, G., Am. J. Clin. Path., 19, 895, 1949.

Leukocyte Differential Count
Neutrophils - Immature (bands)
Neutrophils - Mature (segs)
Monocytes
Basophils
Lymphocytes
Eosinophils
Diff Quik stain procedure
Schalm, O.W., Jain, N.C. and Carroll, E.J. Veterinary Hematology, Hematologic Techniques Chapter, 4th edition, Lee and Febiger, 1986.

Test Directory

STUDY: 107

NO.	ABBR. / UNITS	DESCRIPTION / PRECISION	CALCULATED	OPERAND A	OPERAND B	---LOWER LIMIT--- MALE	---LOWER LIMIT--- FEMALE	---UPPER LIMIT--- MALE	---UPPER LIMIT--- FEMALE
1.	RBC 10^6/cmm	Erythrocytes 0.00	NO			6.40	6.40	8.80	8.80
2.	HGB g/dL	Hemoglobin 0.0	NO			13.0	13.0	16.5	16.5
3.	HCT %	Hematocrit 0.0	NO			40.0	40.0	50.0	50.0
4.	MCV fL	Mean Corpuscular Volume 0.0	NO			55.0	55.0	65.0	65.0
5.	MCH pg	Mean Corpuscular Hemoglobin 0.0	NO			20.0	20.0	25.0	25.0
6.	MCHC g/dL	Mean Corpus. Hemo. Conc. 0.0	NO			10.0	10.0	50.0	50.0
7.	RETICS %RBCs	Reticulocyte Count 0.0	NO			0.0	0.0	1.0	1.0
8.	HB %	Heinz Bodies 0.0	NO			0.0	0.0	20.0	20.0
9.	%METHGB %	% Methemoglobin 0.0	NO			0.0	0.0	3.0	3.0
10.	PLT 10^3/ccm	Platelets Integer	NO			900	900	1300	1300
11.	WBC 10^3/ccm	Leukocytes 0.0	NO			9.0	9.0	18.0	18.0
12.	RETICULO 10^6/cmm	Reticulocyte Count Absolute 0.00	(A x B) / 100	RETICS	RBC	0.00	0.00	0.10	0.10

STUDY 107 MORPHOLOGY DICTIONARY

	ABBR	DESCRIPTION
1.	AN	Anisocytosis
2.	HC	Hypochromia
3.	NR	Nucleated Red Blood Cells
4.	PC	Polychromasia
5.	BS	Basophilic Stippling
6.	MI	Microcytes
7.	OV	Ovalocytes
8.	SK	Sickle Cells
9.	HB	Heinz Bodies
10.	MA	Macrocytes
11.	PK	Poikilocytes
12.	SP	Spherocytes
13.	HJ	Howell-Jolly Bodies
14.	NN	Normocytic & Normochromic
15.	TG	Target Cells
16.	LP	Large Platelets
17.	CP	Clumped Platelets
18.	RF	Rouleaux Formation
19.	NRC	Normal Red Blood Cells
20.	TX	Toxic Granule
21.	PY	Pyknotic Cells
22.	RL	Reactive Lymphocytes
23.	VA	Vacuoles

(END OF REPORT) 30-MAR-1994

STUDY 107 DETAIL DICTIONARY

	ABBR	DESCRIPTION
1.	1	Slight
2.	2	Moderate
3.	3	Mod. to Marked
4.	4	Marked

(END OF REPORT) 30-MAR-1994

APPENDIX 3

Individual Observations (Clinical Signs)

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 1-M SEX: MALE
DAY 0-DAY 92 DOSE: 0(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
301	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
302	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
303	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
304	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
305	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
306	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
307	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
308	Dark Material Around Eyes			DAY 88
	Normal			DAY 0-DAY 87
	Normal			DAY 89-DAY 91
	Scheduled Sacrifice			DAY 92
309	Dark Material Around Eyes			DAY 89
	Normal			DAY 0-DAY 88
	Normal			DAY 90-DAY 91
	Scheduled Sacrifice			DAY 92
310	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92

DRAFT

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 2-M SEX: MALE
DAY 0-DAY 92 DOSE: 0.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
321	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
322	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
323	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
324	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
325	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
326	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
327	Audible Breathing			DAY 10-DAY 11
	Audible Breathing			DAY 13
	Hunched Posture			DAY 9-DAY 11
	Normal			DAY 0-DAY 7
	Normal			DAY 19-DAY 75
	Normal			DAY 77-DAY 90
	Rough Coat			DAY 8-DAY 18
	Rough Coat			DAY 76
	Scheduled Sacrifice			DAY 91
328	Accidental Death			DAY 88
	Normal			DAY 0-DAY 57
	Normal			DAY 59-DAY 75
	Normal			DAY 77-DAY 87
	Rough Coat			DAY 58
	Rough Coat			DAY 76
329	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 2-M SEX: MALE
DAY 0-DAY 92 DOSE: 0.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
330	Normal			DAY 0-DAY 57
	Normal			DAY 61-DAY 73
	Normal			DAY 78
	Normal			DAY 80
	Normal			DAY 83-DAY 87
	Normal			DAY 90
	Rough Coat			DAY 58-DAY 60
	Rough Coat			DAY 74-DAY 77
	Rough Coat			DAY 79
	Rough Coat			DAY 81-DAY 82
	Rough Coat			DAY 88-DAY 89
	Scheduled Sacrifice			DAY 91

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 3-M SEX: MALE
DAY 0-DAY 92 DOSE: 1.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
341	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
342	Accidental Death			DAY 90
	Dark Material Around Eyes			DAY 88-DAY 89
	Hunched Posture			DAY 88-DAY 89
	Labored Breathing			DAY 89
	Normal			DAY 0-DAY 33
	Normal			DAY 35-DAY 42
	Normal			DAY 44-DAY 86
	Rough Coat			DAY 34
	Rough Coat			DAY 43
	Rough Coat			DAY 87-DAY 89
343	Normal			DAY 0-DAY 25
	Normal			DAY 32-DAY 33
	Normal			DAY 35
	Normal			DAY 37
	Normal			DAY 40-DAY 42
	Normal			DAY 45-DAY 49
	Normal			DAY 51-DAY 78
	Normal			DAY 80-DAY 90
	Rough Coat			DAY 26-DAY 31
	Rough Coat			DAY 34
	Rough Coat			DAY 36
	Rough Coat			DAY 38-DAY 39
	Rough Coat			DAY 43-DAY 44
	Rough Coat			DAY 50
	Rough Coat			DAY 79
	Scheduled Sacrifice			DAY 91
344	Normal			DAY 0-DAY 43
	Normal			DAY 46-DAY 78
	Normal			DAY 80-DAY 87
	Normal			DAY 89-DAY 91
	Rough Coat			DAY 44-DAY 45
	Rough Coat			DAY 79
	Rough Coat			DAY 88
	Scheduled Sacrifice			DAY 92

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 3-M SEX: MALE
DAY 0-DAY 92 DOSE: 1.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
345	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
346	Normal			DAY 0-DAY 44
	Normal			DAY 46-DAY 91
	Rough Coat			DAY 45
	Scheduled Sacrifice			DAY 92
347	Normal			DAY 0-DAY 33
	Normal			DAY 36-DAY 57
	Normal			DAY 60-DAY 90
	Rough Coat			DAY 34-DAY 35
	Rough Coat			DAY 58-DAY 59
	Scheduled Sacrifice			DAY 91
348	Normal			DAY 0-DAY 33
	Normal			DAY 35-DAY 91
	Rough Coat			DAY 34
	Scheduled Sacrifice			DAY 92
349	Normal			DAY 0-DAY 33
	Normal			DAY 35-DAY 69
	Normal			DAY 71-DAY 77
	Normal			DAY 81-DAY 86
	Normal			DAY 88
	Normal			DAY 90-DAY 91
	Rough Coat			DAY 34
	Rough Coat			DAY 70
	Rough Coat			DAY 78-DAY 80
	Rough Coat			DAY 87
	Rough Coat			DAY 89
	Scheduled Sacrifice			DAY 92
350	Normal			DAY 0-DAY 29
	Normal			DAY 31-DAY 90
	Rough Coat			DAY 30
	Scheduled Sacrifice			DAY 91

DRAFT

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 4-M SEX: MALE
DAY 0-DAY 92 DOSE: 4.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
361	Hunched Posture			DAY 27-DAY 28
	Normal			DAY 0-DAY 23
	Rough Coat			DAY 24-DAY 28
	Sacrificed Moribund			DAY 28
362	Hunched Posture			DAY 23-DAY 32
	Hunched Posture			DAY 34-DAY 39
	Hunched Posture			DAY 49-DAY 66
	Normal			DAY 0-DAY 14
	Normal			DAY 16
	Normal			DAY 18-DAY 19
	Normal			DAY 47
	Normal			DAY 84
	Rough Coat			DAY 15
	Rough Coat			DAY 17
	Rough Coat			DAY 20-DAY 46
	Rough Coat			DAY 48-DAY 83
	Rough Coat			DAY 85-DAY 91
	Scheduled Sacrifice			DAY 92
363	Animal Found Dead			DAY 24
	Hunched Posture			DAY 23
	Normal			DAY 0-DAY 18
	Rough Coat			DAY 19-DAY 23
364	Hunched Posture			DAY 34
	Hunched Posture			DAY 50-DAY 61
	Hunched Posture			DAY 65
	Normal			DAY 0-DAY 18
	Normal			DAY 21-DAY 25
	Normal			DAY 28-DAY 32
	Normal			DAY 35-DAY 46
	Normal			DAY 48
	Normal			DAY 62
	Normal			DAY 68-DAY 89
	Rough Coat			DAY 19-DAY 20
	Rough Coat			DAY 26-DAY 27

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 4-M SEX: MALE
DAY 0-DAY 92 DOSE: 4.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
	Rough Coat			DAY 33-DAY 34
	Rough Coat			DAY 47
	Rough Coat			DAY 49-DAY 61
	Rough Coat			DAY 63-DAY 67
	Rough Coat			DAY 90
	Scheduled Sacrifice			DAY 91
365	Hunched Posture			DAY 33
	Normal			DAY 0-DAY 18
	Normal			DAY 23-DAY 24
	Normal			DAY 39
	Normal			DAY 46
	Normal			DAY 69
	Normal			DAY 73-DAY 77
	Normal			DAY 81
	Rough Coat			DAY 19-DAY 22
	Rough Coat			DAY 25-DAY 38
	Rough Coat			DAY 40-DAY 45
	Rough Coat			DAY 47-DAY 68
	Rough Coat			DAY 70-DAY 72
	Rough Coat			DAY 78-DAY 80
	Rough Coat			DAY 82-DAY 90
	Scheduled Sacrifice			DAY 91
366	Animal Found Dead			DAY 22
	Normal			DAY 0-DAY 20
	Rough Coat			DAY 21
367	Hunched Posture			DAY 26-DAY 29
	Hunched Posture			DAY 31-DAY 39
	Hunched Posture			DAY 50-DAY 63
	Normal			DAY 0-DAY 14
	Normal			DAY 16
	Normal			DAY 18
	Rough Coat			DAY 15
	Rough Coat			DAY 17
	Rough Coat			DAY 19-DAY 63
	Sacrificed Moribund			DAY 63

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 4-M SEX: MALE
DAY 0-DAY 92 DOSE: 4.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
368	Hunched Posture			DAY 16-DAY 21
	Normal			DAY 0-DAY 14
	Rough Coat			DAY 15-DAY 21
	Sacrificed Moribund			DAY 21
369	Decreased Activity	1		DAY 19
	Hunched Posture			DAY 18-DAY 19
	Normal			DAY 0-DAY 15
	Rough Coat			DAY 16-DAY 19
	Sacrificed Moribund			DAY 19
370	Hunched Posture			DAY 26-DAY 28
	Normal			DAY 0-DAY 19
	Rough Coat			DAY 20-DAY 28
	Sacrificed Moribund			DAY 28

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 1-F SEX: FEMALE
DAY 0-DAY 92 DOSE: 0(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
311	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
312	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
313	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
314	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
315	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
316	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
317	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
318	Dark Material Around Eyes			DAY 89
	Normal			DAY 0-DAY 88
	Normal			DAY 90-DAY 91
	Scheduled Sacrifice			DAY 92
319	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
320	Normal			DAY 0-DAY 88
	Normal			DAY 90-DAY 91
	Rough Coat			DAY 89
	Scheduled Sacrifice			DAY 92

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 2-F SEX: FEMALE
DAY 0-DAY 92 DOSE: 0.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
331	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
332	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
333	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
334	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
335	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92
336	Dark Material Around Eyes			DAY 62
	Normal			DAY 0-DAY 61
	Normal			DAY 63-DAY 91
	Scheduled Sacrifice			DAY 92
337	Dark Material Around Nose			DAY 62
	Normal			DAY 0-DAY 61
	Normal			DAY 63-DAY 78
	Normal			DAY 80-DAY 88
	Normal			DAY 90-DAY 91
	Rough Coat			DAY 79
	Rough Coat			DAY 89
	Scheduled Sacrifice			DAY 92
338	Dark Material Around Eyes			DAY 62
	Normal			DAY 0-DAY 61
	Normal			DAY 63-DAY 91
	Scheduled Sacrifice			DAY 92
339	Normal			DAY 0-DAY 90
	Rough Coat			DAY 91
	Scheduled Sacrifice			DAY 92

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 2-F SEX: FEMALE
DAY 0-DAY 92 DOSE: 0.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
340	Normal			DAY 0-DAY 91
	Scheduled Sacrifice			DAY 92

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 3-F SEX: FEMALE
DAY 0-DAY 92 DOSE: 1.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
351	Normal			DAY 0-DAY 90
	Scheduled Sacrifice			DAY 91
352	Normal			DAY 0-DAY 42
	Normal			DAY 44-DAY 61
	Normal			DAY 64-DAY 83
	Normal			DAY 85-DAY 90
	Rough Coat			DAY 43
	Rough Coat			DAY 62-DAY 63
	Rough Coat			DAY 84
	Scheduled Sacrifice			DAY 91
353	Normal			DAY 0-DAY 33
	Normal			DAY 35-DAY 36
	Normal			DAY 39-DAY 44
	Normal			DAY 46-DAY 60
	Normal			DAY 62-DAY 75
	Normal			DAY 77-DAY 78
	Normal			DAY 80-DAY 82
	Normal			DAY 85
	Normal			DAY 88-DAY 90
	Rough Coat			DAY 34
	Rough Coat			DAY 37-DAY 38
	Rough Coat			DAY 45
	Rough Coat			DAY 61
	Rough Coat			DAY 76
	Rough Coat			DAY 79
	Rough Coat			DAY 83-DAY 84
	Rough Coat			DAY 86-DAY 87
	Scheduled Sacrifice			DAY 91
354	Normal			DAY 0-DAY 60
	Normal			DAY 62-DAY 91
	Rough Coat			DAY 61
	Scheduled Sacrifice			DAY 92
355	Normal			DAY 0-DAY 36

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 3-F SEX: FEMALE
DAY 0-DAY 92 DOSE: 1.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
	Normal			DAY 39-DAY 43
	Normal			DAY 45-DAY 48
	Normal			DAY 50
	Normal			DAY 52-DAY 57
	Normal			DAY 59-DAY 60
	Normal			DAY 64-DAY 65
	Normal			DAY 67-DAY 73
	Normal			DAY 75
	Normal			DAY 78-DAY 81
	Normal			DAY 83
	Normal			DAY 85
	Normal			DAY 88
	Rough Coat			DAY 37-DAY 38
	Rough Coat			DAY 44
	Rough Coat			DAY 49
	Rough Coat			DAY 51-DAY 52
	Rough Coat			DAY 58
	Rough Coat			DAY 61-DAY 63
	Rough Coat			DAY 66
	Rough Coat			DAY 74
	Rough Coat			DAY 76-DAY 77
	Rough Coat			DAY 82
	Rough Coat			DAY 84
	Rough Coat			DAY 86-DAY 87
	Rough Coat			DAY 89-DAY 90
	Scheduled Sacrifice			DAY 91
356	Normal			DAY 0-DAY 40
	Normal			DAY 42-DAY 47
	Normal			DAY 49-DAY 50
	Normal			DAY 53-DAY 58
	Normal			DAY 60-DAY 76
	Normal			DAY 78-DAY 84
	Normal			DAY 86-DAY 87
	Rough Coat			DAY 41
	Rough Coat			DAY 48
	Rough Coat			DAY 51-DAY 52
	Rough Coat			DAY 59

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 3-F SEX: FEMALE
DAY 0-DAY 92 DOSE: 1.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
	Rough Coat			DAY 77
	Rough Coat			DAY 85
	Rough Coat			DAY 88-DAY 91
	Scheduled Sacrifice			DAY 92
357	Normal			DAY 0-DAY 33
	Normal			DAY 36-DAY 40
	Normal			DAY 42-DAY 43
	Normal			DAY 46-DAY 58
	Normal			DAY 60-DAY 62
	Normal			DAY 67
	Normal			DAY 69-DAY 78
	Normal			DAY 80
	Normal			DAY 82-DAY 84
	Normal			DAY 88
	Normal			DAY 90
	Rough Coat			DAY 34-DAY 35
	Rough Coat			DAY 41
	Rough Coat			DAY 44-DAY 45
	Rough Coat			DAY 59
	Rough Coat			DAY 63-DAY 66
	Rough Coat			DAY 68
	Rough Coat			DAY 79
	Rough Coat			DAY 81
	Rough Coat			DAY 85-DAY 87
	Rough Coat			DAY 89
	Scheduled Sacrifice			DAY 91
358	Normal			DAY 0-DAY 33
	Normal			DAY 35-DAY 81
	Normal			DAY 83-DAY 87
	Normal			DAY 89-DAY 90
	Rough Coat			DAY 34
	Rough Coat			DAY 82
	Rough Coat			DAY 88
	Rough Coat			DAY 91
	Scheduled Sacrifice			DAY 92

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 3-F SEX: FEMALE
DAY 0-DAY 92 DOSE: 1.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
359	Dark Material Around Eyes			DAY 62
	Normal			DAY 0-DAY 33
	Normal			DAY 35-DAY 61
	Normal			DAY 63
	Normal			DAY 65-DAY 81
	Normal			DAY 83-DAY 91
	Rough Coat			DAY 34
	Rough Coat			DAY 64
	Rough Coat			DAY 82
	Scheduled Sacrifice			DAY 92
360	Normal			DAY 0-DAY 33
	Normal			DAY 35-DAY 55
	Normal			DAY 58-DAY 64
	Normal			DAY 66-DAY 80
	Normal			DAY 82-DAY 90
	Rough Coat			DAY 34
	Rough Coat			DAY 56-DAY 57
	Rough Coat			DAY 65
	Rough Coat			DAY 81
	Scheduled Sacrifice			DAY 91

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 4-F SEX: FEMALE
DAY 0-DAY 92 DOSE: 4.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
371	Normal			DAY 0-DAY 21
	Normal			DAY 24-DAY 32
	Normal			DAY 34-DAY 90
	Rough Coat			DAY 22-DAY 23
	Rough Coat			DAY 33
	Rough Coat			DAY 91
	Scheduled Sacrifice			DAY 92
372	Dark Material Around Eyes			DAY 62
	Normal			DAY 0-DAY 23
	Normal			DAY 25-DAY 30
	Normal			DAY 37-DAY 45
	Normal			DAY 48
	Normal			DAY 50-DAY 60
	Normal			DAY 64-DAY 90
	Rough Coat			DAY 24
	Rough Coat			DAY 31-DAY 36
	Rough Coat			DAY 46-DAY 47
	Rough Coat			DAY 49
	Rough Coat			DAY 61-DAY 63
	Scheduled Sacrifice			DAY 91
373	Normal			DAY 0-DAY 51
	Normal			DAY 53-DAY 60
	Normal			DAY 63-DAY 73
	Normal			DAY 76-DAY 90
	Rough Coat			DAY 52
	Rough Coat			DAY 61-DAY 62
	Rough Coat			DAY 74-DAY 75
	Scheduled Sacrifice			DAY 91
374	Normal			DAY 0-DAY 24
	Normal			DAY 26-DAY 32
	Normal			DAY 34-DAY 35
	Normal			DAY 38-DAY 43
	Normal			DAY 45
	Normal			DAY 47

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 4-F SEX: FEMALE
DAY 0-DAY 92 DOSE: 4.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
	Normal			DAY 50-DAY 51
	Normal			DAY 53
	Normal			DAY 55-DAY 61
	Normal			DAY 64-DAY 65
	Normal			DAY 69
	Normal			DAY 71-DAY 72
	Normal			DAY 74-DAY 80
	Normal			DAY 85-DAY 87
	Normal			DAY 89
	Rough Coat			DAY 25
	Rough Coat			DAY 33
	Rough Coat			DAY 36-DAY 37
	Rough Coat			DAY 44
	Rough Coat			DAY 46
	Rough Coat			DAY 48-DAY 49
	Rough Coat			DAY 52
	Rough Coat			DAY 54
	Rough Coat			DAY 62-DAY 63
	Rough Coat			DAY 66-DAY 68
	Rough Coat			DAY 70
	Rough Coat			DAY 73
	Rough Coat			DAY 81-DAY 84
	Rough Coat			DAY 88
	Rough Coat			DAY 90-DAY 91
	Scheduled Sacrifice			DAY 92
375	Normal			DAY 0-DAY 21
	Normal			DAY 23-DAY 32
	Normal			DAY 35-DAY 41
	Normal			DAY 44
	Normal			DAY 46-DAY 47
	Normal			DAY 49
	Normal			DAY 51-DAY 60
	Normal			DAY 62-DAY 67
	Normal			DAY 69-DAY 77
	Normal			DAY 81-DAY 83
	Normal			DAY 86-DAY 87
	Rough Coat			DAY 22

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 4-F SEX: FEMALE
DAY 0-DAY 92 DOSE: 4.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
	Rough Coat			DAY 33-DAY 34
	Rough Coat			DAY 42-DAY 43
	Rough Coat			DAY 45
	Rough Coat			DAY 48
	Rough Coat			DAY 50
	Rough Coat			DAY 61
	Rough Coat			DAY 68
	Rough Coat			DAY 78-DAY 80
	Rough Coat			DAY 84-DAY 85
	Rough Coat			DAY 88-DAY 90
	Scheduled Sacrifice			DAY 91
376	Normal			DAY 0-DAY 23
	Normal			DAY 25-DAY 26
	Normal			DAY 28-DAY 30
	Normal			DAY 32-DAY 35
	Normal			DAY 39-DAY 43
	Normal			DAY 46-DAY 51
	Normal			DAY 53-DAY 60
	Normal			DAY 62-DAY 75
	Normal			DAY 77
	Normal			DAY 81-DAY 84
	Normal			DAY 88
	Normal			DAY 90
	Rough Coat			DAY 24
	Rough Coat			DAY 27
	Rough Coat			DAY 31
	Rough Coat			DAY 36-DAY 38
	Rough Coat			DAY 44-DAY 45
	Rough Coat			DAY 52
	Rough Coat			DAY 61
	Rough Coat			DAY 76
	Rough Coat			DAY 78-DAY 80
	Rough Coat			DAY 85-DAY 87
	Rough Coat			DAY 89
	Scheduled Sacrifice			DAY 91
377	Normal			DAY 0-DAY 21

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 4-F SEX: FEMALE
DAY 0-DAY 92 DOSE: 4.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
	Normal			DAY 24-DAY 26
	Normal			DAY 28-DAY 32
	Normal			DAY 34
	Normal			DAY 37
	Normal			DAY 39-DAY 42
	Normal			DAY 47-DAY 54
	Normal			DAY 56-DAY 57
	Normal			DAY 61-DAY 62
	Normal			DAY 66-DAY 69
	Normal			DAY 73-DAY 74
	Normal			DAY 76-DAY 81
	Normal			DAY 83-DAY 85
	Normal			DAY 90
	Rough Coat			DAY 22-DAY 23
	Rough Coat			DAY 27
	Rough Coat			DAY 33
	Rough Coat			DAY 35-DAY 36
	Rough Coat			DAY 38
	Rough Coat			DAY 43-DAY 46
	Rough Coat			DAY 55
	Rough Coat			DAY 58-DAY 60
	Rough Coat			DAY 63-DAY 65
	Rough Coat			DAY 70-DAY 72
	Rough Coat			DAY 75
	Rough Coat			DAY 82
	Rough Coat			DAY 86-DAY 89
	Scheduled Sacrifice			DAY 91
378	Dark Material Around Eyes			DAY 62
	Normal			DAY 0-DAY 23
	Normal			DAY 26-DAY 29
	Normal			DAY 31-DAY 33
	Normal			DAY 40
	Normal			DAY 43-DAY 46
	Normal			DAY 48-DAY 50
	Normal			DAY 57
	Normal			DAY 63
	Normal			DAY 67-DAY 69

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 4-F SEX: FEMALE
DAY 0-DAY 92 DOSE: 4.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
	Normal			DAY 71-DAY 72
	Normal			DAY 74
	Normal			DAY 76-DAY 87
	Normal			DAY 89-DAY 90
	Rough Coat			DAY 24-DAY 25
	Rough Coat			DAY 30
	Rough Coat			DAY 34-DAY 39
	Rough Coat			DAY 41-DAY 42
	Rough Coat			DAY 47
	Rough Coat			DAY 51-DAY 56
	Rough Coat			DAY 58-DAY 62
	Rough Coat			DAY 64-DAY 66
	Rough Coat			DAY 70
	Rough Coat			DAY 73
	Rough Coat			DAY 75
	Rough Coat			DAY 88
	Rough Coat			DAY 91
	Scheduled Sacrifice			DAY 92
379	Normal			DAY 0-DAY 33
	Normal			DAY 36-DAY 38
	Normal			DAY 40
	Normal			DAY 45
	Normal			DAY 48-DAY 49
	Normal			DAY 51-DAY 53
	Normal			DAY 55-DAY 75
	Normal			DAY 81
	Normal			DAY 88
	Rough Coat			DAY 34-DAY 35
	Rough Coat			DAY 39
	Rough Coat			DAY 41-DAY 44
	Rough Coat			DAY 46-DAY 47
	Rough Coat			DAY 50
	Rough Coat			DAY 54
	Rough Coat			DAY 76-DAY 80
	Rough Coat			DAY 82-DAY 87
	Rough Coat			DAY 89-DAY 90
	Scheduled Sacrifice			DAY 91

INDIVIDUAL OBSERVATIONS

STUDY: 107 GROUP: 4-F SEX: FEMALE
DAY 0-DAY 92 DOSE: 4.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
380	Normal			DAY 0-DAY 24
	Normal			DAY 26-DAY 42
	Normal			DAY 46-DAY 64
	Normal			DAY 66-DAY 69
	Normal			DAY 71-DAY 77
	Normal			DAY 81-DAY 88
	Rough Coat			DAY 25
	Rough Coat			DAY 43-DAY 45
	Rough Coat			DAY 65
	Rough Coat			DAY 70
	Rough Coat			DAY 78-DAY 80
	Rough Coat			DAY 89-DAY 90
	Scheduled Sacrifice			DAY 91

DRAFT

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.5 2-M	1.5 3-M	4.5 4-M
DAY 0					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 1					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 2					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 3					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 4					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 5					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 6					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 7					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 8					
No. Observed		10	10	10	10
Normal		10 100%	9 90%	10 100%	10 100%
Rough Coat		0	1 10%	0	0

(mg base/kg/day)

DRAFT

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.5 2-M	1.5 3-M	4.5 4-M (mg base/kg/day)
DAY 9					
No. Observed		10	10	10	10
Normal		10 100%	9 90%	10 100%	10 100%
Hunched Posture		0	1 10%	0	0
Rough Coat		0	1 10%	0	0
DAY 10					
No. Observed		10	10	10	10
Normal		10 100%	9 90%	10 100%	10 100%
Hunched Posture		0	1 10%	0	0
Rough Coat		0	1 10%	0	0
Audible Breathing		0	1 10%	0	0
DAY 11					
No. Observed		10	10	10	10
Normal		10 100%	9 90%	10 100%	10 100%
Hunched Posture		0	1 10%	0	0
Rough Coat		0	1 10%	0	0
Audible Breathing		0	1 10%	0	0
DAY 12					
No. Observed		10	10	10	10
Normal		10 100%	9 90%	10 100%	10 100%
Rough Coat		0	1 10%	0	0
DAY 13					
No. Observed		10	10	10	10
Normal		10 100%	9 90%	10 100%	10 100%
Rough Coat		0	1 10%	0	0
Audible Breathing		0	1 10%	0	0
DAY 14					
No. Observed		10	10	10	10
Normal		10 100%	9 90%	10 100%	10 100%
Rough Coat		0	1 10%	0	0
DAY 15					
No. Observed		10	10	10	10
Normal		10 100%	9 90%	10 100%	7 70%
Rough Coat		0	1 10%	0	3 30%

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.5 2-M	1.5 3-M	4.5 4-M (mg base/kg/day)
DAY 16					
No. Observed		10	10	10	10
Normal		10 100%	9 90%	10 100%	8 80%
Hunched Posture		0	0	0	1 10%
Rough Coat		0	1 10%	0	2 20%
DAY 17					
No. Observed		10	10	10	10
Normal		10 100%	9 90%	10 100%	6 60%
Hunched Posture		0	0	0	1 10%
Rough Coat		0	1 10%	0	4 40%
DAY 18					
No. Observed		10	10	10	10
Normal		10 100%	9 90%	10 100%	8 80%
Hunched Posture		0	0	0	2 20%
Rough Coat		0	1 10%	0	2 20%
DAY 19					
No. Observed		10	10	10	10
Sacrificed Moribund		0	0	0	1 10%
Normal		10 100%	10 100%	10 100%	4 40%
Decreased Activity					
SEV					
1		0	0	0	1 10%
Hunched Posture		0	0	0	2 20%
Rough Coat		0	0	0	6 60%
DAY 20					
No. Observed		10	10	10	9
Normal		10 100%	10 100%	10 100%	2 22%
Hunched Posture		0	0	0	1 11%
Rough Coat		0	0	0	7 77%
DAY 21					
No. Observed		10	10	10	9
Sacrificed Moribund		0	0	0	1 11%
Normal		10 100%	10 100%	10 100%	2 22%
Hunched Posture		0	0	0	1 11%
Rough Coat		0	0	0	7 77%

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.5 2-M	1.5 3-M	4.5 4-M	(mg base/kg/day)
DAY 22						
	No. Observed	10	10	10	8	
	Animal Found Dead	0	0	0	1	12%
	Normal	10 100%	10 100%	10 100%	2	25%
	Rough Coat	0	0	0	5	62%
DAY 23						
	No. Observed	10	10	10	7	
	Normal	10 100%	10 100%	10 100%	3	42%
	Hunched Posture	0	0	0	2	28%
	Rough Coat	0	0	0	4	57%
DAY 24						
	No. Observed	10	10	10	7	
	Animal Found Dead	0	0	0	1	14%
	Normal	10 100%	10 100%	10 100%	2	28%
	Hunched Posture	0	0	0	1	14%
	Rough Coat	0	0	0	4	57%
DAY 25						
	No. Observed	10	10	10	6	
	Normal	10 100%	10 100%	10 100%	1	16%
	Hunched Posture	0	0	0	1	16%
	Rough Coat	0	0	0	5	83%
DAY 26						
	No. Observed	10	10	10	6	
	Normal	10 100%	10 100%	9 90%	0	
	Hunched Posture	0	0	0	3	50%
	Rough Coat	0	0	1 10%	6	100%
DAY 27						
	No. Observed	10	10	10	6	
	Normal	10 100%	10 100%	9 90%	0	
	Hunched Posture	0	0	0	4	66%
	Rough Coat	0	0	1 10%	6	100%

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.5 2-M	1.5 3-M	4.5 4-M	(mg base/kg/day)
DAY 28						
	No. Observed	10	10	10	6	
	Sacrificed Moribund	0	0	0	2	33%
	Normal	10 100%	10 100%	9 90%	1	16%
	Hunched Posture	0	0	0	4	66%
	Rough Coat	0	0	1 10%	5	83%
DAY 29						
	No. Observed	10	10	10	4	
	Normal	10 100%	10 100%	9 90%	1	25%
	Hunched Posture	0	0	0	2	50%
	Rough Coat	0	0	1 10%	3	75%
DAY 30						
	No. Observed	10	10	10	4	
	Normal	10 100%	10 100%	8 80%	1	25%
	Hunched Posture	0	0	0	1	25%
	Rough Coat	0	0	2 20%	3	75%
DAY 31						
	No. Observed	10	10	10	4	
	Normal	10 100%	10 100%	9 90%	1	25%
	Hunched Posture	0	0	0	2	50%
	Rough Coat	0	0	1 10%	3	75%
DAY 32						
	No. Observed	10	10	10	4	
	Normal	10 100%	10 100%	10 100%	1	25%
	Hunched Posture	0	0	0	2	50%
	Rough Coat	0	0	0	3	75%
DAY 33						
	No. Observed	10	10	10	4	
	Normal	10 100%	10 100%	10 100%	0	
	Hunched Posture	0	0	0	2	50%
	Rough Coat	0	0	0	4	100%

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.5 2-M	1.5 3-M	4.5 4-M
DAY 34					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	5 50%	0
	Hunched Posture	0	0	0	3 75%
	Rough Coat	0	0	5 50%	4 100%
DAY 35					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	9 90%	1 25%
	Hunched Posture	0	0	0	2 50%
	Rough Coat	0	0	1 10%	3 75%
DAY 36					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	9 90%	1 25%
	Hunched Posture	0	0	0	2 50%
	Rough Coat	0	0	1 10%	3 75%
DAY 37					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	10 100%	1 25%
	Hunched Posture	0	0	0	2 50%
	Rough Coat	0	0	0	3 75%
DAY 38					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	9 90%	1 25%
	Hunched Posture	0	0	0	2 50%
	Rough Coat	0	0	1 10%	3 75%
DAY 39					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	9 90%	2 50%
	Hunched Posture	0	0	0	2 50%
	Rough Coat	0	0	1 10%	2 50%
DAY 40					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	10 100%	1 25%
	Rough Coat	0	0	0	3 75%

(mg base/kg/day)

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.5 2-M	1.5 3-M	4.5 4-M
DAY 41					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	10 100%	1 25%
	Rough Coat	0	0	0	3 75%
DAY 42					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	10 100%	1 25%
	Rough Coat	0	0	0	3 75%
DAY 43					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	8 80%	1 25%
	Rough Coat	0	0	2 20%	3 75%
DAY 44					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	8 80%	1 25%
	Rough Coat	0	0	2 20%	3 75%
DAY 45					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	8 80%	1 25%
	Rough Coat	0	0	2 20%	3 75%
DAY 46					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	10 100%	2 50%
	Rough Coat	0	0	0	2 50%
DAY 47					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	10 100%	1 25%
	Rough Coat	0	0	0	3 75%

(mg base/kg/day)

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.5 2-M	1.5 3-M	4.5 4-M (mg base/kg/day)
DAY 48					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	10 100%	1 25%
	Rough Coat	0	0	0	3 75%
DAY 49					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	10 100%	0
	Hunched Posture	0	0	0	1 25%
	Rough Coat	0	0	0	4 100%
DAY 50					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	9 90%	0
	Hunched Posture	0	0	0	3 75%
	Rough Coat	0	0	1 10%	4 100%
DAY 51					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	10 100%	0
	Hunched Posture	0	0	0	3 75%
	Rough Coat	0	0	0	4 100%
DAY 52					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	10 100%	0
	Hunched Posture	0	0	0	3 75%
	Rough Coat	0	0	0	4 100%
DAY 53					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	10 100%	0
	Hunched Posture	0	0	0	3 75%
	Rough Coat	0	0	0	4 100%
DAY 54					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	10 100%	0
	Hunched Posture	0	0	0	3 75%
	Rough Coat	0	0	0	4 100%

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.5 2-M	1.5 3-M	4.5 4-M
DAY 55					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	10 100%	0
	Hunched Posture	0	0	0	3 75%
	Rough Coat	0	0	0	4 100%
DAY 56					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	10 100%	0
	Hunched Posture	0	0	0	3 75%
	Rough Coat	0	0	0	4 100%
DAY 57					
	No. Observed	10	10	10	4
	Normal	10 100%	10 100%	10 100%	0
	Hunched Posture	0	0	0	3 75%
	Rough Coat	0	0	0	4 100%
DAY 58					
	No. Observed	10	10	10	4
	Normal	10 100%	8 80%	9 90%	0
	Hunched Posture	0	0	0	3 75%
	Rough Coat	0	2 20%	1 10%	4 100%
DAY 59					
	No. Observed	10	10	10	4
	Normal	10 100%	9 90%	9 90%	0
	Hunched Posture	0	0	0	3 75%
	Rough Coat	0	1 10%	1 10%	4 100%
DAY 60					
	No. Observed	10	10	10	4
	Normal	10 100%	9 90%	10 100%	0
	Hunched Posture	0	0	0	3 75%
	Rough Coat	0	1 10%	0	4 100%

(mg base/kg/day)

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SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.5 2-M	1.5 3-M	4.5 4-M	(mg base/kg/day)
DAY 61						
	No. Observed	10	10	10	4	
	Normal	10 100%	10 100%	10 100%	0	
	Hunched Posture	0	0	0	3	75%
	Rough Coat	0	0	0	4	100%
DAY 62						
	No. Observed	10	10	10	4	
	Normal	10 100%	10 100%	10 100%	1	25%
	Hunched Posture	0	0	0	2	50%
	Rough Coat	0	0	0	3	75%
DAY 63						
	No. Observed	10	10	10	4	
	Sacrificed Moribund	0	0	0	1	25%
	Normal	10 100%	10 100%	10 100%	0	
	Hunched Posture	0	0	0	2	50%
	Rough Coat	0	0	0	4	100%
DAY 64						
	No. Observed	10	10	10	3	
	Normal	10 100%	10 100%	10 100%	0	
	Hunched Posture	0	0	0	1	33%
	Rough Coat	0	0	0	3	100%
DAY 65						
	No. Observed	10	10	10	3	
	Normal	10 100%	10 100%	10 100%	0	
	Hunched Posture	0	0	0	2	66%
	Rough Coat	0	0	0	3	100%
DAY 66						
	No. Observed	10	10	10	3	
	Normal	10 100%	10 100%	10 100%	0	
	Hunched Posture	0	0	0	1	33%
	Rough Coat	0	0	0	3	100%

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.5 2-M	1.5 3-M	4.5 4-M
					(mg base/kg/day)
DAY 67					
	No. Observed	10	10	10	3
	Normal	10 100%	10 100%	10 100%	0
	Rough Coat	0	0	0	3 100%
DAY 68					
	No. Observed	10	10	10	3
	Normal	10 100%	10 100%	10 100%	1 33%
	Rough Coat	0	0	0	2 66%
DAY 69					
	No. Observed	10	10	10	3
	Normal	10 100%	10 100%	10 100%	2 66%
	Rough Coat	0	0	0	1 33%
DAY 70					
	No. Observed	10	10	10	3
	Normal	10 100%	10 100%	9 90%	1 33%
	Rough Coat	0	0	1 10%	2 66%
DAY 71					
	No. Observed	10	10	10	3
	Normal	10 100%	10 100%	10 100%	1 33%
	Rough Coat	0	0	0	2 66%
DAY 72					
	No. Observed	10	10	10	3
	Normal	10 100%	10 100%	10 100%	1 33%
	Rough Coat	0	0	0	2 66%
DAY 73					
	No. Observed	10	10	10	3
	Normal	10 100%	10 100%	10 100%	2 66%
	Rough Coat	0	0	0	1 33%

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.5 2-M	1.5 3-M	4.5 4-M (mg base/kg/day)
DAY 74					
No. Observed		10	10	10	3
Normal		10 100%	9 90%	10 100%	2 66%
Rough Coat		0	1 10%	0	1 33%
DAY 75					
No. Observed		10	10	10	3
Normal		10 100%	9 90%	10 100%	2 66%
Rough Coat		0	1 10%	0	1 33%
DAY 76					
No. Observed		10	10	10	3
Normal		10 100%	7 70%	10 100%	2 66%
Rough Coat		0	3 30%	0	1 33%
DAY 77					
No. Observed		10	10	10	3
Normal		10 100%	9 90%	10 100%	2 66%
Rough Coat		0	1 10%	0	1 33%
DAY 78					
No. Observed		10	10	10	3
Normal		10 100%	10 100%	9 90%	1 33%
Rough Coat		0	0	1 10%	2 66%
DAY 79					
No. Observed		10	10	10	3
Normal		10 100%	9 90%	7 70%	1 33%
Rough Coat		0	1 10%	3 30%	2 66%
DAY 80					
No. Observed		10	10	10	3
Normal		10 100%	10 100%	9 90%	1 33%
Rough Coat		0	0	1 10%	2 66%
DAY 81					
No. Observed		10	10	10	3
Normal		10 100%	9 90%	10 100%	2 66%
Rough Coat		0	1 10%	0	1 33%

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.5 2-M	1.5 3-M	4.5 4-M
DAY 82					
	No. Observed	10	10	10	3
	Normal	10 100%	9 90%	10 100%	1 33%
	Rough Coat	0	1 10%	0	2 66%
DAY 83					
	No. Observed	10	10	10	3
	Normal	10 100%	10 100%	10 100%	1 33%
	Rough Coat	0	0	0	2 66%
OAY 84					
	No. Observed	10	10	10	3
	Normal	10 100%	10 100%	10 100%	2 66%
	Rough Coat	0	0	0	1 33%
DAY 85					
	No. Observed	10	10	10	3
	Normal	10 100%	10 100%	10 100%	1 33%
	Rough Coat	0	0	0	2 66%
DAY 86					
	No. Observed	10	10	10	3
	Normal	10 100%	10 100%	10 100%	1 33%
	Rough Coat	0	0	0	2 66%
DAY 87					
	No. Observed	10	10	10	3
	Normal	10 100%	10 100%	8 80%	1 33%
	Rough Coat	0	0	2 20%	2 66%
DAY 88					
	No. Observed	10	10	10	3
	Accidental Oeath	0	1 10%	0	0
	Normal	9 90%	8 80%	8 80%	1 33%
	Dark Material Around Eyes	1 10%	0	1 10%	0
	Hunched Posture	0	0	1 10%	0
	Rough Coat	0	1 10%	2 20%	2 66%

(mg base/kg/day)

THIRTEEN WEEK ORAL TOXICITY
STUDY OF WR242511 IN RATS

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.5 2-M	1.5 3-M	4.5 4-M
DAY 89					
	No. Observed	10	9	10	3
	Normal	9 90%	8 88%	8 80%	1 33%
	Dark Material Around Eyes	1 10%	0	1 10%	0
	Hunched Posture	0	0	1 10%	0
	Labored Breathing	0	0	1 10%	0
	Rough Coat	0	1 11%	2 20%	2 66%
DAY 90					
	No. Observed	10	9	10	3
	Accidental Death	0	0	1 10%	0
	Normal	10 100%	9 100%	9 90%	0
	Rough Coat	0	0	0	3 100%
DAY 91					
	No. Observed	10	9	9	3
	Scheduled Sacrifice	3 30%	4 44%	3 33%	2 66%
	Normal	7 70%	5 55%	6 66%	0
	Rough Coat	0	0	0	1 33%
DAY 92					
	No. Observed	7	5	6	1
	Scheduled Sacrifice	7 100%	5 100%	6 100%	1 100%

(mg base/kg/day)

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.5 2-F	1.5 3-F	4.5 4-F	(mg base/kg/day)
DAY 0						
No. Observed		10	10	10	10	
Normal		10 100%	10 100%	10 100%	10 100%	
DAY 1						
No. Observed		10	10	10	10	
Normal		10 100%	10 100%	10 100%	10 100%	
DAY 2						
No. Observed		10	10	10	10	
Normal		10 100%	10 100%	10 100%	10 100%	
DAY 3						
No. Observed		10	10	10	10	
Normal		10 100%	10 100%	10 100%	10 100%	
DAY 4						
No. Observed		10	10	10	10	
Normal		10 100%	10 100%	10 100%	10 100%	
DAY 5						
No. Observed		10	10	10	10	
Normal		10 100%	10 100%	10 100%	10 100%	
DAY 6						
No. Observed		10	10	10	10	
Normal		10 100%	10 100%	10 100%	10 100%	
DAY 7						
No. Observed		10	10	10	10	
Normal		10 100%	10 100%	10 100%	10 100%	
DAY 8						
No. Observed		10	10	10	10	
Normal		10 100%	10 100%	10 100%	10 100%	
DAY 9						
No. Observed		10	10	10	10	
Normal		10 100%	10 100%	10 100%	10 100%	

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.5 2-F	1.5 3-F	4.5 4-F (mg base/kg/day)
DAY 10					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 11					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 12					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 13					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 14					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 15					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 16					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 17					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 18					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 19					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.5 2-F	1.5 3-F	4.5 4-F
DAY 20					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 21					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 22					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	7 70%
Rough Coat		0	0	0	3 30%
DAY 23					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	8 80%
Rough Coat		0	0	0	2 20%
DAY 24					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	7 70%
Rough Coat		0	0	0	3 30%
DAY 25					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	7 70%
Rough Coat		0	0	0	3 30%
DAY 26					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 27					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	8 80%
Rough Coat		0	0	0	2 20%
DAY 28					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%

(mg base/kg/day)

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.5 2-F	1.5 3-F	4.5 4-F (mg base/kg/day)
DAY 29					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 30					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	9 90%
Rough Coat		0	0	0	1 10%
DAY 31					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	8 80%
Rough Coat		0	0	0	2 20%
DAY 32					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	9 90%
Rough Coat		0	0	0	1 10%
DAY 33					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	5 50%
Rough Coat		0	0	0	5 50%
DAY 34					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	5 50%	6 60%
Rough Coat		0	0	5 50%	4 40%
DAY 35					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	9 90%	6 60%
Rough Coat		0	0	1 10%	4 40%
DAY 36					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	5 50%
Rough Coat		0	0	0	5 50%

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.5 2-F	1.5 3-F	4.5 4-F
DAY 37					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	8 80%	7 70%
Rough Coat		0	0	2 20%	3 30%
DAY 38					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	8 80%	7 70%
Rough Coat		0	0	2 20%	3 30%
DAY 39					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	8 80%
Rough Coat		0	0	0	2 20%
DAY 40					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 41					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	8 80%	8 80%
Rough Coat		0	0	2 20%	2 20%
DAY 42					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	7 70%
Rough Coat		0	0	0	3 30%
DAY 43					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	9 90%	6 60%
Rough Coat		0	0	1 10%	4 40%
DAY 44					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	8 80%	5 50%
Rough Coat		0	0	2 20%	5 50%

(mg base/kg/day)

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.5 2-F	1.5 3-F	4.5 4-F
					(mg base/kg/day)
DAY 45					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	8 80%	6 60%
Rough Coat		0	0	2 20%	4 40%
DAY 46					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	6 60%
Rough Coat		0	0	0	4 40%
DAY 47					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	7 70%
Rough Coat		0	0	0	3 30%
DAY 48					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	9 90%	8 80%
Rough Coat		0	0	1 10%	2 20%
DAY 49					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	9 90%	8 80%
Rough Coat		0	0	1 10%	2 20%
DAY 50					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	8 80%
Rough Coat		0	0	0	2 20%
DAY 51					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	8 80%	9 90%
Rough Coat		0	0	2 20%	1 10%
DAY 52					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	9 90%	6 60%
Rough Coat		0	0	2 20%	4 40%

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.5 2-F	1.5 3-F	4.5 4-F
DAY 53					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	9 90%
Rough Coat		0	0	0	1 10%
DAY 54					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	7 70%
Rough Coat		0	0	0	3 30%
DAY 55					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	8 80%
Rough Coat		0	0	0	2 20%
DAY 56					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	9 90%	9 90%
Rough Coat		0	0	1 10%	1 10%
DAY 57					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	9 90%	10 100%
Rough Coat		0	0	1 10%	0
DAY 58					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	9 90%	8 80%
Rough Coat		0	0	1 10%	2 20%
DAY 59					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	8 80%	8 80%
Rough Coat		0	0	2 20%	2 20%
DAY 60					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	8 80%
Rough Coat		0	0	0	2 20%

(mg base/kg/day)

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.5 2-F	1.5 3-F	4.5 4-F
		(mg base/kg/day)			
DAY 61					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	7 70%	5 50%
Rough Coat		0	0	3 30%	5 50%
DAY 62					
No. Observed		10	10	10	10
Normal		10 100%	7 70%	7 70%	6 60%
Dark Material Around Eyes		0	2 20%	1 10%	2 20%
Dark Material Around Nose		0	1 10%	0	0
Rough Coat		0	0	2 20%	4 40%
DAY 63					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	7 70%	7 70%
Rough Coat		0	0	3 30%	3 30%
DAY 64					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	8 80%	8 80%
Rough Coat		0	0	2 20%	2 20%
DAY 65					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	8 80%	7 70%
Rough Coat		0	0	2 20%	3 30%
DAY 66					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	8 80%	8 80%
Rough Coat		0	0	2 20%	2 20%
DAY 67					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	9 90%
Rough Coat		0	0	0	1 10%

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.5 2-F	1.5 3-F	4.5 4-F (mg base/kg/day)
DAY 68					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	9 90%	8 80%
Rough Coat		0	0	1 10%	2 20%
DAY 69					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	10 100%
DAY 70					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	6 60%
Rough Coat		0	0	0	4 40%
DAY 71					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	9 90%
Rough Coat		0	0	0	1 10%
DAY 72					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	9 90%
Rough Coat		0	0	0	1 10%
DAY 73					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	8 80%
Rough Coat		0	0	0	2 20%
DAY 74					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	9 90%	9 90%
Rough Coat		0	0	1 10%	1 10%
DAY 75					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	10 100%	7 70%
Rough Coat		0	0	0	3 30%

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.5 2-F	1.5 3-F	4.5 4-F
DAY 76					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	8 80%	8 80%
	Rough Coat	0	0	2 20%	2 20%
DAY 77					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	8 80%	9 90%
	Rough Coat	0	0	2 20%	1 10%
DAY 78					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	6 60%
	Rough Coat	0	0	0	4 40%
DAY 79					
	No. Observed	10	10	10	10
	Normal	10 100%	9 90%	8 80%	6 60%
	Rough Coat	0	1 10%	2 20%	4 40%
DAY 80					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	10 100%	6 60%
	Rough Coat	0	0	0	4 40%
DAY 81					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	8 80%	9 90%
	Rough Coat	0	0	2 20%	1 10%
DAY 82					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	7 70%	7 70%
	Rough Coat	0	0	3 30%	3 30%
DAY 83					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	9 90%	8 80%
	Rough Coat	0	0	1 10%	2 20%

(mg base/kg/day)

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.5 2-F	1.5 3-F	4.5 4-F
DAY 84					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	7 70%	7 70%
Rough Coat		0	0	3 30%	3 30%
DAY 85					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	8 80%	7 70%
Rough Coat		0	0	2 20%	3 30%
DAY 86					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	7 70%	7 70%
Rough Coat		0	0	3 30%	3 30%
DAY 87					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	7 70%	7 70%
Rough Coat		0	0	3 30%	3 30%
DAY 88					
No. Observed		10	10	10	10
Normal		10 100%	10 100%	8 80%	6 60%
Rough Coat		0	0	2 20%	4 40%

(mg base/kg/day)

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 107 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.5 2-F	1.5 3-F	4.5 4-F
					(mg base/kg/day)
DAY 89					
	No. Observed	10	10	10	10
	Normal	8 80%	9 90%	7 70%	5 50%
	Dark Material Around Eyes	1 10%	0	0	0
	Rough Coat	1 10%	1 10%	3 30%	5 50%
DAY 90					
	No. Observed	10	10	10	10
	Normal	10 100%	10 100%	8 80%	6 60%
	Rough Coat	0	0	2 20%	4 40%
DAY 91					
	No. Observed	10	10	10	10
	Scheduled Sacrifice	5 50%	4 40%	6 60%	7 70%
	Normal	5 50%	5 50%	2 20%	0
	Rough Coat	0	1 10%	2 20%	3 30%
DAY 92					
	No. Observed	5	6	4	3
	Scheduled Sacrifice	5 100%	6 100%	4 100%	3 100%