Toxicology Research Laboratory

UIC The University of Illinois at Chicago

Department of Pharmacology (M/C 868)
1940 W. Taylor St.
Chicago, Illinois 60612-7353

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Draft Report for Task Order No. UIC-7C

TWO WEEK ORAL DOSE RANGE-FINDING 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

July 8, 1993

Performing Laboratory

TOXICOLOGY RESEARCH LABORATORY (TRL)
University of Illinois at Chicago (UIC)
Department of Pharmacology
1940 West Taylor St.
Chicago, IL 60612-7353

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This study evaluated the toxicity of WR242511 tartrate in rats following two weeks of daily oral administration by gavage. Dose levels studied were 0 (vehicle control), 0.5, 2.0 and 6.2 mg base/kg/day. The primary toxic effects of WR242511 tartrate included anemia, hepatotoxicity and leukocytosis. Females were more sensitive than males to the anemic state whereas the reverse was true for hepatotoxicity. Anemia was seen in mid and high dose females, whereas hepatotoxicity was only observed in high dose males and may have been associated with the death of one high dose male on Day 13. Generalized leukocytosis occurred in the high dose animals and in mid dose females. Toxicity was not apparent in low dose animals. Significant methemoglobinemia was noted in mid and high animals, and possibly at the low dose. As this is the desired pharmacologic effect of WR242511 tartrate, its occurrence was not considered indicative of toxicity. The purpose of this study was to select dose levels for a three month toxicity study in rats. It is anticipated that significant toxicity would occur at the high dose, marginal or no toxicity would be observed at the mid dose, and no toxicity would occur at the low dose level. On this basis, the following three dose level ranges are suggested: 0.5, 1 - 1.5, and 2 - 4.5 mg base/kg/day.

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STATEMENT OF COMPLIANCE

To the best of my knowledge, Study No. 106 entitled "Two Week Oral Dose Range-Finding 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: TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR242511 IN RATS

STUDY NUMBER: 106

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 monitors each of these phases over a series of studies. Procedures, equipment, documentation, etc., are examined in order to assure that the study is performed in accordance with the Good Laboratory Practice regulations of the Food and Drug Administration and the Environmental Protection Agency to assure that the study is conducted according to the protocol.

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

INSPECT ON 12/7/92, TO STUDY DIR 12/7/92, TO MGMT 12/7/92
PHASES: PROTOCOL REVIEW

INSPECT ON 6/24/93, TO STUDY DIR 6/25/93, TO MGMT 6/28/93
PHASES: ROOM ENVIRONMENT, BODY WEIGHT, DOSING, CLINICAL OBSERVATION AND FOOD CONSUMPTION

INSPECT ON 8/23/93, TO STUDY DIR 8/24/93, TO MGMT 8/26/93
PHASES: ANALYTICAL LABORATORY RAW DATA AUDIT

INSPECT ON 8/24/93, TO STUDY DIR 8/24/93, TO MGMT 8/26/93
PHASES: ANALYTICAL LABORATORY REPORT

INSPECT ON 8/24/93, TO STUDY DIR 8/24/93, TO MGMT 8/26/93
PHASES: DRAFT PATHOLOGY REPORT

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TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR242511 IN RATS

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Sponsor: US Army Medical Materiel
Development Activity
Fort Detrick
Frederick, MD 21702-5014

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

Testing Facility: TOXICOLOGY RESEARCH LABORATORY (TRL)
University of Illinois at Chicago (UIC)
Department of Pharmacology
1940 West Taylor St.
Chicago, IL 60612-7353

_____ _____

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

_____ _____

Clyde W. Wheeler, Ph.D. Date
Toxicologist

Study Initiation: December 3, 1992
Dosing Initiation: June 24, 1993
In-Life Completion: July 8, 1993

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1. SUMMARY

This study evaluated the toxicity of WR242511 tartrate in rats following two weeks of daily oral administration by gavage. Dose levels studied were 0 (vehicle control), 0.5, 2.0 and 6.2 mg base/kg/day. The results are summarized in Table 1. The primary toxic effects of WR242511 tartrate included anemia, hepatotoxicity and leukocytosis. Females were more sensitive than males to the anemic state whereas the reverse was true for hepatotoxicity. Anemia was seen in mid and high dose females, whereas hepatotoxicity was only observed in high dose males and may have been associated with the death of one high dose male on Day 13. Generalized leukocytosis occurred in the high dose animals and in mid dose females. Toxicity was not apparent in low dose animals. Significant methemoglobinemia was noted in mid and high animals, and possibly at the low dose. As this is the desired pharmacologic effect of WR242511 tartrate, its occurrence was not considered indicative of toxicity. The purpose of this study was to select dose levels for a three month toxicity study in rats. It is anticipated that significant toxicity would occur at the high dose, marginal or no toxicity would be observed at the mid dose, and no toxicity would occur at the low dose level. On this basis, the following three dose level ranges are suggested: 0.5, 1 - 1.5, and 2 - 4.5 mg base/kg/day.

2. INTRODUCTION

This study was conducted to determine the toxicity of WR242511 tartrate in CD® rats following two weeks of daily gavage administration. The rat is 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 June 24, 1993 and the in-life portion was terminated on July 8, 1993.

3. MATERIALS AND METHODS

3.1 Test Article

WR242511 tartrate (Bottle Lot No. BM 05816), a fine, yellow powder, was received on December 15, 1992 from Herner & Co. The chemical name of the test article is 8-[(4-Amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline DL-tartrate and the mole fraction of the base is 0.71. It was stored at -20 to -15°C and ambient humidity in the freezer, and was protected from light (the container was wrapped in aluminum foil).

The Analytical Chemistry Report is contained in Appendix 1. The test article was initially identified by GC-MS and the purity was determined (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 ± 0.04%. Thus, the test article was stable under storage conditions.

3.2 Animals

Male and female CD® Virus Antibody Free (VAF) rats were obtained from Charles River Breeding Laboratories on June 16, 1993. The animals were approximately 6 weeks old (date of birth May 5, 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.

Purina Certified Rodent Chow No. 5002 (Ralston Purina Company, 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 for necropsy. Tap water from an automatic watering system in which the room distribution lines were flushed daily was provided *ad libitum*. The water was untreated 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 are documented in files maintained by Quality Assurance.

3.3 Experimental Design

Near the end of the quarantine/pretest period, 20 animals of each sex were randomized by sex into the groups shown in the table below using a computer-generated randomization program, stratified on the basis of body weight.

Treatment Group	Treatment	Dose Level (mg base/kg/day)	Number of Males	Number of Females
1	Vehicle Control	0	5	5
2	WR242511 tartrate	0.5	5	5
3	WR242511 tartrate	2.0	5	5
4	WR242511 tartrate	6.2	5	5

Dose levels were supplied by the Sponsor based on the results of an acute oral toxicity study in rats (UIC/TRL 104).

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.

The test article dosing suspensions were prepared every 48 hours. Prior testing indicated that dosing suspensions were stable for 48 hours at concentrations which bracketed those present in the dosage formulations. The dosage formulations were prepared by suspending the appropriate quantity of test article in the vehicle (1% methylcellulose/0.2% Tween 80) using a mortar and pestle to result in concentrations necessary to administer the dosage formulations at a volume of 5 ml/kg. The quantity of the test article was calculated as mg base/kg/day. All dosage formulations used on the onset of Weeks 1 and 2 were analyzed for test article concentration. The results of these analyses are included in Table 2 and in Appendix 1.

The test article was administered by oral gavage once daily for two weeks beginning on June 24, 1993 (Day 0). Control animals received the vehicle (aqueous 1% methylcellulose/0.2% Tween 80). The actual dosing volume (ml) was adjusted on the basis of each animal's most recent body weight. The animals were dosed up to and including the day prior to scheduled necropsy (Day 14). The animals were approximately seven weeks old and weighed 216 - 250 g (males) and 164 - 202 g (females) at initiation of treatment.

Non-fasted body weights were recorded at randomization in Week -1, on Day 0 prior to dosing, and twice weekly thereafter. Fasted body weights were collected at scheduled termination. Clinical signs were recorded once daily, approximately 1 - 2 hours after dosing. The general behavior, posture, locomotion, breathing pattern and haircoat 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 twice weekly thereafter. Food consumption was measured for all animals twice weekly commencing with Week -1. Hematology and clinical chemistry parameters were measured on Day 14 (at scheduled necropsy). 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 are contained in Appendix 2.

Hematology

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

[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

Albumin (A)	Creatinine
Albumin/Globulin (A/G) ratio (calc.)	Globulin (calculated)
Alkaline phosphatase	Glucose
Alanine aminotransferase (ALT/SGPT)	Inorganic phosphorus
	Potassium
Aspartate aminotransferase (AST/SGOT)	Sodium
	Total bile acids
Calcium	Total protein
Chloride	Triglycerides
Cholesterol	Urea nitrogen (BUN)

All animals which died on test were necropsied on that day. All surviving animals were sacrificed and necropsied in random order on Days 14. 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).

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

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

Those tissues and organs marked with an asterisk (*) collected at scheduled necropsy were examined microscopically for all rats in all groups.

3.4 Statistical Analyses

For each sex, Analysis of Variance (ANOVA) tests were conducted on body weight, food consumption, hematology, clinical chemistry and organ weight data. Organ weight analysis considered absolute weights and weights relative to body weight. Organ weight assessment generally consisted of comparison of organ weight/body weight ratios (% body weight), although brain and testis weight comparisons were usually considered on the basis of absolute values. If significant body weight loss occurs, organ weight/body weight ratios are often artificially elevated.

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 control group. The level of significance was $p \leq 0.05$. All summary and individual data are expressed on the basis of mg base/kg/day.

4. RESULTS

4.1 Analysis of Dosage Formulations

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

All dosing suspensions used were within 10% of their target concentration.

4.2 Mortality and Clinical Signs/Observations

Summaries of clinical signs are presented in Tables 3 (males) and 4 (females). Individual clinical signs, daily incidence of clinical signs and summaries of twice weekly clinical observations are contained in Appendix 3.

One high dose male (no. 335) was found dead on Day 13. The cause of death may have been related to hepatocellular necrosis as discussed in Section 4.7 (Pathology). No other animals died during the treatment period.

Treatment-related daily clinical signs (1 - 2 hrs post-dosing) included rough coat and hunched posture. Rough coat was seen in all groups, but was primarily limited to the initial days of treatment in low and mid dose animals. Rough coat was also noted in a few control males during the first few study days. Hunched posture was observed in the mid and high dose males and in high dose females.

4.3 Body Weight

Summary of body weights and summary of weight gains for males are in Tables 5 and 6, respectively. The corresponding summaries for females are in Tables 7 and 8, respectively. Individual body weights and weight gains are contained in Appendix 4.

Decreased body weight gains were apparent in high dose males throughout the study. This included body weight loss during the second week of dosing. Severe body weight loss was noted for the nonsurviving high dose male. Although not statistically significant, a slight decrease in body weight gains ($\approx$ 23%) was also seen in high dose females. Body weights were not significantly affected at the lower dose levels.

4.4 Food Consumption

Summaries of food consumption are in Tables 9 and 10 for males and females, respectively. Individual food consumption data are shown in Appendix 5.

Significantly reduced food consumption was apparent in high dose males and females. This was not observed at the lower dose levels.

4.5 Clinical Pathology

Summaries of clinical chemistry tests for males and females are in Tables 11 and 12, respectively. Individual clinical chemistry data are in Appendix 7. Summaries of hematological tests for males and females are in Tables 13 and 14, respectively. Individual hematology data are in Appendix 8.

Significant increases in serum AST and ALT were observed in high dose males. Although not statistically significant, serum total bile acids were also somewhat elevated in high dose males (one high dose female also had an elevated TBA, however the values for the remaining four high dose females were similar to the control animals). High dose males also demonstrated a slight decrease in serum inorganic phosphorus. None of these changes was observed at the lower doses.

Significant anemia (decreased RBC count, hemoglobin and/or hematocrit) was apparent in mid and high dose females but not males. At the high dose, the MCV was increased, and RBCs were hypochromic, polychromatic and anisocytotic compared to control animal RBCs. Reticulocytosis was also observed as a compensatory response in these animals. Some of the mid dose females also demonstrated hypochromatic and/or anisocytotic RBCs.

Generalized leukocytosis consisting of increased mature neutrophils, immature neutrophils, monocytes, and/or lymphocytes was seen in high dose males and females and in mid dose males. This was not seen in mid dose females or in low dose animals.

No other clinical pathology parameters were altered by WR242511 tartrate treatment.

Significant methemoglobinemia, the anticipated pharmacologic effect, was observed in high and mid dose males and females. Although not statistically significant, an approximate two-fold increase was also seen in low dose animals of both sexes.

4.6 Organ Weights

Organ weight summaries of percent body weight and absolute values for males are in Tables 15 and 16, respectively. Corresponding summaries for females are in Tables 17 and 18. Individual organ weight data are contained in Appendix 8.

Statistically significant increases in relative liver weights were seen in high dose males but not females at necropsy (Table 15). This was not seen in the lower dose levels. Significant increases in relative splenic weights occurred in mid and high dose females and in high dose males (Tables 17). Although not statistically significant (possibly as a function of variability), an approximate 50% increase in relative splenic weights was also seen in mid dose males, and as such was considered biologically significant.

4.7 Pathology

The Pathology Report is contained in Appendix 9. A summary of microscopic lesions is shown in Table 19.

Coagulative liver necrosis was observed in three out of five high dose males. This lesion consisted of individual or small clusters of hepatocyte oriented around or along central veins. Although the necrosis was of low severity in surviving animals, lesion incidence indicated that it was related to drug treatment. For the high dose male which died on Day 13, a grade 3 severity was noted, which may have contributed to its death. In addition, this animal demonstrated splenic lymphocyte depletion, typically seen in response to generalized toxicity.

Splenic extramedullary hematopoiesis (EMH) consisting of increased amounts of myeloid, erythroid, and megakaryocytic cells in the red pulp was observed in mid and high dose animals. Because erythroid cells were more prominent than myeloid cells, and because of a lack of accompanying inflammation, the EMH was interpreted as secondary to anemia and not a direct effect of the test article.

No other test article-related histopathologic changes were seen. All other microscopic changes were considered incidental.

5. DISCUSSION/CONCLUSION

This study evaluated the oral toxicity of WR242511 tartrate in Sprague-Dawley rats following two weeks of daily oral administration. The results are summarized in Table 1. One high dose male died on Day 13. Prior to death, this animal lost significant body weight. Histologically, the animal demonstrated significant coagulative liver necrosis (grade 3) and splenic lymphocyte depletion.

Clinical signs of toxicity in WR242511 tartrate-treated rats were limited to the appearance of rough coat and hunched posture primarily at the higher dose levels. Body weight gains and food consumption were decreased in high dose animals, but not at the lower dose levels.

Treatment-related anemia was seen in high and mid dose females. At the high dose, RBCs, were hypochromic, anisocytotic and macrocytic, and slightly increased reticulocyte counts were seen as a compensatory physiologic response. Hypochromia and/or anisotytosis was also evident in mid dose females. Splenic extramedullary hematopoiesis supported by splenomegaly was secondary to the anemic state in mid and high dose animals. It is unclear why enlarged spleens and this histologic change were also noted in mid and/or high dose males, as clinical anemia was not apparent in these animals.

Drug-induced hepatotoxicity was indicated on the basis of clinical chemistry, organ weight and tissue morphology changes. Slight increases in serum levels of ALT, AST and possibly total bile acids were observed in high dose males. These changes were associated with coagulative liver necrosis and hepatomegaly. Liver toxicity was not seen in high dose females or in the lower dose levels.

Leukocytosis was seen in mid and high dose males, and in high dose females. The effect was generalized as all major cell types were typically increased. Serum inorganic phosphorus was also decreased in high dose males. The biologic significance of this change is unclear.

The expected pharmacologic action of WR242511 tartrate, methemoglobinemia, was observed in mid and high dose animals, and possibly at the low dose.

In summary, the primary toxic effects of WR242511 tartrate included anemia, hepatotoxicity and leukocytosis. Females were more sensitive than males to the anemic state whereas the reverse was true for hepatotoxicity. Anemia was seen in mid and high dose females, whereas hepatotoxicity was only observed in high dose males and may have been associated with the death of one high dose male on Day 13. Generalized leukocytosis occurred in the high dose animals and in mid dose females. Toxicity was not apparent in low dose animals. Significant methemoglobinemia was noted in mid and high animals, and possibly at the low dose. As this is the desired pharmacologic effect of WR242511 tartrate, its occurrence was not considered indicative of toxicity. The purpose of this study was to select dose levels for a three month toxicity study in rats. It is anticipated that significant toxicity would occur at the high dose, marginal or no toxicity would be observed at the mid dose, and no toxicity would occur at the low dose level. On this basis, the following three dose level ranges are suggested: 0.5, 1 - 1.5, and 2 - 4.5 mg base/kg/day.

6. PERSONNEL

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
Toxicologist	Clyde W. Wheeler, Ph.D.
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.
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

Report preparation was assisted by Dr. Clyde W. Wheeler.

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 West Taylor St., Chicago, IL 60612-7353.

Table 1

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

Summary of Toxic Responses

Dose (mg base/kg/day)	0	0.5	2.0	6.2
Rats/Sex	5	5	5	5
Deaths	-	-	-	1
Body Weight Gain	-	-	-	↓ (M) ↓ (F?)
Food Consumption	-	-	-	1
Clinical Observations[a]	RC (M)	RC	RC HP (M)	RC, HP
Hematology[b]	-	↑ METHGB (?)	↑ METHGB ↓ RBC (F) ↓ HCT (F) ↓ HGB (F) ↑ WBC (M)	↑ METHGB ↓ RBC (F) ↓ HGB (F) ↓ HCT (F) ↓ MCHC (F) ↑ MCV (F) ↑ RETIC (F) ↑ WBC
Clinical Chemistry[c]	-	-	-	↑ AST (M) ↑ ALT (M) ↑ IP (M) ↑ TBA (M) (?)
Organ Weights	-	-	↑ Spleen	↑ Spleen ↑ Liver (M)
Histopathology[d]	-	-	Splenic EMH	Liver necrosis (M) Splenic EMH
CONCLUSIONS	Toxicity was seen at the mid and high dose levels. The primary toxic effects occurred in the RBC and liver. Anemia (females only) was observed at the mid and high dose levels, and was supported by splenomegaly and splenic EMH. Slight increases in serum ALT, AST, and possibly TBA, hepatomegaly and coagulative liver necrosis in high dose males indicated hepatotoxicity. Leukocytosis was observed in high dose females and in mid and high dose males. Methemoglobinemia, the pharmacologic effect of WR242511 tartrate, was apparent at the mid and high dose levels, and possibly is low dose animals. The low dose represents the no observed toxic effect level. On the basis of this study, the following dose level ranges are suggested for the three month study: 0.5, 1 - 1.5, and 2 - 4.5 mg base/kg/day.			

[a]RC = rough coat, HP = hunched posture

[b]METHGB = methemoglobin, RBC = red blood cells, HCT = hematocrit, HGB = hemoglobin, MCV = mean corpuscular volume, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, RETIC = reticulocyte.

[c]AST = aspartate aminotransferase, ALT = alanine aminotransferase, TBA = total bile acids, IP = inorganic phosphorus.

[d]EMH = Extramedullary hematopoiesis.

? = Possible marginal effect

Table 2

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

Dosage Formulation Analyses[a]

Target Concentration (mg/ml)	Day 0	% Target	Day 7	% Target
0	0.00	----	0.00	----
0.1	0.1003 ± 0.0037	100.3	0.0986 ± 0.0003	98.5
0.4	0.3992 ± 0.0067	99.8	0.4091 ± 0.0036	102.3
1.24	1.2044 ± 0.0037	97.1	1.2670 ± 0.0136	102.2

[a]Mean ± standard deviation for triplicate runs.

Table 3

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

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SUMMARY OF CLINICAL SIGNS

STUDY: 106 SEX: MALE

DOSE:(mg/kg)	0	0.5	2.0	6.2
GROUP:	1-M	2-M	3-M	4-M
Scheduled Sacrifice	5	5	5	4
Animal Found Dead	0	0	0	1
Hunched Posture	0	0	4	5
Rough Coat	3	5	5	5
Total Number of Animals	5	5	5	5

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL SIGNS

STUDY: 106 SEX: FEMALE

DOSE:(mg/kg)	0	0.5	2.0	6.2
GROUP:	1-F	2-F	3-F	4-F
Scheduled Sacrifice	5	5	5	5
Hunched Posture	0	0	0	3
Rough Coat	0	4	4	5
Total Number of Animals	5	5	5	5

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR242511 IN RATS

DRAFT

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 106 SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1-M	0.5 2-M	2.0 3-M	6.2 4-M
DAY -3	MEAN	207.2	208.2	209.0	208.7
	S.D.	9.31	9.32	8.43	8.25
	N	5	5	5	5
DAY 0	MEAN	231.7	233.9	228.6	233.9
	S.D.	9.68	10.24	11.59	11.16
	N	5	5	5	5
DAY 4	MEAN	265.0	263.2	263.4	257.1
	S.D.	10.50	9.53	14.64	13.55
	N	5	5	5	5
DAY 7	MEAN	283.6	279.2	277.3	262.0
	S.D.	11.86	7.24	19.32	19.19
	N	5	5	5	5
DAY 10	MEAN	296.1	293.9	289.0	249.7**
	S.D.	12.62	11.07	22.50	29.07
	N	5	5	5	5
DAY 13	MEAN	311.8	310.6	308.2	253.4*
	S.D.	13.54	10.67	25.22	58.74
	N	5	5	5	4

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

Analysis of Variance using DUNNETT'S Procedure

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 106 SEX: MALE

PERIOD[a]	DOSE: (mg/kg) GROUP:	0 1-M	0.5 2-M	2.0 3-M	6.2 4-M
DAY 4[b]	MEAN	33.3	29.3	34.9	23.2*
	S.D.	3.59	3.74	4.50	9.23
	N	5	5	5	5
DAY 7	MEAN	18.6	16.0	13.8	4.9**
	S.D.	2.37	3.53	7.06	6.37
	N	5	5	5	5
DAY 10	MEAN	12.5	14.8	11.7	-12.3**
	S.D.	2.17	4.01	13.26	16.44
	N	5	5	5	5
DAY 13	MEAN	15.7	16.7	19.2	-3.9
	S.D.	3.73	3.90	14.17	34.16
	N	5	5	5	4
TOTAL GAIN	MEAN	80.1	76.7	79.6	17.2**
	S.D.	8.95	8.42	16.90	54.14
	N	5	5	5	4

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

Analysis of Variance using DUNNETT'S Procedure

a = Successive periods
b = Baseline is Day 0

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR242511 IN RATS

DRAFT

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 106 SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1-F	0.5 2-F	2.0 3-F	6.2 4-F
DAY -3	MEAN	166.4	167.6	166.5	167.4
	S.D.	7.71	9.37	7.56	10.01
	N	5	5	5	5
DAY 0	MEAN	177.1	179.1	182.7	178.5
	S.D.	10.80	11.82	13.26	12.36
	N	5	5	5	5
DAY 4	MEAN	187.1	195.8	201.9	187.0
	S.D.	11.73	13.79	17.32	7.77
	N	5	5	5	5
DAY 7	MEAN	199.1	206.3	211.7	192.7
	S.D.	15.33	9.06	12.26	8.61
	N	5	5	5	5
DAY 10	MEAN	212.7	217.4	225.4	199.9
	S.D.	15.25	11.16	18.02	10.52
	N	5	5	5	5
DAY 13	MEAN	221.8	228.1	236.8	213.0
	S.D.	15.22	12.04	24.10	12.06
	N	5	5	5	5

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

Analysis of Variance using DUNNETT'S Procedure

Table 8

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

DRAFT

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 106 SEX: FEMALE

PERIOD [a]	DOSE: (mg/kg) GROUP:	0 1-F	0.5 2-F	2.0 3-F	6.2 4-F
DAY 4 [b]	MEAN	10.0	16.7	19.2	8.5
	S.D.	3.80	4.16	4.45	12.54
	N	5	5	5	5
DAY 7	MEAN	12.0	10.5	9.9	5.8
	S.D.	9.48	9.03	9.15	8.84
	N	5	5	5	5
DAY 10	MEAN	13.6	11.0	13.7	7.2
	S.D.	12.03	6.95	7.45	2.22
	N	5	5	5	5
DAY 13	MEAN	9.1	10.7	11.4	13.1
	S.D.	7.08	2.16	8.16	6.78
	N	5	5	5	5
TOTAL GAIN	MEAN	44.6	49.0	54.1	34.5
	S.D.	7.15	5.94	13.44	12.01
	N	5	5	5	5

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

Analysis of Variance using DUNNETT'S Procedure

a = Successive periods
b = Baseline is Day 0

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR242511 IN RATS

DRAFT

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 106 SEX: MALE

PERIOD [a]	DOSE:(mg/kg) GROUP:	0 1-M	0.5 2-M	2.0 3-M	6.2 4-M
DAY 0 [b]	INTAKE (g)	20.6	20.6	18.9	20.6
	S.D.	0.67	0.98	2.52	2.33
	N	5	5	5	5
DAY 4	INTAKE (g)	23.1	22.9	22.3	20.0
	S.D.	1.07	2.36	2.01	2.50
	N	5	5	5	5
DAY 7	INTAKE (g)	24.9	23.6	23.0	18.0**
	S.D.	1.04	1.08	2.23	2.76
	N	5	5	5	5
DAY 10	INTAKE (g)	27.2	40.7	23.8	12.4
	S.D.	3.40	20.51	4.61	6.31
	N	4	4	5	5
DAY 13	INTAKE (g)	25.1	24.0	24.5	13.7**
	S.D.	1.21	0.15	2.03	10.39
	N	5	5	5	4

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

Analysis of Variance using DUNNETT'S Procedure

a = Successive periods
b = Food was weighed in on Day -5

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

DRAFT

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 106 SEX: FEMALE

PERIOD[a]	DOSE:(mg/kg) GROUP:	0 1-F	0.5 2-F	2.0 3-F	6.2 4-F
DAY 0[b]	INTAKE (g)	15.2	14.7	17.6	15.5
	S.D.	1.40	1.97	2.04	2.48
	N	5	5	5	5
DAY 4	INTAKE (g)	16.2	16.8	18.7	13.9
	S.D.	1.91	1.50	1.78	2.40
	N	5	5	5	5
DAY 7	INTAKE (g)	19.4	19.3	20.5	14.9*
	S.D.	2.25	0.67	2.74	2.51
	N	5	5	5	5
DAY 10	INTAKE (g)	27.9	20.6	22.5	16.1*
	S.D.	7.55	3.91	4.75	4.94
	N	4	5	5	5
DAY 13	INTAKE (g)	21.0	19.0	20.6	17.6
	S.D.	4.52	1.42	2.27	1.39
	N	5	5	5	5

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

Analysis of Variance using DUNNETT'S Procedure

a = Successive peroids
b = Food was weighed in on Day -5

Table 11

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: DAY 14

STUDY ID: 106
STUDY NO: 106

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	ALT	AST	TP	ALB	GLOB	A/G	TBA	ALKP	CHOL
UNITS:	U/L	U/L	g/dL	g/dL	g/dL	-	mg/dL	U/L	mg/dL
Group: 1-M : 0 mg base/kg/day									
MEAN	58	101	7.6	4.1	3.5	1.16	58.8	296	54
SD	6.8	8.8	0.34	0.34	0.18	0.123	34.14	76.2	8.4
N	5	5	5	5	5	5	5	5	5
Group: 2-M : 0.5 mg base/kg/day									
MEAN	54	99	6.9	3.7	3.1	1.20	47.6	334	49
SD	6.8	21.5	0.33	0.19	0.24	0.102	10.61	66.5	2.9
N	5	5	5	5	5	5	5	5	5
Group: 3-M : 2.0 mg base/kg/day									
MEAN	58	116	7.4	4.1	3.3	1.27	54.6	276	58
SD	5.0	18.1	0.39	0.30	0.21	0.117	20.61	64.2	5.5
N	5	5	5	5	5	5	5	5	5
Group: 4-M : 6.2 mg base/kg/day									
MEAN	213**	303**	7.4	4.2	3.2	1.32	96.6	278	52
SD	116.0	117.8	1.02	0.52	0.56	0.126	63.97	54.1	11.9
N	4	4	4	4	4	4	4	4	4

**-Significant Difference from Control P < .01

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: DAY 14

STUDY ID: 106
STUDY NO: 106

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	TRY	BUN	CREA	NA	K	CL	CA	IP	GLU
UNITS:	mg/dL	mg/dL	mg/dL	mmol/L	mmol/L	mEq/L	mg/dL	mg/dL	mg/dL
Group: 1-M : 0 mg base/kg/day									
MEAN	81	18.7	0.49	144	6.15	117	11.1	11.1	137
SD	50.8	2.18	0.037	2.3	0.282	1.8	0.27	0.50	13.7
N	5	5	5	5	5	5	5	5	5
Group: 2-M : 0.5 mg base/kg/day									
MEAN	46	16.9	0.51	142	5.97	116	10.7	10.6	133
SD	14.1	3.26	0.042	1.9	0.328	5.0	0.43	1.15	17.0
N	5	5	5	5	5	5	5	5	5
Group: 3-M : 2.0 mg base/kg/day									
MEAN	64	19.2	0.52	143	6.64	117	11.4	11.9	125
SD	25.5	2.17	0.082	2.1	0.605	1.6	0.28	1.28	15.7
N	5	5	5	5	5	5	5	4	5
Group: 4-M : 6.2 mg base/kg/day									
MEAN	37	22.1	0.55	145	5.97	115	11.0	9.3*	119
SD	8.6	6.86	0.037	1.7	0.317	2.5	0.40	0.98	8.2
N	4	4	4	4	4	4	4	4	4

*-Significant Difference from Control P < .05

Table 12

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: DAY 14

STUDY ID: 106
STUDY NO: 106

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	ALT	AST	TP	ALB	GLOB	A/G	TBA	ALKP	CHOL
UNITS:	U/L	U/L	g/dL	g/dL	g/dL	-	mg/dL	U/L	mg/dL
Group: 1-F : 0 mg base/kg/day									
MEAN	57	100	7.3	4.1	3.2	1.27	23.0	239	60
SD	8.1	11.0	0.35	0.15	0.23	0.061	7.61	85.9	9.7
N	5	5	5	5	5	5	5	5	5
Group: 2-F : 0.5 mg base/kg/day									
MEAN	65	110	7.5	4.1	3.4	1.20	32.3	212	56
SD	12.7	18.8	0.66	0.33	0.37	0.077	6.08	63.0	7.1
N	5	5	5	5	5	5	5	5	5
Group: 3-F : 2.0 mg base/kg/day									
MEAN	54	100	6.9	3.8	3.1	1.23	23.0	215	56
SD	2.7	15.0	0.27	0.11	0.20	0.070	7.55	53.7	4.6
N	5	5	5	5	5	5	5	5	5
Group: 4-F : 6.2 mg base/kg/day									
MEAN	68	124	7.6	4.3	3.3	1.28	79.1	160	70
SD	13.9	22.2	0.46	0.21	0.33	0.115	79.91	19.9	7.3
N	5	5	5	5	5	5	5	5	5

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: DAY 14

STUDY ID: 106
STUDY NO: 106

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	TRY	BUN	CREA	NA	K	CL	CA	IP	GLU
UNITS:	mg/dL	mg/dL	mg/dL	mmol/L	mmol/L	mEq/L	mg/dL	mg/dL	mg/dL
Group: 1-F : 0 mg base/kg/day									
MEAN	35	15.7	0.51	143	5.90	114	11.2	9.6	135
SD	3.9	3.33	0.024	2.6	0.220	4.5	0.37	0.57	15.7
N	5	5	5	5	5	5	5	5	5
Group: 2-F : 0.5 mg base/kg/day									
MEAN	44	15.6	0.53	142	5.93	118	11.2	9.9	122
SD	13.0	1.70	0.038	1.1	0.549	1.8	0.24	0.77	17.3
N	5	5	5	5	5	5	5	5	5
Group: 3-F : 2.0 mg base/kg/day									
MEAN	42	13.4	0.52	142	5.89	114	10.8	10.0	114
SD	10.9	2.84	0.033	2.9	0.264	3.4	0.29	0.44	14.5
N	5	5	5	5	5	5	5	5	5
Group: 4-F : 6.2 mg base/kg/day									
MEAN	53	15.7	0.55	144	5.68	116	11.2	9.9	140
SD	13.3	1.66	0.058	1.8	0.169	3.5	0.19	0.93	29.5
N	5	5	5	5	5	5	5	5	5

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
PERIOD: DAY 14

STUDY ID: 106 SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	RBC	HGB	HCT	MCV	MCH	MCHC	RETICS	NRBC	HB
UNITS:	10^6/cmm	g/dL	%	fL	pg	g/dL	% RBCs	COUNT	%
Group: 1-M : 0 mg base/kg/day									
MEAN	7.43	16.0	44.3	59.7	21.5	36.0	1.2	0	0.0
SD	0.350	0.39	1.30	1.40	0.50	0.43	0.84	0.0	0.04
N	5	5	5	5	5	5	5	5	5
Group: 2-M : 0.5 mg base/kg/day									
MEAN	7.19	15.4	42.6	59.3	21.5	36.2	0.5	0	0.0
SD	0.230	0.49	1.41	1.57	0.73	0.76	0.35	0.9	0.00
N	5	5	5	5	5	5	5	5	5
Group: 3-M : 2.0 mg base/kg/day									
MEAN	7.23	15.9	44.8	62.0	22.0	35.6	1.2	0	0.0
SD	0.219	0.69	1.53	1.60	0.74	0.35	0.66	0.9	0.00
N	5	5	5	5	5	5	5	5	5
Group: 4-M : 6.2 mg base/kg/day									
MEAN	7.26	15.9	44.6	61.8	21.9	35.6	3.5	0	0.0
SD	0.721	1.32	1.07	4.75	0.58	2.33	3.85	0.0	0.00
N	4	4	4	4	4	4	4	4	4

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
PERIOD: DAY 14

STUDY ID: 106 SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	%METHGB	PLT	WBC M	Neutroph I	Neutroph	Lymphocyte	Monocytes	Eosinophil	Basophils
UNITS:	%	10^3/ccm	10^3/cmm	10^3/cmm	10^3/cmm	10^3/cmm	10^3/cmm	10^3/cmm	10^3/cmm
Group: 1-M : 0 mg base/kg/day									
MEAN	0.4	1223	18.1	2.0	0.5	15.4	0.3	0.0	0.0
SD	0.24	75.2	3.45	0.96	0.42	2.63	0.31	0.00	0.00
N	5	5	5	5	5	5	5	5	5
Group: 2-M : 0.5 mg base/kg/day									
MEAN	0.9	1164	17.4	1.9	0.4	14.5	0.4	0.2	0.0
SD	0.37	62.7	2.30	0.65	0.31	2.68	0.25	0.04	0.00
N	5	5	5	5	5	5	5	5	5
Group: 3-M : 2.0 mg base/kg/day									
MEAN	5.5**	1047	23.7*	2.0	0.8	20.4*	0.3	0.1	0.0
SD	0.39	116.7	3.08	0.76	0.13	2.61	0.24	0.22	0.00
N	5	5	5	5	5	5	5	5	5
Group: 4-M : 6.2 mg base/kg/day									
MEAN	5.4**	1065	24.4*	3.1	1.1	18.9	1.3**	0.0	0.0
SD	3.55	164.0	4.50	1.14	0.58	4.07	0.60	0.00	0.00
N	4	4	4	4	4	4	4	4	4

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
PERIOD: DAY 14

STUDY ID: 106 SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	RBC	HGB	HCT	MCV	MCH	MCHC	RETICS	NRBC	HB
UNITS:	10^6/cmm	g/dL	%	fL	pg	g/dL	% RBCs	COUNT	%
Group: 1-F : 0 mg base/kg/day									
MEAN	7.11	16.1	43.3	60.9	22.6	37.2	0.7	0	0.0
SD	0.354	0.76	1.83	0.83	0.18	0.38	0.33	0.0	0.00
N	5	5	5	5	5	5	5	5	5
Group: 2-F : 0.5 mg base/kg/day									
MEAN	7.03	15.6	42.0	59.8	22.3	37.3	0.9	0	0.0
SD	0.378	0.81	1.55	1.22	0.25	0.92	0.32	0.4	0.00
N	5	5	5	5	5	5	5	5	5
Group: 3-F : 2.0 mg base/kg/day									
MEAN	6.43	14.5**	39.7*	61.9	22.7	36.6	1.0	0	0.0
SD	0.486	0.45	1.33	3.66	1.57	0.65	0.42	0.0	0.00
N	5	5	5	5	5	5	5	5	5
Group: 4-F : 6.2 mg base/kg/day									
MEAN	5.91**	13.7**	39.6*	67.1**	23.2	34.5**	3.5**	0	0.0
SD	0.529	0.82	2.28	2.51	0.89	0.65	1.72	0.5	0.00
N	5	5	5	5	5	5	5	5	5

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

SUMMARY OF HEMATOLOGY TESTS
PERIOD: DAY 14

STUDY ID: 106 SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	%METHGB	PLT	WBC M	Neutroph I	Neutroph	Lymphocyte	Monocytes	Eosinophil	Basophils
UNITS:	%	10^3/ccm	10^3/cmm	10^3/cmm	10^3/cmm	10^3/cmm	10^3/cmm	10^3/cmm	10^3/cmm
Group: 1-F : 0 mg base/kg/day									
MEAN	0.5	1058	12.5	1.0	0.3	10.7	0.3	0.2	0.0
SD	0.33	179.5	4.91	0.28	0.29	4.84	0.15	0.20	0.00
N	5	5	5	5	5	5	5	5	5
Group: 2-F : 0.5 mg base/kg/day									
MEAN	1.0	1104	15.1	2.7	0.6	11.3	0.3	0.1	0.0
SD	1.25	173.8	3.09	1.24	0.18	2.54	0.38	0.11	0.04
N	5	5	5	5	5	5	5	5	5
Group: 3-F : 2.0 mg base/kg/day									
MEAN	3.6**	1107	14.7	2.5	0.2	11.4	0.5	0.1	0.0
SD	0.85	110.5	1.70	1.72	0.25	2.74	0.20	0.09	0.00
N	5	5	5	5	5	5	5	5	5
Group: 4-F : 6.2 mg base/kg/day									
MEAN	5.3**	940	25.7**	3.2*	1.5**	20.5*	0.4	0.2	0.0
SD	0.91	136.5	7.99	1.00	0.93	6.90	0.29	0.18	0.00
N	5	5	5	5	5	5	5	5	5

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

Table 15

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR242511 IN RATS

DRAFT

ORGAN WEIGHT SUMMARY (% BODY WEIGHT)

STUDY: 106
SEX: MALE

ALL FATES ALL DAYS ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(1) 1-M	(2) 2-M	(3) 3-M	(4) 4-M
BRAIN (% BODY WEIGHT)					
	MEAN	0.683	0.658	0.690	0.856
	SD	0.0338	0.0306	0.0441	0.2160
	N	5	5	5	4
HEART (% BODY WEIGHT)					
	MEAN	0.407	0.376	0.394	0.429
	SD	0.0341	0.0280	0.0199	0.0401
	N	5	5	5	4
KIDNEYS (% BODY WEIGHT)					
	MEAN	0.957	0.968	0.995	1.012
	SD	0.1114	0.0699	0.0808	0.1187
	N	5	5	5	4
LIVER (% BODY WEIGHT)					
	MEAN	4.261	4.334	4.102	5.045*
	SD	0.3357	0.4018	0.3547	0.2311
	N	5	5	5	4
SPLEEN (% BODY WEIGHT)					
	MEAN	0.205	0.219	0.290	0.390**
	SD	0.0219	0.0191	0.0315	0.1407
	N	5	5	5	4
TESTES (% BODY WEIGHT)					
	MEAN	1.357	1.318	1.360	1.618
	SD	0.0656	0.1050	0.0909	0.4277
	N	5	5	5	4

(1)-0 mg base/kg/day
(2)-0.5 mg base/kg/day
(3)-2.0 mg base/kg/day
(4)-6.2 mg base/kg/day
* - Significant difference P<.05
** - Significant difference P<.01

Table 16

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

DRAFT

ORGAN WEIGHT SUMMARY (ABSOLUTE)

STUDY: 106
SEX: MALE

ALL FATES ALL DAYS ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(1) 1-M	(2) 2-M	(3) 3-M	(4) 4-M
BODY WEIGHT (G)					
	MEAN	292.3	289.1	289.5	237.8*
	SD	11.11	9.66	20.78	54.03
	N	5	5	5	4
BRAIN (G)					
	MEAN	1.993	1.900	1.991	1.952
	SD	0.0286	0.0768	0.0745	0.0952
	N	5	5	5	4
HEART (G)					
	MEAN	1.190	1.088	1.141	1.031
	SD	0.0994	0.0933	0.1147	0.3120
	N	5	5	5	4
KIDNEYS (G)					
	MEAN	2.797	2.798	2.872	2.394
	SD	0.3538	0.2056	0.1583	0.5469
	N	5	5	5	4
LIVER (G)					
	MEAN	12.465	12.518	11.852	11.916
	SD	1.2465	1.1171	0.9823	2.3009
	N	5	5	5	4
SPLEEN (G)					
	MEAN	0.597	0.633	0.840	0.983
	SD	0.0412	0.0626	0.1150	0.5515
	N	5	5	5	4
TESTES (G)					
	MEAN	3.963	3.815	3.927	3.696
	SD	0.1747	0.3874	0.1688	0.3729
	N	5	5	5	4

(1)-0 mg base/kg/day
(2)-0.5 mg base/kg/day
(3)-2.0 mg base/kg/day
(4)-6.2 mg base/kg/day
* - Significant difference P<.05

Table 17

DRAFT

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR242511 IN RATS

ORGAN WEIGHT SUMMARY (% BODY WEIGHT)

STUDY: 106
SEX: FEMALE

ALL FATES ALL DAYS ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(5) 1-F	(6) 2-F	(7) 3-F	(8) 4-F
BRAIN (% BODY WEIGHT)					
	MEAN	0.882	0.879	0.838	0.938
	SD	0.0398	0.0813	0.0470	0.0175
	N	5	5	5	5
HEART (% BODY WEIGHT)					
	MEAN	0.431	0.415	0.404	0.471
	SD	0.0271	0.0246	0.0234	0.0613
	N	5	5	5	5
KIONEYS (% BODY WEIGHT)					
	MEAN	1.016	0.965	1.031	0.982
	SD	0.0725	0.0717	0.0426	0.0704
	N	5	5	5	5
LIVER (% BODY WEIGHT)					
	MEAN	4.342	4.194	4.365	4.480
	SD	0.2893	0.1820	0.3566	0.3522
	N	5	5	5	5
OVARY (% BODY WEIGHT)					
	MEAN	0.064	0.063	0.067	0.055
	SD	0.0145	0.0110	0.0077	0.0140
	N	5	5	5	5
SPLEEN (% BODY WEIGHT)					
	MEAN	0.257	0.268	0.347*	0.605**
	SD	0.0463	0.0273	0.0264	0.0721
	N	5	5	5	5

(5)-0 mg base/kg/day
(6)-0.5 mg base/kg/day
(7)-2.0 mg base/kg/day
(8)-6.2 mg base/kg/day
* - Significant difference P<.05
** - Significant difference P<.01

Table 18

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

DRAFT

ORGAN WEIGHT SUMMARY (ABSOLUTE)

STUDY: 106
SEX: FEMALE

ALL FATES ALL DAYS ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

	GROUP:	(5) 1-F	(6) 2-F	(7) 3-F	(8) 4-F
BODY WEIGHT (G)					
	MEAN	206.8	213.2	220.6	198.1
	SD	11.28	10.27	19.63	10.08
	N	5	5	5	5
BRAIN (G)					
	MEAN	1.822	1.867	1.842	1.857
	SD	0.0696	0.0901	0.0932	0.0727
	N	5	5	5	5
HEART (G)					
	MEAN	0.892	0.886	0.889	0.932
	SD	0.0722	0.0715	0.0782	0.1344
	N	5	5	5	5
KIDNEYS (G)					
	MEAN	2.107	2.054	2.273	1.947
	SD	0.2503	0.1333	0.1979	0.1981
	N	5	5	5	5
LIVER (G)					
	MEAN	8.982	8.944	9.617	8.884
	SD	0.7986	0.6129	1.0087	0.9634
	N	5	5	5	5
OVARY (G)					
	MEAN	0.131	0.135	0.146	0.110
	SD	0.0294	0.0253	0.0076	0.0238
	N	5	5	5	5
SPLEEN (G)					
	MEAN	0.535	0.571	0.764**	1.197**
	SD	0.1203	0.0695	0.0559	0.1457
	N	5	5	5	5

(5)-0 mg base/kg/day
(6)-0.5 mg base/kg/day
(7)-2.0 mg base/kg/day
(8)-6.2 mg base/kg/day
** - Significant difference P<.01

Table 19

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

Summary of Microscopic Lesions[a]

		Dose (mg base/kg/day)			
ORGAN - lesion	Sex	0	0.5	2.0	6.2
Liver - Necrosis	M	0/5 (0.00)	0/5 (0.00)	0/5 (0.00)	3/5 (1.00)
	F	0/5 (0.00)	0/5 (0.00)	0/5 (0.00)	0/5 (0.00)
Spleen - Extramedullary hematopoiesis	M	0/5 (0.00)	0/5 (0.00)	3/5 (0.60)	2/5 (0.60)
	F	0/5 (0.00)	0/5 (0.00)	1/5 (0.20)	5/5 (1.80)

[a]Incidence (mean group severity) - Mean group severity was determined by dividing the sum of all severity scores for a finding by the number of tissues examined. See Pathology Report in Appendix 9.

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APPENDIX 1

Analytical Chemistry Methodology and Dosage Formulation Analysis

DRAFT

PURITY AND IDENTITY STUDY AND SAMPLES IN 1% METHYLCELLULOSE AND 0.2% TWEEN 80 ANALYSIS OF 8-[(4-AMINO-1-METHYLBUTYL)AMINO]-5-(1-HEXYLOXY-6-METHOXY-4-METHYLQUINOLINE DL-TARTRATE (WR242511). STUDY NO. 106

ANALYSTS: ADAM NEGRUSZ
A.KARL LARSEN, JR.

STUDY SITE: FORENSIC TOXICOLOGY 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: AUGUST 16, 1993

APPROVED: AUGUST 16, 1993
DR. EUGENE F. WOODS, Ph.D.

E. Woods

OBJECTIVE

The objective of this study was to confirm the initial identity, establish the purity of WR242511 and to develop the analytical method for dosage formulation analysis.

WR242511 samples were submitted for analysis June 22, 1993 and June 30, 1993. Results are found on pages 10 and 11.

In low concentration WR242511 is stable for 48 hours (<10% loss). In high concentration drug is stable during two weeks period of time. This will be reported with the longer term toxicological studies.

EXPERIMENTAL

The subject sample - WR242511 was supplied by the Toxicology Research Laboratory and stored at -20^{0}C when it was not analyzed.

Description

A fine yellow powder, no obvious odor.

Spectrum

An ultraviolet spectrum (Figure I) recorded on a Shimadzu Spectronic 200 UV spectrometer (dual beam), was obtained from 20 ug/ml solution of WR242511 prepared in mobile phase. The sample was found with maximal absorptivity observed at 212 nm and 264 nm.

ANALYTICAL METHOD

Reagents

Subject sample (WR242511) 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 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 (ug 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^{0}C until analyzed.

Controls

Control A (0.639 mg base/ml), control B (2.84 mg base/ml) and control C (7.81 mg base/ml) were prepared by weighing 90 mg, 400 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^{0}C until analyzed.

Analytical Procedure

One set of WR242511 calibration standards and three vials of each stock control solutions were removed from a -20^{0}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.

HPLC System

See 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:

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

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

PURITY

HPLC System

Solvent Delivery System:	Perkin-Elmer Series 3B Pump
Injector:	Rheodyne 7125 with 50 ul sample loop
Analytical Column:	Spherisorb CN 5u, 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 ul 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:

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

Results

Typical chromatograms are shown in Figure II. 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%, follow 99.59% ± 0.04%. The assay results are presented in Table I and II.

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^{0}C, oven temp. 70^{0}C initial, 280^{0}C final, 15^{0}C/minute ramp, carrier gas - helium, flow rate 2 ml/minute, split ratio 10:1

Procedure

Subject sample (WR242511) was submitted from the Toxicology Research Laboratory. The sample was dissolved in methanol to a concentration of 0.71 ug base/ml and a 2 ul 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 molecular weight. Major fragments of WR242511 sample are m/e 84, 175, 203, 288.

Figure III shows the mass spectrum of the initial WR242511 sample.

FIGURE I

DRAFT

ULTRAVIOLET SPECTRUM OF WR242511

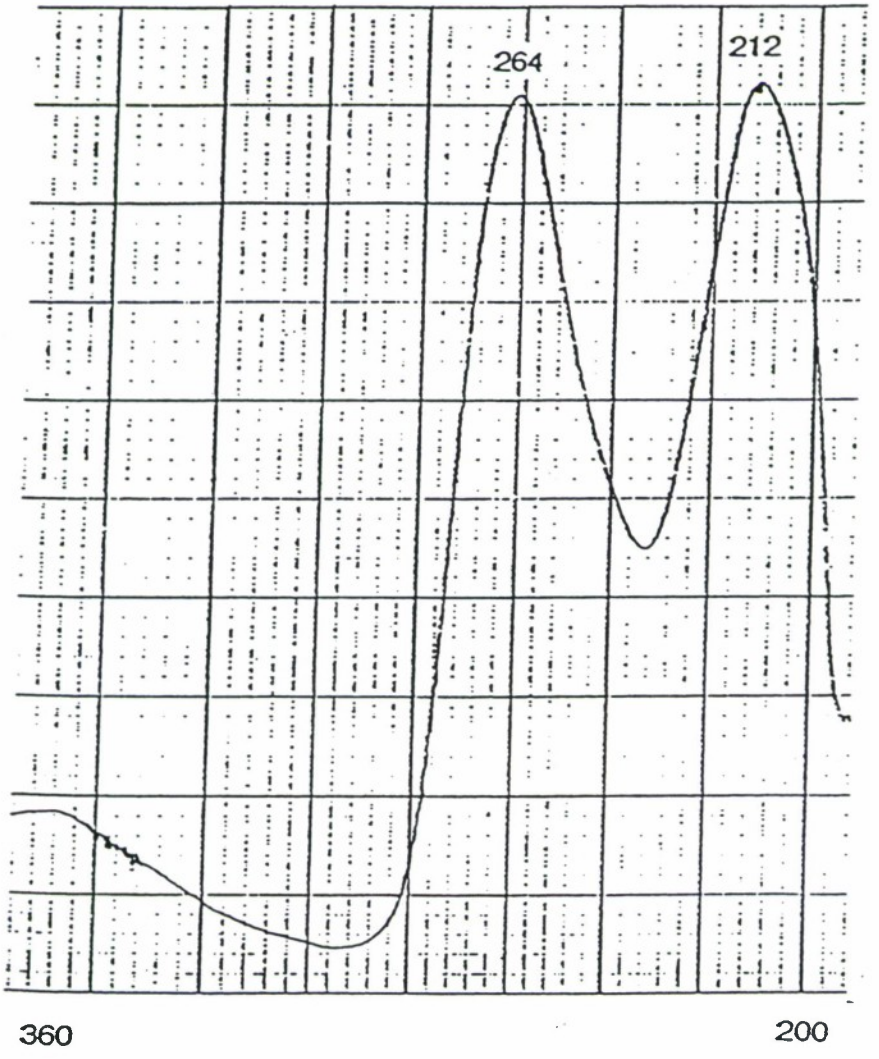
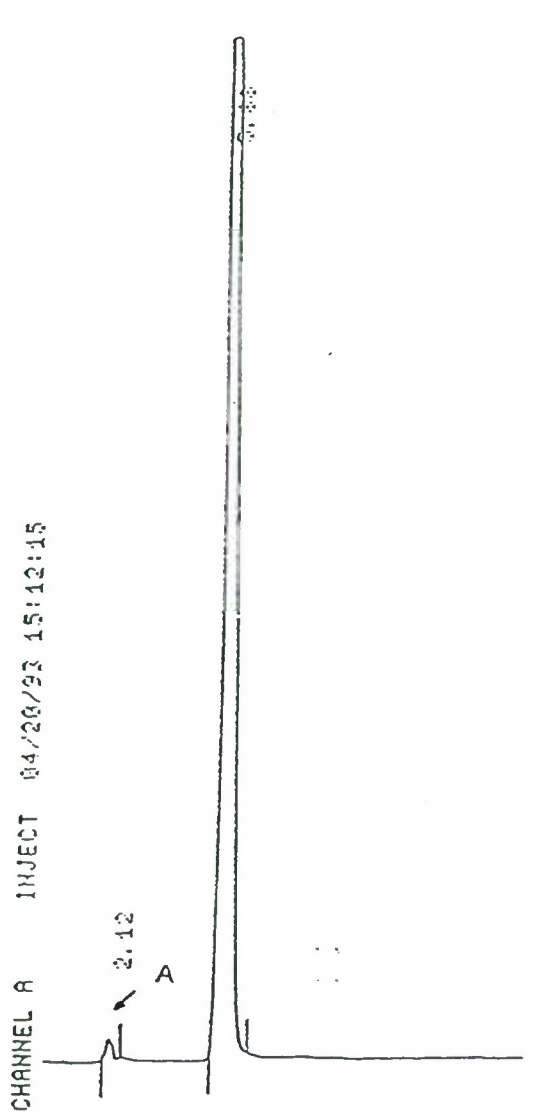


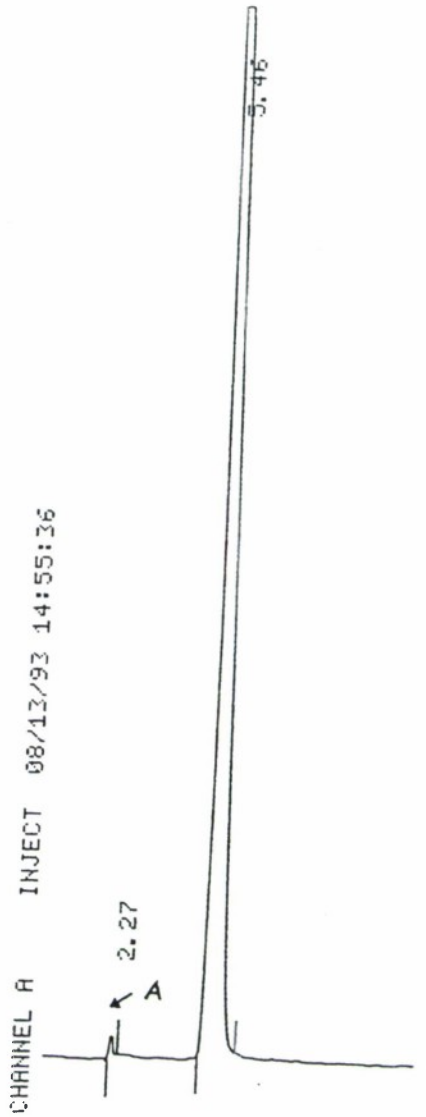
FIGURE II

DRAFT

CHROMATOGRAMS OF WR242511 SAMPLE (CONCENTRATION 0.71 MG BASE/ML, 225 NM)
A - INITIAL SAMPLE, B - FOLLOW SAMPLE



A



B

FIGURE III

DRAFT

MASS SPECTRUM OF INITIAL WR242511 SAMPLE

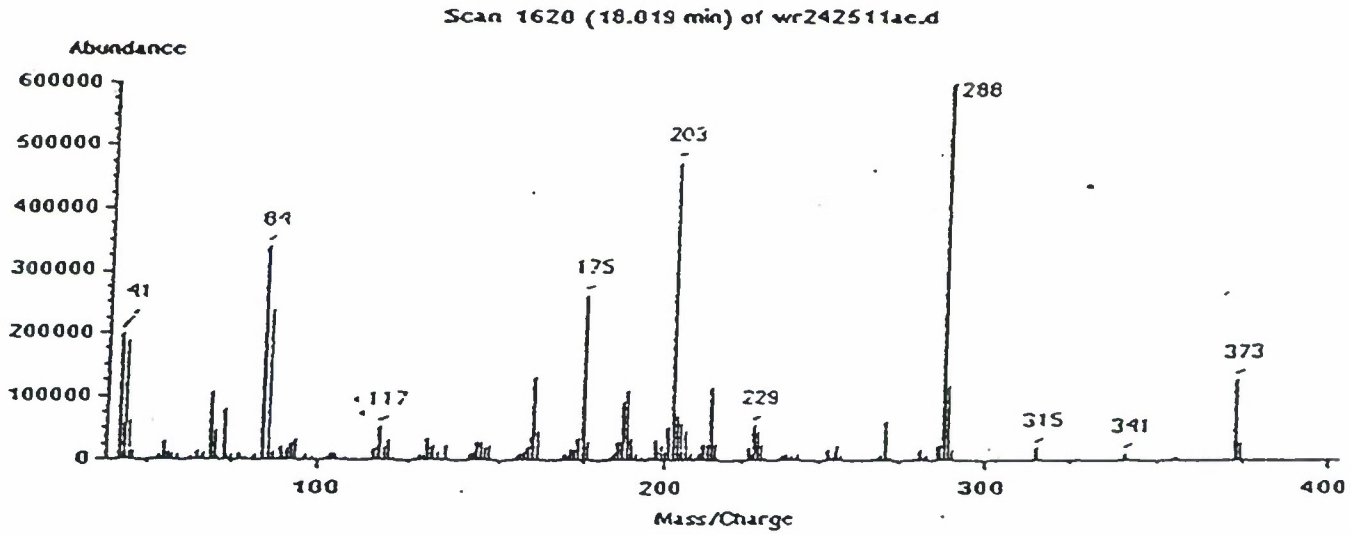


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TABLE I

PURITY DATA FOR WR242511 PRIOR TO INITIATING STUDY NO. 106

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 II

PURITY DATA FOR WR242511 FOLLOWING COMPLETION OF STUDY NO. 106

Solutions

Peak Identity	1	2	3	4	5	6
A	2624	2553	2838	2756	2666	2752
WR242511	686608	679701	699864	692324	692938	695120
% Purity	99.567	99.626	99.530	99.603	99.617	99.600

Mean ± S.D. - 99.591 ± 0.036

MEMO DRAFT

DATE: June 23, 1993

TO: Dr. Barry S. Levine

FROM: Adam Negrusz
Forensic Toxicology Laboratory
College of Pharmacy

RE: WR242511 samples submitted for analysis June 23, 1993.

WR242511 Concentration
(mg base/ml)

Sample Identification	Mean (± SD)
YELLOW (0.1)	0.1003 ± 0.0037
GREEN (0.4)	0.3992 ± 0.0067
ORANGE (1.24)	1.2044 ± 0.0037

MEMO DRAFT

DATE: June 30, 1993

TO: Dr. Barry S. Levine

FROM: Adam Negrusz
Forensic Toxicology Laboratory
College of Pharmacy

RE: WR242511 samples submitted for analysis June 30, 1993.

WR242511 Concentration
(mg base/ml)

Sample Identification	Mean (± SD)
YELLOW (0.1)	0.0986 ± 0.0003
GREEN (0.4)	0.4091 ± 0.0036
ORANGE (1.24)	1.2670 ± 0.0136
YELLOW WITH BLACK DOT (1.9)	1.9721 ± 0.0410

APPENDIX 2

Clinical Pathology Methodology

HEMATOLOGY

DRAFT

Hemoglobin
Cyanomethemoglobin method
Sysmex 180A Hematology Analyzer

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

Erythrocyte Count
Electronic counting procedure
Sysmex 180A Hematology Analyzer

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

Leukocyte Count
Electronic counting procedure
Sysmex 180A Hematology Analyzer

Platelet Count
Electronic counting procedure
Sysmex 180A Hematology Analyzer

Reticulocyte Count
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.

Glucose
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.

Heinz Bodies
Methyl Violet staining technique

Methemoglobin
Cyanomethemoglobin Method
Ciba-Corning 550 Express Clinical Chemistry System
Evelyn, K.A., and Malloy, H.T.
J. Biol. Chem., 126, 655, 1938

Test Directory

STUDY: 106

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.	RETICS % RBCs	Reticulocytes (%RBCs) 0.0	NO			0.0	0.0	1.0	1.0
6.	HB %	Heinz Bodies 0.0	NO			0.0	0.0	20.0	20.0
7.	%METHGB %	% Methemoglobin 0.0	NO			0.0	0.0	3.0	3.0
8.	PLT 10^3/ccm	Platelets Integer	NO			900	900	1300	1300
9.	WBC 10^3/cmm	Leukocytes 0.0	NO			9.0	9.0	18.0	18.0
10.	MCH pg	Mean Corpuscular Hemo. 0.0	NO			10.0	10.0	60.0	60.0
11.	MCHC g/dL	Mean Corpus. Hemo. Conc. 0.0	NO			10.0	10.0	50.0	50.0

STUDY 106 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) 10-SEP-1993

STUDY 106 DETAIL DICTIONARY

	ABBR	DESCRIPTION
1.	S	Slight
2.	M	Moderate
3.	G	Gross
4.	1	Slight
5.	2	Moderate
6.	3	Mod. to Marked
7.	4	Marked

(END OF REPORT) 10-SEP-1993

Glucose
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.

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

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

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

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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.

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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.

Aspartate Aminotransferase (AST/GOT)
Based on the methodology of the IFCC
Ciba-Corning 550 Express Clinical Chemistry System
IFCC, Committee on Standards, Part 2. IFCC
Method for Aspartate Aminotransferase, Amsterdam,
Elsevier Scientific Publishing Company (1975)

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)

Na+, K+

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

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
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Chloride

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.

Cholesterol

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Ciba-Corning 550 Express Clinical Chemistry System
Allain, C. C., et al.
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Triglycerides

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.

Total Bile Acids

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.

Test Directory

STUDY: 106

NO.	ABBR. UNITS	DESCRIPTION PRECISION	CALCULATED	OPERAND A	OPERAND B	---LOWER LIMIT--- MALE	FEMALE	---UPPER LIMIT--- MALE	FEMALE
1.	ALT U/L	Alanine Aminotransferase Integer	NO			30	30	70	70
2.	TP g/dL	Total Protein 0.0	NO			5.3	5.3	8.5	8.5
3.	ALB g/dL	Albumin 0.0	NO			3.4	3.4	5.6	5.6
4.	TBA mg/dL	Total Bile Acid 0.0	NO			0.0	0.0	100.0	100.0
5.	ALKP U/L	Alkaline Phosphatase Integer	NO			60	60	300	300
6.	CHOL mg/dL	Cholesterol Integer	NO			25	25	100	100
7.	TRY mg/dL	Triglycerides Integer	NO			25	25	100	100
8.	BUN mg/dL	Blood Urea Nitrogen 0.0	NO			7.0	7.0	22.0	22.0
9.	CREA mg/dL	Creatinine 0.00	NO			0.40	0.40	0.80	0.80
10.	NA mmol/L	Sodium Integer	NO			140	140	148	148
11.	K mmol/L	Potassium 0.00	NO			5.00	5.00	7.00	7.00
12.	CL mEq/L	Chloride Integer	NO			95.0	95.0	112.0	112.0
13.	CA mg/dL	Calcium 0.0	NO			9.5	9.5	12.0	12.0
14.	IP mg/dL	Inorganic Phosphorus 0.0	NO			9.5	9.5	12.0	12.0
15.	GLU mg/dL	Glucose Integer	NO			80	80	150	150

Test Directory

STUDY: 106

NO.	ABBR. / UNITS	DESCRIPTION / PRECISION	CALCULATED	OPERAND A	OPERAND B	---LOWER LIMIT--- MALE	---LOWER LIMIT--- FEMALE	---UPPER LIMIT--- MALE	---UPPER LIMIT--- FEMALE
16.	GLOB g/dL	Globulin 0.0	Operand A - Operand B	TP	ALB	2.0	2.0	4.5	4.5
17.	A/G -	A/G Ratio 0.00	Operand A / Operand B	ALB	GLOB	1.00	1.00	2.00	2.00
18.	AST U/L	Aspartate Aminotransferase Integer	NO			50	50	160	160

(END OF REPORT)

07-SEP-1993

APPENDIX 3

Individual Observations

INDIVIDUAL OBSERVATIONS

STUDY: 106 GROUP: 1-M SEX: MALE
DAY 0-DAY 14 DOSE: 0(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
301	Normal			DAY 0-DAY 1
	Normal			DAY 3-DAY 13
	Rough Coat			DAY 2
	Scheduled Sacrifice			DAY 14
302	Normal			DAY 0-DAY 1
	Normal			DAY 3-DAY 13
	Rough Coat			DAY 2
	Scheduled Sacrifice			DAY 14
303	Normal			DAY 0-DAY 1
	Normal			DAY 4-DAY 13
	Rough Coat			DAY 2-DAY 3
	Scheduled Sacrifice			DAY 14
304	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14
305	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14

INDIVIDUAL OBSERVATIONS

STUDY: 106 GROUP: 2-M SEX: MALE
DAY 0-DAY 14 DOSE: 0.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
311	Normal			DAY 0-DAY 1
	Normal			DAY 4-DAY 13
	Rough Coat			DAY 2-DAY 3
	Scheduled Sacrifice			DAY 14
312	Normal			DAY 0-DAY 1
	Normal			DAY 4-DAY 13
	Rough Coat			DAY 2-DAY 3
	Scheduled Sacrifice			DAY 14
313	Normal			DAY 0-DAY 1
	Normal			DAY 5
	Normal			DAY 8-DAY 13
	Rough Coat			DAY 2-DAY 4
	Rough Coat			DAY 6-DAY 7
	Scheduled Sacrifice			DAY 14
314	Normal			DAY 0-DAY 1
	Normal			DAY 5-DAY 13
	Rough Coat			DAY 2-DAY 4
	Scheduled Sacrifice			DAY 14
315	Normal			DAY 0-DAY 1
	Normal			DAY 4-DAY 13
	Rough Coat			DAY 2-DAY 3
	Scheduled Sacrifice			DAY 14

INDIVIDUAL OBSERVATIONS

STUDY: 106 GROUP: 4-M SEX: MALE
DAY 0-DAY 14 DOSE: 6.2(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
331	Hunched Posture			DAY 2
	Normal			DAY 0-DAY 1
	Normal			DAY 4
	Normal			DAY 7-DAY 12
	Rough Coat			DAY 2-DAY 3
	Rough Coat			DAY 5-DAY 6
	Rough Coat			DAY 13
	Scheduled Sacrifice			DAY 14
332	Hunched Posture			DAY 2
	Normal			DAY 0-DAY 1
	Normal			DAY 4-DAY 12
	Rough Coat			DAY 2-DAY 3
	Rough Coat			DAY 13
	Scheduled Sacrifice			DAY 14
333	Hunched Posture			DAY 2-DAY 4
	Hunched Posture			DAY 12-DAY 13
	Normal			DAY 0-DAY 1
	Normal			DAY 6-DAY 11
	Rough Coat			DAY 2-DAY 5
	Rough Coat			DAY 12-DAY 13
	Scheduled Sacrifice			DAY 14
334	Hunched Posture			DAY 2-DAY 3
	Hunched Posture			DAY 12-DAY 13
	Normal			DAY 0-DAY 1
	Normal			DAY 4-DAY 5
	Normal			DAY 8-DAY 11
	Rough Coat			DAY 2-DAY 3
	Rough Coat			DAY 6-DAY 7
	Rough Coat			DAY 12-DAY 13
	Scheduled Sacrifice			DAY 14
335	Animal Found Dead			DAY 13
	Hunched Posture			DAY 2-DAY 3
	Hunched Posture			DAY 12

INDIVIDUAL OBSERVATIONS

STUDY: 106 GROUP: 4-M SEX: MALE
DAY 0-DAY 14 DOSE: 6.2(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
335	Normal			DAY 0-DAY 1
(contd.)	Normal			DAY 4-DAY 7
	Normal			DAY 10-DAY 11
	Rough Coat			DAY 2-DAY 3
	Rough Coat			DAY 8-DAY 9
	Rough Coat			DAY 12

INDIVIDUAL OBSERVATIONS

STUDY: 106 GROUP: 1-F SEX: FEMALE
DAY 0-DAY 14 DOSE: 0(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
306	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14
307	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14
308	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14
309	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14
310	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14

INDIVIDUAL OBSERVATIONS

STUDY: 106 GROUP: 2-F SEX: FEMALE
DAY 0-DAY 14 DOSE: 0.5(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
316	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14
317	Normal			DAY 0-DAY 2
	Normal			DAY 4-DAY 13
	Rough Coat			DAY 3
	Scheduled Sacrifice			DAY 14
318	Normal			DAY 0-DAY 1
	Normal			DAY 4-DAY 5
	Normal			DAY 8-DAY 13
	Rough Coat			DAY 2-DAY 3
	Rough Coat			DAY 6-DAY 7
	Scheduled Sacrifice			DAY 14
319	Normal			DAY 0-DAY 1
	Normal			DAY 4-DAY 13
	Rough Coat			DAY 2-DAY 3
	Scheduled Sacrifice			DAY 14
320	Normal			DAY 0-DAY 1
	Normal			DAY 4-DAY 6
	Normal			DAY 8-DAY 13
	Rough Coat			DAY 2-DAY 3
	Rough Coat			DAY 7
	Scheduled Sacrifice			DAY 14

INDIVIDUAL OBSERVATIONS

STUDY: 106 GROUP: 3-F SEX: FEMALE
DAY 0-DAY 14 DOSE: 2.0(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
326	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14
327	Normal			DAY 0-DAY 1
	Normal			DAY 5-DAY 13
	Rough Coat			DAY 2-DAY 4
	Scheduled Sacrifice			DAY 14
328	Normal			DAY 0-DAY 1
	Normal			DAY 3-DAY 13
	Rough Coat			DAY 2
	Scheduled Sacrifice			DAY 14
329	Normal			DAY 0-DAY 1
	Normal			DAY 4-DAY 13
	Rough Coat			DAY 2-DAY 3
	Scheduled Sacrifice			DAY 14
330	Normal			DAY 0-DAY 1
	Normal			DAY 4-DAY 13
	Rough Coat			DAY 2-DAY 3
	Scheduled Sacrifice			DAY 14

INDIVIDUAL OBSERVATIONS

STUDY: 106 GROUP: 4-F SEX: FEMALE
DAY 0-DAY 14 DOSE: 6.2(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
336	Hunched Posture			DAY 3
	Normal			DAY 0-DAY 1
	Normal			DAY 4
	Normal			DAY 6-DAY 13
	Rough Coat			DAY 2-DAY 3
	Rough Coat			DAY 5
	Scheduled Sacrifice			DAY 14
337	Normal			DAY 0-DAY 1
	Normal			DAY 4-DAY 13
	Rough Coat			DAY 2-DAY 3
	Scheduled Sacrifice			DAY 14
338	Hunched Posture			DAY 2-DAY 3
	Normal			DAY 0-DAY 1
	Normal			DAY 4
	Normal			DAY 6-DAY 13
	Rough Coat			DAY 2-DAY 3
	Rough Coat			DAY 5
	Scheduled Sacrifice			DAY 14
339	Normal			DAY 0-DAY 1
	Normal			DAY 4-DAY 5
	Normal			DAY 8-DAY 11
	Rough Coat			DAY 2-DAY 3
	Rough Coat			DAY 6-DAY 7
	Rough Coat			DAY 12-DAY 13
	Scheduled Sacrifice			DAY 14
340	Hunched Posture			DAY 2-DAY 3
	Normal			DAY 0-DAY 1
	Normal			DAY 4
	Normal			DAY 6-DAY 13
	Rough Coat			DAY 2-DAY 3
	Rough Coat			DAY 5
	Scheduled Sacrifice			DAY 14

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APPENDIX 4

Individual Body Weights and Body Weight Gains

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 106 GROUP: 1-M SEX: MALE
DOSE: 0(mg/kg)

ANIMAL #	DAY -3	DAY 0	DAY 4	DAY 7	DAY 10	DAY 13
301	206.4	234.2	272.1	293.3	305.2	326.9
302	204.6	229.5	265.7	283.8	299.4	315.1
303	193.7	217.2	247.4	265.1	276.7	292.7
304	218.1	243.9	273.9	294.6	308.0	320.2
305	213.4	233.8	265.9	281.3	291.1	304.1
MEAN	207.2	231.7	265.0	283.6	296.1	311.8
S.D.	9.31	9.68	10.50	11.86	12.62	13.54
N	5	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 106 GROUP: 2-M SEX: MALE
DOSE: 0.5(mg/kg)

ANIMAL #	DAY -3	DAY 0	DAY 4	DAY 7	DAY 10	DAY 13
311	219.7	244.9	268.3	282.8	298.4	311.5
312	198.1	221.6	253.3	272.2	285.0	299.1
313	215.0	243.0	275.3	285.9	303.4	317.8
314	208.0	233.9	265.3	284.4	303.4	323.8
315	200.0	225.9	253.8	270.5	279.4	300.8
MEAN	208.2	233.9	263.2	279.2	293.9	310.6
S.D.	9.32	10.24	9.53	7.24	11.07	10.67
N	5	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 106 GROUP: 3-M SEX: MALE
DOSE: 2.0(mg/kg)

ANIMAL #	DAY -3	DAY 0	DAY 4	DAY 7	DAY 10	DAY 13
321	202.8	225.2	264.1	284.4	272.7	315.6
322	199.1	216.0	249.5	264.6	280.0	295.3
323	208.3	230.1	263.2	275.8	292.2	304.4
324	215.4	224.3	253.3	255.7	273.3	279.2
325	219.3	247.2	287.1	305.8	326.7	346.5
MEAN	209.0	228.6	263.4	277.3	289.0	308.2
S.D.	8.43	11.59	14.64	19.32	22.50	25.22
N	5	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 106 GROUP: 4-M SEX: MALE
DOSE: 6.2(mg/kg)

ANIMAL #	DAY -3	DAY 0	DAY 4	DAY 7	DAY 10	DAY 13
331	219.7	250.2	279.5	291.5	276.9	317.5
332	202.9	226.6	258.5	269.9	281.5	286.7
333	213.7	240.9	251.3	253.9	247.7	218.9
334	208.2	227.3	243.9	242.6	223.1	190.6
335	199.1	224.6	252.3	252.1	219.4	c
MEAN	208.7	233.9	257.1	262.0	249.7	253.4
S.D.	8.25	11.16	13.55	19.19	29.07	58.74
N	5	5	5	5	5	4

--: Data Unavailable c: Animal Found Dead

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 106 GROUP: 1-M SEX: MALE
DOSE: 0(mg/kg)

ANIMAL #	DAY 4[b]	DAY 7	DAY 10	DAY 13	TOTAL GAIN
301	37.9	21.2	11.9	21.7	92.7
302	36.2	18.1	15.6	15.7	85.6
303	30.2	17.7	11.6	16.0	75.5
304	30.0	20.7	13.4	12.2	76.3
305	32.1	15.4	9.8	13.0	70.3
MEAN	33.3	18.6	12.5	15.7	80.1
S.D.	3.59	2.37	2.17	3.73	8.95
N	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 0

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 106 GROUP: 2-M SEX: MALE
DOSE: 0.5(mg/kg)

ANIMAL #	DAY 4[b]	DAY 7	DAY 10	DAY 13	TOTAL GAIN
311	23.4	14.5	15.6	13.1	66.6
312	31.7	18.9	12.8	14.1	77.5
313	32.3	10.6	17.5	14.4	74.8
314	31.4	19.1	19.0	20.4	89.9
315	27.9	16.7	8.9	21.4	74.9
MEAN	29.3	16.0	14.8	16.7	76.7
S.D.	3.74	3.53	4.01	3.90	8.42
N	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 0

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 106 GROUP: 3-M SEX: MALE
DOSE: 2.0(mg/kg)

ANIMAL #	DAY 4[b]	DAY 7	DAY 10	DAY 13	TOTAL GAIN
321	38.9	20.3	-11.7	42.9	90.4
322	33.5	15.1	15.4	15.3	79.3
323	33.1	12.6	16.4	12.2	74.3
324	29.0	2.4	17.6	5.9	54.9
325	39.9	18.7	20.9	19.8	99.3
MEAN	34.9	13.8	11.7	19.2	79.6
S.D.	4.50	7.06	13.26	14.17	16.90
N	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 0

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 106 GROUP: 4-M SEX: MALE
DOSE: 6.2(mg/kg)

ANIMAL #	DAY 4[b]	DAY 7	DAY 10	DAY 13	TOTAL GAIN
331	29.3	12.0	-14.6	40.6	67.3
332	31.9	11.4	11.6	5.2	60.1
333	10.4	2.6	-6.2	-28.8	-22.0
334	16.6	-1.3	-19.5	-32.5	-36.7
335	27.7	-0.2	-32.7	c	--
MEAN	23.2	4.9	-12.3	-3.9	17.2
S.D.	9.23	6.37	16.44	34.16	54.14
N	5	5	5	4	4

--: Data Unavailable c: Animal Found Dead

a = Successive periods
b = Baseline is Day 0

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 106 GROUP: 1-F SEX: FEMALE
DOSE: 0(mg/kg)

ANIMAL #	DAY -3	DAY 0	DAY 4	DAY 7	DAY 10	DAY 13
306	164.1	170.3	176.8	193.7	197.1	217.2
307	154.8	163.5	175.1	190.1	196.8	200.2
308	173.7	187.1	202.5	217.1	229.9	241.9
309	173.1	188.7	195.0	213.1	224.1	227.7
310	166.4	176.1	186.3	181.5	215.6	221.8
MEAN	166.4	177.1	187.1	199.1	212.7	221.8
S.D.	7.71	10.80	11.73	15.33	15.25	15.22
N	5	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 106 GROUP: 2-F SEX: FEMALE
DOSE: 0.5(mg/kg)

ANIMAL #	DAY -3	DAY 0	DAY 4	DAY 7	DAY 10	DAY 13
316	180.4	193.4	212.6	207.6	230.0	242.7
317	171.8	188.1	203.2	215.5	221.7	229.5
318	161.7	176.9	191.9	209.8	221.9	234.9
319	167.9	173.2	195.7	207.5	212.4	222.1
320	156.0	163.8	175.6	191.2	200.8	211.3
MEAN	167.6	179.1	195.8	206.3	217.4	228.1
S.D.	9.37	11.82	13.79	9.06	11.16	12.04
N	5	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 106 GROUP: 3-F SEX: FEMALE
DOSE: 2.0(mg/kg)

ANIMAL #	DAY -3	DAY 0	DAY 4	DAY 7	DAY 10	DAY 13
326	174.7	201.9	227.7	223.6	249.6	273.2
327	156.6	165.6	180.0	193.6	204.5	217.3
328	172.2	185.4	201.8	222.3	237.2	249.7
329	167.8	183.7	204.8	211.9	221.4	223.8
330	161.1	176.9	195.1	207.3	214.4	220.0
MEAN	166.5	182.7	201.9	211.7	225.4	236.8
S.D.	7.56	13.26	17.32	12.26	18.02	24.10
N	5	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 106 GROUP: 4-F SEX: FEMALE
DOSE: 6.2(mg/kg)

ANIMAL #	DAY -3	DAY 0	DAY 4	DAY 7	DAY 10	DAY 13
336	178.9	188.3	182.5	200.1	209.0	229.0
337	162.9	172.6	192.7	194.3	203.6	215.5
338	152.8	163.5	175.6	183.8	189.5	196.1
339	173.0	193.9	190.1	183.8	187.9	208.2
340	169.3	174.3	194.0	201.7	209.6	216.3
MEAN	167.4	178.5	187.0	192.7	199.9	213.0
S.D.	10.01	12.36	7.77	8.61	10.52	12.06
N	5	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 106 GROUP: 1-F SEX: FEMALE
DOSE: 0(mg/kg)

ANIMAL #	DAY 4[b]	DAY 7	DAY 10	DAY 13	TOTAL GAIN
306	6.5	16.9	3.4	20.1	46.9
307	11.6	15.0	6.7	3.4	36.7
308	15.4	14.6	12.8	12.0	54.8
309	6.3	18.1	11.0	3.6	39.0
310	10.2	-4.8	34.1	6.2	45.7
MEAN	10.0	12.0	13.6	9.1	44.6
S.D.	3.80	9.48	12.03	7.08	7.15
N	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 0

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 106 GROUP: 2-F SEX: FEMALE
DOSE: 0.5(mg/kg)

ANIMAL #	DAY 4[b]	DAY 7	DAY 10	DAY 13	TOTAL GAIN
316	19.2	-5.0	22.4	12.7	49.3
317	15.1	12.3	6.2	7.8	41.4
318	15.0	17.9	12.1	13.0	58.0
319	22.5	11.8	4.9	9.7	48.9
320	11.8	15.6	9.6	10.5	47.5
MEAN	16.7	10.5	11.0	10.7	49.0
S.D.	4.16	9.03	6.95	2.16	5.94
N	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 0

INDIVIDUAL WEIGHT GAIN (Grams) [a]

STUDY: 106 GROUP: 3-F SEX: FEMALE
DOSE: 2.0(mg/kg)

ANIMAL #	DAY 4 [b]	DAY 7	DAY 10	DAY 13	TOTAL GAIN
326	25.8	-4.1	26.0	23.6	71.3
327	14.4	13.6	10.9	12.8	51.7
328	16.4	20.5	14.9	12.5	64.3
329	21.1	7.1	9.5	2.4	40.1
330	18.2	12.2	7.1	5.6	43.1
MEAN	19.2	9.9	13.7	11.4	54.1
S.D.	4.45	9.15	7.45	8.16	13.44
N	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 0

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 106 GROUP: 4-F SEX: FEMALE
DOSE: 6.2(mg/kg)

ANIMAL #	DAY 4[b]	DAY 7	DAY 10	DAY 13	TOTAL GAIN
336	-5.8	17.6	8.9	20.0	40.7
337	20.1	1.6	9.3	11.9	42.9
338	12.1	8.2	5.7	6.6	32.6
339	-3.8	-6.3	4.1	20.3	14.3
340	19.7	7.7	7.9	6.7	42.0
MEAN	8.5	5.8	7.2	13.1	34.5
S.D.	12.54	8.84	2.22	6.78	12.01
N	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 0

APPENDIX 5

Individual Food Consumption Data

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 106 GROUP: 1-M SEX: MALE
DOSE: 0(mg/kg)

ANIMAL #	DAY 0	DAY 4	DAY 7	DAY 10	DAY 13
301	21.3	24.4	26.3	27.0	27.1
302	21.0	23.6	24.3	24.8	24.3
303	19.7	21.5	25.5	32.1	24.7
304	20.9	22.9	24.9	--	25.2
305	20.1	23.2	23.6	25.0	24.1
MEAN	20.6	23.1	24.9	27.2	25.1
S.D.	0.67	1.07	1.04	3.40	1.21
N	5	5	5	4	5

--: Data Unavailable

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 106 GROUP: 2-M SEX: MALE
DOSE: 0.5(mg/kg)

ANIMAL #	DAY 0	DAY 4	DAY 7	DAY 10	DAY 13
311	21.2	21.7	22.8	57.8	24.2
312	20.8	22.3	24.2	23.7	24.0
313	21.7	27.1	22.9	59.0	24.2
314	19.4	21.5	22.8	--	23.9
315	19.7	22.0	25.2	22.1	23.9
MEAN	20.6	22.9	23.6	40.7	24.0
S.D.	0.98	2.36	1.08	20.51	0.15
N	5	5	5	4	5

--: Data Unavailable

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 106 GROUP: 3-M SEX: MALE
DOSE: 2.0(mg/kg)

ANIMAL #	DAY 0	DAY 4	DAY 7	DAY 10	DAY 13
321	18.1	22.8	24.8	29.6	26.4
322	16.1	21.9	24.7	23.4	24.8
323	19.5	21.7	22.0	24.2	23.2
324	18.1	19.9	19.6	16.8	21.7
325	22.9	25.4	24.1	25.2	26.3
MEAN	18.9	22.3	23.0	23.8	24.5
S.D.	2.52	2.01	2.23	4.61	2.03
N	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 106 GROUP: 4-M SEX: MALE
DOSE: 6.2(mg/kg)

ANIMAL #	DAY 0	DAY 4	DAY 7	DAY 10	DAY 13
331	24.1	23.3	19.6	16.8	24.4
332	20.9	21.8	20.8	19.8	20.7
333	20.8	19.2	14.0	13.0	4.9
334	17.7	17.5	19.2	8.4	4.6
335	19.6	18.0	16.4	4.1	--
MEAN	20.6	20.0	18.0	12.4	13.7
S.D.	2.33	2.50	2.76	6.31	10.39
N	5	5	5	5	4

--: Data Unavailable

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 106 GROUP: 1-F SEX: FEMALE
DOSE: 0(mg/kg)

ANIMAL #	DAY 0	DAY 4	DAY 7	DAY 10	DAY 13
306	14.6	15.8	19.1	34.2	17.6
307	14.2	16.0	21.6	34.7	18.9
308	17.5	19.0	20.6	20.9	21.0
309	15.7	16.7	19.8	--	28.8
310	14.2	13.7	15.7	21.9	18.8
MEAN	15.2	16.2	19.4	27.9	21.0
S.D.	1.40	1.91	2.25	7.55	4.52
N	5	5	5	4	5

--: Data Unavailable

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 106 GROUP: 2-F SEX: FEMALE
DOSE: 0.5(mg/kg)

ANIMAL #	DAY 0	DAY 4	DAY 7	DAY 10	DAY 13
316	16.6	18.6	19.5	26.5	20.0
317	16.7	17.5	19.5	18.1	20.4
318	14.8	15.9	19.0	17.6	19.7
319	13.4	17.1	20.1	22.7	18.0
320	12.2	14.7	18.3	18.0	17.1
MEAN	14.7	16.8	19.3	20.6	19.0
S.D.	1.97	1.50	0.67	3.91	1.42
N	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 106 GROUP: 3-F SEX: FEMALE
DOSE: 2.0(mg/kg)

ANIMAL #	DAY 0	DAY 4	DAY 7	DAY 10	DAY 13
326	20.0	20.7	20.0	25.7	23.7
327	15.5	16.8	19.9	19.5	19.0
328	19.4	19.8	25.2	28.3	21.9
329	17.0	19.5	18.9	22.4	20.5
330	15.9	16.9	18.3	16.4	18.0
MEAN	17.6	18.7	20.5	22.5	20.6
S.D.	2.04	1.78	2.74	4.75	2.27
N	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 106 GROUP: 4-F SEX: FEMALE
DOSE: 6.2 (mg/kg)

ANIMAL #	DAY 0	DAY 4	DAY 7	DAY 10	DAY 13
336	16.3	10.6	16.2	14.4	19.2
337	13.6	16.1	16.7	18.4	17.6
338	14.4	15.9	15.3	14.4	16.0
339	19.5	12.3	10.5	10.2	16.4
340	13.7	14.8	15.8	23.3	18.7
MEAN	15.5	13.9	14.9	16.1	17.6
S.D.	2.48	2.40	2.51	4.94	1.39
N	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL FOOD CONSUMPTION (Grams)

STUDY: 106 GROUP: 1-M SEX: MALE
DOSE: 0(mg/kg)

ANIMAL #	DAY 4	DAY 7	DAY 10	DAY 13
301	97.4	79.0	81.1	81.3
302	94.2	72.8	74.3	72.9
303	86.0	76.4	96.4	74.2
304	91.6	74.6	--	75.5
305	92.6	70.7	75.0	72.4
MEAN	92.4	74.7	81.7	75.3
S.D.	4.18	3.20	10.26	3.59
N	5	5	4	5

--: Data Unavailable

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INDIVIDUAL FOOD CONSUMPTION (Grams)

STUDY: 106 GROUP: 1-F SEX: FEMALE
DOSE: 0(mg/kg)

ANIMAL #	DAY 4	DAY 7	DAY 10	DAY 13
306	63.0	57.4	102.5	52.8
307	63.8	64.8	104.0	56.8
308	76.1	61.9	62.7	63.0
309	66.7	59.3	--	86.4
310	54.6	47.1	65.8	56.5
MEAN	64.8	58.1	83.8	63.1
S.D.	7.74	6.75	22.56	13.53
N	5	5	4	5

--: Data Unavailable

INDIVIDUAL FOOD CONSUMPTION (Grams)

STUDY: 106 GROUP: 2-M SEX: MALE
DOSE: 0.5(mg/kg)

ANIMAL #	DAY 4	DAY 7	DAY 10	DAY 13
311	86.9	68.3	173.5	72.7
312	89.3	72.7	71.0	72.0
313	108.3	68.8	176.9	72.5
314	85.9	68.3	--	71.7
315	87.9	75.5	66.3	71.8
MEAN	91.7	70.7	121.9	72.1
S.D.	9.39	3.25	61.56	0.44
N	5	5	4	5

--: Data Unavailable

INDIVIDUAL FOOD CONSUMPTION (Grams)

STUDY: 106 GROUP: 2-F SEX: FEMALE
DOSE: 0.5(mg/kg)

ANIMAL #	DAY 4	DAY 7	DAY 10	DAY 13
316	74.4	58.6	79.4	59.9
317	70.1	58.6	54.3	61.3
318	63.4	57.0	52.9	59.1
319	68.4	60.3	68.0	54.0
320	58.6	55.0	54.0	51.2
MEAN	67.0	57.9	61.7	57.1
S.D.	6.12	2.00	11.67	4.30
N	5	5	5	5

--: Data Unavailable

INDIVIDUAL FOOD CONSUMPTION (Grams)

STUDY: 106 GROUP: 3-M SEX: MALE
DOSE: 2.0(mg/kg)

ANIMAL #	DAY 4	DAY 7	DAY 10	DAY 13
321	91.1	74.4	88.9	79.1
322	87.6	74.1	70.3	74.4
323	86.8	65.9	72.7	69.6
324	79.4	58.7	50.5	65.1
325	101.7	72.3	75.6	79.0
MEAN	89.3	69.1	71.6	73.4
S.D.	8.13	6.74	13.81	6.09
N	5	5	5	5

--: Data Unavailable

INDIVIDUAL FOOD CONSUMPTION (Grams)

STUDY: 106 GROUP: 3-F SEX: FEMALE
DOSE: 2.0(mg/kg)

ANIMAL #	DAY 4	DAY 7	DAY 10	DAY 13
326	82.8	60.0	77.2	71.2
327	67.0	59.7	58.6	57.1
328	79.2	75.5	84.8	65.6
329	77.8	56.7	67.1	61.6
330	67.4	55.0	49.2	54.1
MEAN	74.8	61.4	67.4	61.9
S.D.	7.21	8.17	14.21	6.79
N	5	5	5	5

--: Data Unavailable

INDIVIDUAL FOOD CONSUMPTION (Grams)

STUDY: 106 GROUP: 4-M SEX: MALE
DOSE: 6.2(mg/kg)

ANIMAL #	DAY 4	DAY 7	DAY 10	DAY 13
331	93.2	58.9	50.5	73.3
332	87.0	62.5	59.3	62.2
333	76.6	42.0	38.9	14.8
334	70.0	57.6	25.1	13.9
335	71.9	49.3	12.2	--
MEAN	79.7	54.1	37.2	41.1
S.D.	10.00	8.30	18.97	31.16
N	5	5	5	4

--: Data Unavailable

INDIVIDUAL FOOD CONSUMPTION (Grams)

STUDY: 106 GROUP: 4-F SEX: FEMALE
DOSE: 6.2(mg/kg)

ANIMAL #	DAY 4	DAY 7	DAY 10	DAY 13
336	42.4	48.7	43.3	57.7
337	64.4	50.0	55.3	52.9
338	63.4	45.9	43.2	48.0
339	49.0	31.6	30.7	49.2
340	59.3	47.3	70.0	56.2
MEAN	55.7	44.7	48.5	52.8
S.D.	9.61	7.48	14.84	4.23
N	5	5	5	5

--: Data Unavailable

APPENDIX 6

Individual Clinical Chemistry Data

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: DAY 14

STUDY ID: 106
STUDY NO: 106
SEX: MALE

ANIMAL ID	ALT U/L	AST U/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBA mg/dL	ALKP U/L
GROUP: 1-M:0 mg base/kg/day								
301	57	103	8.0	4.3	3.7	1.16	36.0	197
302	59	91	7.1	3.7	3.4	1.09	117.6	253
303	58	100	7.7	4.4	3.3	1.33	44.5	306
304	67	114	7.7	4.2	3.5	1.20	36.9	399
305	48	95	7.4	3.7	3.7	1.00	59.1	325
MEAN	58	101	7.6	4.1	3.5	1.16	58.8	296
SD	6.8	8.8	0.34	0.34	0.18	0.123	34.14	76.2
N	5	5	5	5	5	5	5	5
GROUP: 2-M:0.5 mg base/kg/day								
311	61	98	6.8	3.8	3.0	1.27	53.1	388
312	54	101	7.2	4.0	3.2	1.25	54.7	392
313	51	85	7.2	3.8	3.4	1.12	56.5	348
314	45	77	6.8	3.5	3.3	1.06	31.5	230
315	61	133	6.4	3.6	2.8	1.29	42.0	314
MEAN	54	99	6.9	3.7	3.1	1.20	47.6	334
SD	6.8	21.5	0.33	0.19	0.24	0.102	10.61	66.5
N	5	5	5	5	5	5	5	5
GROUP: 3-M:2.0 mg base/kg/day								
321	50	131	6.8	3.6	3.2	1.13	34.0	245
322	58	90	7.4	4.3	3.1	1.39	73.6	200
323	60	129	7.9	4.3	3.6	1.19	76.0	288
324	61	104	7.4	4.3	3.1	1.39	33.3	272
325	63	126	7.5	4.2	3.3	1.27	56.1	374
MEAN	58	116	7.4	4.1	3.3	1.27	54.6	276
SD	5.0	18.1	0.39	0.30	0.21	0.117	20.61	64.2
N	5	5	5	5	5	5	5	5
GROUP: 4-M:6.2 mg base/kg/day								
331	129	189	8.1	4.3	3.8	1.13	40.1	358
332	133	234	8.5	4.9	3.6	1.36	57.6	255
333	211	336	6.6	3.8	2.8	1.36	105.7	256
334	377	454	6.5	3.8	2.7	1.41	183.1	241
335	--	--	--	--	--	--	--	--
MEAN	213	303	7.4	4.2	3.2	1.32	96.6	278
SD	116.0	117.8	1.02	0.52	0.56	0.126	63.97	54.1
N	4	4	4	4	4	4	4	4

(--)-Data Unavailable

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: DAY 14

STUDY ID: 106
STUDY NO: 106

SEX: MALE

ANIMAL ID	CHOL mg/dL	TRY mg/dL	BUN mg/dL	CREA mg/dL	NA mmol/L	K mmol/L	CL mEq/L	CA mg/dL
GROUP: 1-M:0 mg base/kg/day								
301	56	163	16.1	0.43	141	6.17	119	11.4
302	50	47	18.1	0.50	144	5.96	115	11.3
303	58	67	21.7	0.49	142	5.82	115	11.1
304	41	35	17.5	0.53	144	6.22	118	10.7
305	63	93	19.9	0.50	147	6.56	117	11.0
MEAN	54	81	18.7	0.49	144	6.15	117	11.1
SD	8.4	50.8	2.18	0.037	2.3	0.282	1.8	0.27
N	5	5	5	5	5	5	5	5
GROUP: 2-M:0.5 mg base/kg/day								
311	51	45	14.7	0.48	143	5.40	110	10.4
312	46	57	21.3	0.51	142	6.20	122	11.2
313	53	61	19.4	0.58	144	6.02	112	11.1
314	50	43	14.3	0.49	141	6.05	118	10.8
315	47	25	14.6	0.48	139	6.18	119	10.2
MEAN	49	46	16.9	0.51	142	5.97	116	10.7
SD	2.9	14.1	3.26	0.042	1.9	0.328	5.0	0.43
N	5	5	5	5	5	5	5	5
GROUP: 3-M:2.0 mg base/kg/day								
321	57	86	16.8	0.56	141	7.26	118	11.9
322	62	89	21.5	0.47	142	5.95	115	11.3
323	63	34	20.7	0.43	145	7.17	116	11.4
324	57	40	17.0	0.51	146	6.08	118	11.2
325	49	69	20.0	0.64	143	6.74	119	11.3
MEAN	58	64	19.2	0.52	143	6.64	117	11.4
SD	5.5	25.5	2.17	0.082	2.1	0.605	1.6	0.28
N	5	5	5	5	5	5	5	5
GROUP: 4-M:6.2 mg base/kg/day								
331	69	48	15.6	0.55	147	6.44	118	11.5
332	51	31	17.0	0.54	144	5.84	115	11.2
333	41	29	29.6	0.59	143	5.76	114	10.6
334	48	38	26.2	0.50	145	5.83	112	10.8
335	--	--	--	--	--	--	--	--
MEAN	52	37	22.1	0.55	145	5.97	115	11.0
SD	11.9	8.6	6.86	0.037	1.7	0.317	2.5	0.40
N	4	4	4	4	4	4	4	4

(--)-Data Unavailable

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: DAY 14

STUDY ID: 106
STUDY NO: 106

SEX: MALE

ANIMAL ID	IP mg/dL	GLU mg/dL
GROUP: 1-M:0 mg base/kg/day		
301	11.7	159
302	10.9	122
303	11.4	132
304	10.4	138
305	11.0	133
MEAN	11.1	137
SD	0.50	13.7
N	5	5
GROUP: 2-M:0.5 mg base/kg/day		
311	9.8	121
312	12.6	155
313	10.6	117
314	9.9	124
315	10.2	147
MEAN	10.6	133
SD	1.15	17.0
N	5	5
GROUP: 3-M:2.0 mg base/kg/day		
321	11.9	152
322	11.3	123
323	--	117
324	10.6	114
325	13.6	117
MEAN	11.9	125
SD	1.28	15.7
N	4	5
GROUP: 4-M:6.2 mg base/kg/day		
331	10.7	108
332	9.1	128
333	8.4	120
334	9.0	118
335	--	--
MEAN	9.3	119
SD	0.98	8.2
N	4	4

(--)-Data Unavailable

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: DAY 14

STUDY ID: 106
STUDY NO: 106

SEX: FEMALE

ANIMAL ID	ALT U/L	AST U/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBA mg/dL	ALKP U/L
GROUP: 1-F:0 mg base/kg/day								
306	58	98	7.0	4.0	3.0	1.33	18.6	282
307	68	94	7.9	4.3	3.6	1.19	24.1	358
308	51	113	7.1	3.9	3.2	1.22	35.8	209
309	62	109	7.3	4.1	3.2	1.28	16.9	217
310	48	86	7.2	4.1	3.1	1.32	19.8	129
MEAN	57	100	7.3	4.1	3.2	1.27	23.0	239
SD	8.1	11.0	0.35	0.15	0.23	0.061	7.61	85.9
N	5	5	5	5	5	5	5	5
GROUP: 2-F:0.5 mg base/kg/day								
316	55	95	7.1	4.0	3.1	1.29	24.2	139
317	65	106	7.9	4.1	3.8	1.08	36.7	242
318	58	96	7.0	3.8	3.2	1.19	31.9	158
319	87	114	8.4	4.6	3.8	1.21	39.5	293
320	61	141	6.9	3.8	3.1	1.23	29.0	226
MEAN	65	110	7.5	4.1	3.4	1.20	32.3	212
SD	12.7	18.8	0.66	0.33	0.37	0.077	6.08	63.0
N	5	5	5	5	5	5	5	5
GROUP: 3-F:2.0 mg base/kg/day								
326	53	96	7.0	3.9	3.1	1.26	23.4	255
327	52	120	7.2	3.8	3.4	1.12	15.2	191
328	51	110	6.9	3.8	3.1	1.23	16.0	289
329	54	95	6.5	3.6	2.9	1.24	27.5	175
330	58	81	6.7	3.8	2.9	1.31	32.9	167
MEAN	54	100	6.9	3.8	3.1	1.23	23.0	215
SD	2.7	15.0	0.27	0.11	0.20	0.070	7.55	53.7
N	5	5	5	5	5	5	5	5
GROUP: 4-F:6.2 mg base/kg/day								
336	55	106	6.8	4.0	2.8	1.43	26.3	143
337	54	103	7.7	4.1	3.6	1.14	36.4	158
338	87	142	7.8	4.5	3.3	1.36	51.6	162
339	74	117	8.0	4.4	3.6	1.22	61.1	146
340	71	153	7.7	4.3	3.4	1.26	220.0	193
MEAN	68	124	7.6	4.3	3.3	1.28	79.1	160
SD	13.9	22.2	0.46	0.21	0.33	0.115	79.91	19.9
N	5	5	5	5	5	5	5	5

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IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: DAY 14

STUDY ID: 106
STUDY NO: 106

SEX: FEMALE

ANIMAL ID	CHOL mg/dL	TRY mg/dL	BUN mg/dL	CREA mg/dL	NA mmol/L	K mmol/L	CL mEq/L	CA mg/dL
GROUP: 1-F:0 mg base/kg/day								
306	63	34	13.5	0.50	145	5.67	107	10.9
307	72	40	18.7	0.49	146	5.84	112	11.8
308	64	35	20.0	0.52	140	5.95	118	11.1
309	54	35	13.5	0.55	141	6.25	117	10.9
310	47	29	13.0	0.50	142	5.79	116	11.1
MEAN	60	35	15.7	0.51	143	5.90	114	11.2
SD	9.7	3.9	3.33	0.024	2.6	0.220	4.5	0.37
N	5	5	5	5	5	5	5	5
GROUP: 2-F:0.5 mg base/kg/day								
316	64	39	13.4	0.48	144	5.60	117	11.0
317	47	27	17.4	0.56	142	6.90	118	11.3
318	53	42	15.1	0.50	141	5.74	118	11.1
319	63	50	15.0	0.53	143	5.63	115	11.5
320	55	62	17.3	0.57	142	5.76	120	10.9
MEAN	56	44	15.6	0.53	142	5.93	118	11.2
SD	7.1	13.0	1.70	0.038	1.1	0.549	1.8	0.24
N	5	5	5	5	5	5	5	5
GROUP: 3-F:2.0 mg base/kg/day								
326	59	61	10.4	0.50	144	5.63	116	10.7
327	52	41	12.4	0.48	145	5.91	112	11.3
328	51	32	13.1	0.52	140	5.63	116	10.6
329	61	39	13.0	0.55	138	6.25	117	10.6
330	59	39	18.1	0.56	141	6.01	109	10.9
MEAN	56	42	13.4	0.52	142	5.89	114	10.8
SD	4.6	10.9	2.84	0.033	2.9	0.264	3.4	0.29
N	5	5	5	5	5	5	5	5
GROUP: 4-F:6.2 mg base/kg/day								
336	71	49	14.5	0.53	142	5.52	114	11.0
337	61	45	13.6	0.48	146	5.89	115	11.3
338	67	76	16.1	0.64	145	5.76	114	11.1
339	70	52	16.5	0.54	144	5.73	114	11.5
340	81	43	17.8	0.56	142	5.49	122	11.3
MEAN	70	53	15.7	0.55	144	5.68	116	11.2
SD	7.3	13.3	1.66	0.058	1.8	0.169	3.5	0.19
N	5	5	5	5	5	5	5	5

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IND. ANIMAL CLINICAL CHEMISTRY REPORT BY GROUP
PERIOD: DAY 14

STUDY ID: 106
STUDY NO: 106

SEX: FEMALE

ANIMAL ID	IP mg/dL	GLU mg/dL
GROUP: 1-F:0 mg base/kg/day		
306	9.1	120
307	9.8	140
308	10.1	160
309	10.1	126
310	8.9	130
MEAN	9.6	135
SD	0.57	15.7
N	5	5
GROUP: 2-F:0.5 mg base/kg/day		
316	9.4	120
317	10.2	113
318	11.0	104
319	9.9	150
320	9.0	125
MEAN	9.9	122
SD	0.77	17.3
N	5	5
GROUP: 3-F:2.0 mg base/kg/day		
326	10.0	113
327	10.4	91
328	9.4	129
329	10.5	123
330	9.9	116
MEAN	10.0	114
SD	0.44	14.5
N	5	5
GROUP: 4-F:6.2 mg base/kg/day		
336	10.2	124
337	9.3	131
338	8.6	127
339	10.6	127
340	10.8	193
MEAN	9.9	140
SD	0.93	29.5
N	5	5

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APPENDIX 7

Individual Hematology Data

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: DAY 14

STUDY ID: 106 SEX: MALE

ANIMAL ID	RBC 10^6/cmm	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	NRBC COUNT
GROUP: 1-M:0 mg base/kg/day								
301	7.48	16.1	44.4	59.4	21.5	36.3	2.5	0
302	7.11	15.6	43.9	61.7	21.9	35.5	0.2	0
303	7.91	16.4	45.7	57.8	20.7	35.9	0.8	0
304	7.59	16.2	45.3	59.7	21.3	35.8	1.1	0
305	7.07	15.5	42.4	60.0	21.9	36.6	1.2	0
MEAN	7.43	16.0	44.3	59.7	21.5	36.0	1.2	0
SD	0.350	0.39	1.30	1.40	0.50	0.43	0.84	0.0
N	5	5	5	5	5	5	5	5
GROUP: 2-M:0.5 mg base/kg/day								
311	7.12	15.9	43.1	60.5	22.3	36.9	0.3	0
312	6.97	15.5	42.1	60.4	22.2	36.8	1.0	0
313	7.33	15.5	44.3	60.4	21.1	35.0	0.3	0
314	7.51	15.6	43.0	57.3	20.8	36.3	0.1	0
315	7.00	14.6	40.5	57.9	20.9	36.0	0.6	2
MEAN	7.19	15.4	42.6	59.3	21.5	36.2	0.5	0
SD	0.230	0.49	1.41	1.57	0.73	0.76	0.35	0.9
N	5	5	5	5	5	5	5	5
GROUP: 3-M:2.0 mg base/kg/day								
321	7.39	16.7	46.6	63.1	22.6	35.8	1.1	0
322	6.85	15.4	43.4	63.4	22.5	35.5	1.1	2
323	7.30	16.0	45.0	61.6	21.9	35.6	0.7	0
324	7.25	15.1	43.1	59.4	20.8	35.0	0.7	0
325	7.36	16.5	45.9	62.4	22.4	35.9	2.3	0
MEAN	7.23	15.9	44.8	62.0	22.0	35.6	1.2	0
SD	0.219	0.69	1.53	1.60	0.74	0.35	0.66	0.9
N	5	5	5	5	5	5	5	5
GROUP: 4-M:6.2 mg base/kg/day								
331	6.44	14.6	43.1	66.9	22.7	33.9	7.7	0
332	6.93	15.1	44.4	64.1	21.8	34.0	5.9	0
333	8.09	17.6	45.3	56.0	21.8	38.9	0.4	0
334	7.56	16.1	45.4	60.1	21.3	35.5	0.1	0
335	--	--	--	--	--	--	--	--
MEAN	7.26	15.9	44.6	61.8	21.9	35.6	3.5	0
SD	0.721	1.32	1.07	4.75	0.58	2.33	3.85	0.0
N	4	4	4	4	4	4	4	4

(--)-Data Unavailable

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INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: DAY 14

STUDY ID: 106 SEX: MALE

ANIMAL ID	HB %	%METHGB %	PLT 10^3/ccm	WBC 10^3/cmm	M Neutroph 10^3/cmm	I Neutroph 10^3/cmm	Lymphocyte 10^3/cmm	Monocytes 10^3/cmm
GROUP: 1-M:0 mg base/kg/day								
301	0.0	0.5	1251	19.2	2.7	1.0	15.6	0.0
302	0.0	0.3	1223	20.9	3.3	0.2	17.1	0.2
303	0.0	0.3	1334	20.9	1.7	0.8	18.2	0.2
304	0.1	0.8	1152	16.9	1.2	0.3	14.5	0.8
305	0.0	0.2	1156	12.7	1.1	0.0	11.4	0.1
MEAN	0.0	0.4	1223	18.1	2.0	0.5	15.4	0.3
SD	0.04	0.24	75.2	3.45	0.96	0.42	2.63	0.31
N	5	5	5	5	5	5	5	5
GROUP: 2-M:0.5 mg base/kg/day								
311	0.0	1.0	1122	18.0	2.2	0.7	14.8	0.2
312	0.0	0.2	1152	20.5	1.2	0.8	17.6	0.6
313	0.0	1.0	1274	14.4	2.7	0.1	10.7	0.7
314	0.0	1.0	1128	17.9	1.3	0.2	16.1	0.2
315	0.0	1.1	1144	16.0	2.2	0.3	13.1	0.2
MEAN	0.0	0.9	1164	17.4	1.9	0.4	14.5	0.4
SD	0.00	0.37	62.7	2.30	0.65	0.31	2.68	0.25
N	5	5	5	5	5	5	5	5
GROUP: 3-M:2.0 mg base/kg/day								
321	0.0	5.8	920	28.1	2.2	0.6	24.7	0.6
322	0.0	5.8	1111	23.3	1.9	0.9	20.0	0.5
323	0.0	4.9	945	22.4	1.6	0.9	19.5	0.2
324	0.0	5.3	1201	19.8	1.2	0.8	17.6	0.2
325	0.0	5.7	1058	24.9	3.2	0.7	20.4	0.0
MEAN	0.0	5.5	1047	23.7	2.0	0.8	20.4	0.3
SD	0.00	0.39	116.7	3.08	0.76	0.13	2.61	0.24
N	5	5	5	5	5	5	5	5
GROUP: 4-M:6.2 mg base/kg/day								
331	0.0	4.1	1003	30.0	3.9	0.6	24.0	1.5
332	0.0	4.9	996	24.6	2.2	1.5	20.4	0.5
333	0.0	10.4	1309	19.0	2.1	0.6	15.2	1.1
334	0.0	2.1	953	24.1	4.3	1.7	16.1	1.9
335	--	--	--	--	--	--	--	--
MEAN	0.0	5.4	1065	24.4	3.1	1.1	18.9	1.3
SD	0.00	3.55	164.0	4.50	1.14	0.58	4.07	0.60
N	4	4	4	4	4	4	4	4

(--)-Data Unavailable

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: DAY 14

STUDY IO: 106 SEX: MALE

ANIMAL IO	Eosinophil 10^3/cmm	Basophils 10^3/cmm
GROUP: 1-M:0 mg base/kg/day		
301	0.0	0.0
302	0.0	0.0
303	0.0	0.0
304	0.0	0.0
305	0.0	0.0
MEAN	0.0	0.0
SD	0.00	0.00
N	5	5
GROUP: 2-M:0.5 mg base/kg/day		
311	0.2	0.0
312	0.2	0.0
313	0.1	0.0
314	0.2	0.0
315	0.2	0.0
MEAN	0.2	0.0
SD	0.04	0.00
N	5	5
GROUP: 3-M:2.0 mg base/kg/day		
321	0.0	0.0
322	0.0	0.0
323	0.2	0.0
324	0.0	0.0
325	0.5	0.0
MEAN	0.1	0.0
SD	0.22	0.00
N	5	5
GROUP: 4-M:6.2 mg base/kg/day		
331	0.0	0.0
332	0.0	0.0
333	0.0	0.0
334	0.0	0.0
335	--	--
MEAN	0.0	0.0
SD	0.00	0.00
N	4	4

(--)-Data Unavailable

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INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: DAY 14

STUDY ID: 106 SEX: FEMALE

ANIMAL ID	RBC 10^6/cmm	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	NRBC COUNT
GROUP: 1-F:0 mg base/kg/day								
306	6.68	15.1	41.3	61.8	22.6	36.6	0.3	0
307	7.40	16.7	45.1	60.9	22.6	37.0	0.8	0
308	7.39	16.8	45.1	61.0	22.7	37.3	0.6	0
309	7.32	16.4	43.6	59.6	22.4	37.6	0.6	0
310	6.78	15.5	41.6	61.4	22.9	37.3	1.2	0
MEAN	7.11	16.1	43.3	60.9	22.6	37.2	0.7	0
SD	0.354	0.76	1.83	0.83	0.18	0.38	0.33	0.0
N	5	5	5	5	5	5	5	5
GROUP: 2-F:0.5 mg base/kg/day								
316	6.45	14.5	39.4	61.1	22.5	36.8	0.5	0
317	7.18	16.0	42.7	59.5	22.3	37.5	1.4	0
318	7.08	15.9	41.9	59.2	22.5	37.9	0.9	1
319	7.48	16.6	43.5	58.2	22.2	38.2	0.9	0
320	6.95	15.2	42.3	60.9	21.9	35.9	0.8	0
MEAN	7.03	15.6	42.0	59.8	22.3	37.3	0.9	0
SD	0.378	0.81	1.55	1.22	0.25	0.92	0.32	0.4
N	5	5	5	5	5	5	5	5
GROUP: 3-F:2.0 mg base/kg/day								
326	5.58	14.1	38.1	68.3	25.3	37.0	1.0	0
327	6.65	14.6	40.2	60.5	22.0	36.3	0.5	0
328	6.59	14.0	38.9	59.0	21.2	36.0	1.5	0
329	6.79	15.0	41.6	61.3	22.1	36.1	1.4	0
330	6.56	14.9	39.7	60.5	22.7	37.5	0.8	0
MEAN	6.43	14.5	39.7	61.9	22.7	36.6	1.0	0
SD	0.486	0.45	1.33	3.66	1.57	0.65	0.42	0.0
N	5	5	5	5	5	5	5	5
GROUP: 4-F:6.2 mg base/kg/day								
336	6.40	14.1	41.7	65.2	22.0	33.8	4.0	1
337	5.90	13.9	39.2	66.4	23.6	35.5	2.7	0
338	5.95	14.0	40.5	68.1	23.5	34.6	4.0	1
339	6.26	14.1	40.6	64.9	22.5	34.7	1.0	0
340	5.04	12.2	35.8	71.0	24.2	34.1	5.6	0
MEAN	5.91	13.7	39.6	67.1	23.2	34.5	3.5	0
SD	0.529	0.82	2.28	2.51	0.89	0.65	1.72	0.5
N	5	5	5	5	5	5	5	5

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INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: DAY 14

STUDY ID: 106 SEX: FEMALE

ANIMAL ID	HB %	%METHGB %	PLT 10^3/ccm	WBC 10^3/cmm	M Neutroph 10^3/cmm	I Neutroph 10^3/cmm	Lymphocyte 10^3/cmm	Monocytes 10^3/cmm
GROUP: 1-F:0 mg base/kg/day								
306	0.0	0.5	1153	8.5	0.9	0.1	7.1	0.3
307	0.0	0.3	1046	10.7	1.1	0.2	8.5	0.5
308	0.0	0.5	1242	21.0	0.8	0.8	19.1	0.2
309	0.0	0.1	766	12.0	0.7	0.1	10.6	0.2
310	0.0	1.0	1082	10.3	1.4	0.3	8.4	0.1
MEAN	0.0	0.5	1058	12.5	1.0	0.3	10.7	0.3
SD	0.00	0.33	179.5	4.91	0.28	0.29	4.84	0.15
N	5	5	5	5	5	5	5	5
GROUP: 2-F:0.5 mg base/kg/day								
316	0.0	0.4	1075	12.8	1.8	0.8	10.1	0.0
317	0.0	0.5	1083	12.5	3.6	0.6	8.0	0.1
318	0.0	0.4	1331	14.3	1.1	0.4	11.4	0.9
319	0.0	0.3	1178	20.1	4.0	0.8	14.9	0.4
320	0.0	3.2	854	15.8	3.2	0.5	12.0	0.0
MEAN	0.0	1.0	1104	15.1	2.7	0.6	11.3	0.3
SD	0.00	1.25	173.8	3.09	1.24	0.18	2.54	0.38
N	5	5	5	5	5	5	5	5
GROUP: 3-F:2.0 mg base/kg/day								
326	0.0	3.2	1205	12.5	1.3	0.6	10.1	0.4
327	0.0	2.5	1100	14.6	5.3	0.3	8.5	0.6
328	0.0	3.5	1098	13.9	3.1	0.3	10.1	0.4
329	0.0	4.6	933	15.3	1.5	0.0	12.9	0.8
330	0.0	4.3	1201	17.1	1.4	0.0	15.4	0.3
MEAN	0.0	3.6	1107	14.7	2.5	0.2	11.4	0.5
SD	0.00	0.85	110.5	1.70	1.72	0.25	2.74	0.20
N	5	5	5	5	5	5	5	5
GROUP: 4-F:6.2 mg base/kg/day								
336	0.0	5.0	885	22.3	2.7	0.9	17.8	0.7
337	0.0	4.8	855	39.6	4.4	2.4	32.5	0.0
338	0.0	5.6	1085	25.3	3.8	1.0	19.7	0.5
339	0.0	6.8	1084	20.1	1.8	0.6	17.1	0.6
340	0.0	4.5	790	21.3	3.2	2.6	15.3	0.2
MEAN	0.0	5.3	940	25.7	3.2	1.5	20.5	0.4
SD	0.00	0.91	136.5	7.99	1.00	0.93	6.90	0.29
N	5	5	5	5	5	5	5	5

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INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: DAY 14

STUDY ID: 106 SEX: FEMALE

ANIMAL ID	Eosinophil 10^3/cmm	Basophils 10^3/cmm
GROUP: 1-F:0 mg base/kg/day		
306	0.1	0.0
307	0.4	0.0
308	0.0	0.0
309	0.4	0.0
310	0.0	0.0
MEAN	0.2	0.0
SD	0.20	0.00
N	5	5
GROUP: 2-F:0.5 mg base/kg/day		
316	0.1	0.0
317	0.1	0.0
318	0.3	0.1
319	0.0	0.0
320	0.2	0.0
MEAN	0.1	0.0
SD	0.11	0.04
N	5	5
GROUP: 3-F:2.0 mg base/kg/day		
326	0.1	0.0
327	0.0	0.0
328	0.0	0.0
329	0.2	0.0
330	0.0	0.0
MEAN	0.1	0.0
SD	0.09	0.00
N	5	5
GROUP: 4-F:6.2 mg base/kg/day		
336	0.2	0.0
337	0.4	0.0
338	0.3	0.0
339	0.0	0.0
340	0.0	0.0
MEAN	0.2	0.0
SD	0.18	0.00
N	5	5

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WHITE DIFFERENTIAL COUNTS

STUDY ID: 106

GROUP: 1-M : 0 mg base/kg/day

SEX: MALE

ANIMAL ID		DAY 14 REL	DAY 14 ABS
301	Nucleated Red Cells	0	
	M Neutrophils	14	2.7
	I Neutrophils	5	1.0
	Lymphocytes	81	15.6
	Monocytes	0	0.0
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		19.2
302	Nucleated Red Cells	0	
	M Neutrophils	16	3.3
	I Neutrophils	1	0.2
	Lymphocytes	82	17.1
	Monocytes	1	0.2
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		20.9
303	Nucleated Red Cells	0	
	M Neutrophils	8	1.7
	I Neutrophils	4	0.8
	Lymphocytes	87	18.2
	Monocytes	1	0.2
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		20.9
304	Nucleated Red Cells	0	
	M Neutrophils	7	1.2
	I Neutrophils	2	0.3
	Lymphocytes	86	14.5
	Monocytes	5	0.8
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		16.9
305	Nucleated Red Cells	0	
	M Neutrophils	9	1.1
	I Neutrophils	0	0.0
	Lymphocytes	90	11.4
	Monocytes	1	0.1
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		12.7

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WHITE DIFFERENTIAL COUNTS

STUDY ID: 106

GROUP: 2-M : 0.5 mg base/kg/day

SEX: MALE

ANIMAL ID		DAY 14 REL	DAY 14 ABS
311	Nucleated Red Cells	0	
	M Neutrophils	12	2.2
	I Neutrophils	4	0.7
	Lymphocytes	82	14.8
	Monocytes	1	0.2
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		18.0
312	Nucleated Red Cells	0	
	M Neutrophils	6	1.2
	I Neutrophils	4	0.8
	Lymphocytes	86	17.6
	Monocytes	3	0.6
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		20.5
313	Nucleated Red Cells	0	
	M Neutrophils	19	2.7
	I Neutrophils	1	0.1
	Lymphocytes	74	10.7
	Monocytes	5	0.7
	Eosinophils	1	0.1
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		14.4
314	Nucleated Red Cells	0	
	M Neutrophils	7	1.3
	I Neutrophils	1	0.2
	Lymphocytes	90	16.1
	Monocytes	1	0.2
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.9
315	Nucleated Red Cells	2	
	M Neutrophils	14	2.2
	I Neutrophils	2	0.3
	Lymphocytes	82	13.1
	Monocytes	1	0.2
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		16.0

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WHITE DIFFERENTIAL COUNTS

STUDY ID: 106

GROUP: 4-M : 6.2 mg base/kg/day

SEX: MALE

ANIMAL ID		DAY 14 REL	DAY 14 ABS
331	Nucleated Red Cells	0	
	M Neutrophils	13	3.9
	I Neutrophils	2	0.6
	Lymphocytes	80	24.0
	Monocytes	5	1.5
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		30.0
332	Nucleated Red Cells	0	
	M Neutrophils	9	2.2
	I Neutrophils	6	1.5
	Lymphocytes	83	20.4
	Monocytes	2	0.5
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		24.6
333	Nucleated Red Cells	0	
	M Neutrophils	11	2.1
	I Neutrophils	3	0.6
	Lymphocytes	80	15.2
	Monocytes	6	1.1
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		19.0
334	Nucleated Red Cells	0	
	M Neutrophils	18	4.3
	I Neutrophils	7	1.7
	Lymphocytes	67	16.1
	Monocytes	8	1.9
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		24.1
335	Nucleated Red Cells	--	
	M Neutrophils	--	--
	I Neutrophils	--	--
	Lymphocytes	--	--
	Monocytes	--	--
	Eosinophils	--	--
	Basophils	--	--
	Atypical Lymphocytes	--	--
	WBC		--

(--)-Data Unavailable

DRAFT

WHITE DIFFERENTIAL COUNTS

STUDY ID: 106

GROUP: 2-F : 0.5 mg base/kg/day

SEX: FEMALE

ANIMAL ID		DAY 14 REL	DAY 14 ABS
316	Nucleated Red Cells	0	
	M Neutrophils	14	1.8
	I Neutrophils	6	0.8
	Lymphocytes	79	10.1
	Monocytes	0	0.0
	Eosinophils	1	0.1
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		12.8
317	Nucleated Red Cells	0	
	M Neutrophils	29	3.6
	I Neutrophils	5	0.6
	Lymphocytes	64	8.0
	Monocytes	1	0.1
	Eosinophils	1	0.1
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		12.5
318	Nucleated Red Cells	1	
	M Neutrophils	8	1.1
	I Neutrophils	3	0.4
	Lymphocytes	80	11.4
	Monocytes	6	0.9
	Eosinophils	2	0.3
	Basophils	1	0.1
	Atypical Lymphocytes	0	0.0
	WBC		14.3
319	Nucleated Red Cells	0	
	M Neutrophils	20	4.0
	I Neutrophils	4	0.8
	Lymphocytes	74	14.9
	Monocytes	2	0.4
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		20.1
320	Nucleated Red Cells	0	
	M Neutrophils	20	3.2
	I Neutrophils	3	0.5
	Lymphocytes	76	12.0
	Monocytes	0	0.0
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		15.8

WHITE DIFFERENTIAL COUNTS

STUDY IO: 106

GROUP: 3-F : 2.0 mg base/kg/day

SEX: FEMALE

ANIMAL ID		DAY 14 REL	DAY 14 ABS
326	Nucleated Red Cells	0	
	M Neutrophils	10	1.3
	I Neutrophils	5	0.6
	Lymphocytes	81	10.1
	Monocytes	3	0.4
	Eosinophils	1	0.1
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		12.5
327	Nucleated Red Cells	0	
	M Neutrophils	36	5.3
	I Neutrophils	2	0.3
	Lymphocytes	58	8.5
	Monocytes	4	0.6
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		14.6
328	Nucleated Red Cells	0	
	M Neutrophils	22	3.1
	I Neutrophils	2	0.3
	Lymphocytes	73	10.1
	Monocytes	3	0.4
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		13.9
329	Nucleated Red Cells	0	
	M Neutrophils	10	1.5
	I Neutrophils	0	0.0
	Lymphocytes	84	12.9
	Monocytes	5	0.8
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		15.3
330	Nucleated Red Cells	0	
	M Neutrophils	8	1.4
	I Neutrophils	0	0.0
	Lymphocytes	90	15.4
	Monocytes	2	0.3
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.1

WHITE DIFFERENTIAL COUNTS

STUDY ID: 106

GROUP: 4-F : 6.2 mg base/kg/day

SEX: FEMALE

ANIMAL ID		DAY 14 REL	DAY 14 ABS
336	Nucleated Red Cells	1	
	M Neutrophils	12	2.7
	I Neutrophils	4	0.9
	Lymphocytes	80	17.8
	Monocytes	3	0.7
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		22.3
337	Nucleated Red Cells	0	
	M Neutrophils	11	4.4
	I Neutrophils	6	2.4
	Lymphocytes	82	32.5
	Monocytes	0	0.0
	Eosinophils	1	0.4
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		39.6
338	Nucleated Red Cells	1	
	M Neutrophils	15	3.8
	I Neutrophils	4	1.0
	Lymphocytes	78	19.7
	Monocytes	2	0.5
	Eosinophils	1	0.3
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		25.3
339	Nucleated Red Cells	0	
	M Neutrophils	9	1.8
	I Neutrophils	3	0.6
	Lymphocytes	85	17.1
	Monocytes	3	0.6
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		20.1
340	Nucleated Red Cells	0	
	M Neutrophils	15	3.2
	I Neutrophils	12	2.6
	Lymphocytes	72	15.3
	Monocytes	1	0.2
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		21.3

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MORPHOLOGY OBSERVATIONS

STUDY ID: 106

SEX: MALE

GROUP: 1-M : 0 mg base/kg/day

ANIMAL ID	DAY 14
301	Anisocytosis,Slight
302	Anisocytosis,Slight
303	Anisocytosis,Slight
304	Poikilocytes,Slight; Target Cells,Slight; Anisocytosis,Slight
305	Poikilocytes,Slight; Anisocytosis,Slight

DRAFT

MORPHOLOGY OBSERVATIONS

STUDY ID: 106

SEX: MALE

GROUP: 2-M : 0.5 mg base/kg/day

ANIMAL ID	DAY 14
311	Poikilocytes,Slight; Target Cells,Slight; Anisocytosis,Slight
312	Anisocytosis,Slight
313	Anisocytosis,Slight
314	Normal Red Blood Cells
315	Poikilocytes,Slight; Anisocytosis,Slight

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MORPHOLOGY OBSERVATIONS

STUDY ID: 106 SEX: MALE

GROUP: 3-M : 2.0 mg base/kg/day

ANIMAL ID	DAY 14
321	Anisocytosis,Slight
322	Anisocytosis,Slight
323	Anisocytosis,Slight
324	Anisocytosis,Slight
325	Anisocytosis,Slight

MORPHOLOGY OBSERVATIONS

STUDY ID: 106

SEX: MALE

GROUP: 4-M : 6.2 mg base/kg/day

ANIMAL ID	DAY 14
331	Anisocytosis,Slight
332	Anisocytosis,Slight
333	Anisocytosis,Slight
334	Poikilocytes,Slight; Anisocytosis, Moderate
335	--

(--)-Data Unavailable

MORPHOLOGY OBSERVATIONS

STUDY ID: 106

SEX: FEMALE

GROUP: 1-F : 0 mg base/kg/day

ANIMAL ID	DAY 14
306	Anisocytosis,Slight
307	Normal Red Blood Cells
308	Anisocytosis,Slight
309	Clumped Platelets, Moderate; Poikilocytes,Slight; Anisocytosis,Slight
310	Anisocytosis,Slight

MORPHOLOGY OBSERVATIONS

STUDY ID: 106

SEX: FEMALE

GROUP: 2-F : 0.5 mg base/kg/day

ANIMAL ID	DAY 14
316	Normal Red Blood Cells
317	Normal Red Blood Cells
318	Anisocytosis,Slight
319	Anisocytosis,Slight
320	Normal Red Blood Cells

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MORPHOLOGY OBSERVATIONS

STUDY ID: 106

SEX: FEMALE

GROUP: 3-F : 2.0 mg base/kg/day

ANIMAL ID	DAY 14
326	Polychromasia,Slight Anisocytosis, Moderate
327	Anisocytosis,Slight
328	Anisocytosis,Slight
329	Polychromasia,Slight Anisocytosis,Slight
330	Poikilocytes,Slight; Anisocytosis,Slight

MORPHOLOGY OBSERVATIONS

STUDY ID: 106

SEX: FEMALE

GROUP: 4-F : 6.2 mg base/kg/day

ANIMAL ID	DAY 14
336	Anisocytosis, Moderate
337	Polychromasia,Slight Target Cells,Slight; Anisocytosis, Moderate
338	Polychromasia,Slight Poikilocytes,Slight; Anisocytosis, Moderate
339	Anisocytosis, Moderate
340	Anisocytosis,Slight

APPENDIX 8

Individual Organ Weights

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 106
SEX: MALE

GROUP: 1-M - 0 mg base/kg/day
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	301	302	303	304	305
BODY WEIGHT (G)	306.0	287.7	278.4	301.0	288.3
BRAIN (G)	1.943	2.004	2.008	1.997	2.013
HEART (G)	1.131	1.083	1.144	1.299	1.293
KIDNEYS (G)	3.340	2.752	2.718	2.353	2.821
LIVER (G)	14.048	11.895	10.933	12.054	13.397
SPLEEN (G)	0.547	0.621	0.653	0.573	0.593
TESTES (G)	4.189	3.985	4.026	3.904	3.712

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INDIVIDUAL ORGAN WEIGHTS

STUDY: 106
SEX: MALE

GROUP: 2-M - 0.5 mg base/kg/day
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	311	312	313	314	315
BODY WEIGHT (G)	290.6	281.9	295.8	300.2	276.8
BRAIN (G)	1.840	2.000	1.881	1.957	1.820
HEART (G)	1.116	0.950	1.210	1.082	1.080
KIDNEYS (G)	2.681	2.513	2.821	3.018	2.957
LIVER (G)	10.971	12.187	14.018	12.419	12.997
SPLEEN (G)	0.669	0.608	0.562	0.722	0.605
TESTES (G)	3.896	3.936	3.844	4.224	3.174

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INDIVIDUAL ORGAN WEIGHTS

STUDY: 106
SEX: MALE

GROUP: 3-M - 2.0 mg base/kg/day
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	321	322	323	324	325
BODY WEIGHT (G)	293.9	281.7	288.6	263.1	320.3
BRAIN (G)	1.949	2.090	2.001	1.893	2.022
HEART (G)	1.223	1.140	1.139	0.956	1.249
KIDNEYS (G)	2.937	3.110	2.777	2.702	2.834
LIVER (G)	12.292	13.147	11.289	10.564	11.966
SPLEEN (G)	0.828	0.960	0.811	0.670	0.933
TESTES (G)	3.784	3.778	4.156	3.866	4.050

INDIVIDUAL ORGAN WEIGHTS

STUDY: 106
SEX: MALE

GROUP: 4-M - 6.2 mg base/kg/day
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	331	332	333	334
BODY WEIGHT (G)	298.1	266.6	205.5	180.8
BRAIN (G)	1.950	1.956	1.835	2.068
HEART (G)	1.375	1.215	0.768	0.765
KIDNEYS (G)	2.753	2.961	1.840	2.020
LIVER (G)	14.627	12.997	10.315	9.725
SPLEEN (G)	1.621	1.265	0.543	0.501
TESTES (G)	3.681	3.893	3.179	4.029

INDIVIDUAL ORGAN WEIGHTS

STUDY: 106
SEX: FEMALE

GROUP: 1-F - 0 mg base/kg/day
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	306	307	308	309	310
BODY WEIGHT (G)	196.2	193.9	218.9	215.6	209.4
BRAIN (G)	1.864	1.710	1.858	1.879	1.799
HEART (G)	0.895	0.779	0.942	0.877	0.965
KIDNEYS (G)	1.945	1.751	2.275	2.347	2.216
LIVER (G)	8.827	7.874	9.664	8.695	9.849
OVARY (G)	0.121	0.126	0.094	0.137	0.175
SPLEEN (G)	0.446	0.459	0.743	0.512	0.514

INDIVIDUAL ORGAN WEIGHTS

STUDY: 106
SEX: FEMALE

GROUP: 2-F - 0.5 mg base/kg/day
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	316	317	318	319	320
BODY WEIGHT (G)	225.2	215.5	217.5	210.4	197.5
BRAIN (G)	1.752	1.818	1.935	1.855	1.977
HEART (G)	0.885	0.975	0.933	0.841	0.795
KIDNEYS (G)	2.240	1.897	2.055	1.963	2.114
LIVER (G)	9.683	9.402	8.949	8.233	8.453
OVARY (G)	0.144	0.103	0.150	0.163	0.114
SPLEEN (G)	0.649	0.506	0.558	0.638	0.505

INDIVIDUAL ORGAN WEIGHTS

STUDY: 106
SEX: FEMALE

GROUP: 3-F - 2.0 mg base/kg/day
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	326	327	328	329	330
BODY WEIGHT (G)	248.8	199.7	231.9	213.6	209.1
BRAIN (G)	1.946	1.776	1.917	1.724	1.847
HEART (G)	0.973	0.809	0.943	0.804	0.918
KIDNEYS (G)	2.593	2.184	2.305	2.215	2.068
LIVER (G)	10.860	9.343	9.628	10.120	8.135
OVARY (G)	0.136	0.151	0.155	0.141	0.147
SPLEEN (G)	0.811	0.780	0.819	0.709	0.701

INDIVIDUAL ORGAN WEIGHTS

STUDY: 106
SEX: FEMALE

GROUP: 4-F - 6.2 mg base/kg/day
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	336	337	338	339	340
BODY WEIGHT (G)	208.5	202.0	183.3	192.6	203.9
BRAIN (G)	1.908	1.866	1.745	1.836	1.931
HEART (G)	1.140	0.938	0.950	0.785	0.848
KIDNEYS (G)	1.980	2.188	1.637	1.940	1.988
LIVER (G)	10.049	9.204	8.464	7.483	9.221
OVARY (G)	0.100	0.125	0.140	0.078	0.105
SPLEEN (G)	1.145	1.424	1.189	1.022	1.204

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APPENDIX 9

Pathology Report

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DRAFT PATHOLOGY REPORT FOR TRL STUDY NUMBER 106 TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR242511 IN RATS

PREPARED
BY
PATHOLOGY ASSOCIATES, INC.
10 WEST 35TH STREET
CHICAGO, IL 60616

FOR
TOXICOLOGY RESEARCH LABORATORY
UNIVERSITY OF ILLINOIS AT CHICAGO (UIC)
DEPARTMENT OF PHARMACOLOGY
P.O. BOX 6998
CHICAGO, IL 60680

AUGUST 16, 1993

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SECTION I

PATHOLOGY NARRATIVE

DRAFT PATHOLOGY REPORT

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR242511 IN RATS

INTRODUCTION

This pathology report, submitted by Pathology Associates, Inc. (PAI) to Toxicology Research Laboratory (TRL), represents the pathology findings for the study designated as "Two Week Oral Dose Range-Finding Toxicity Study of WR242511 in Rats," TRL Study Number 106.

EXPERIMENTAL DESIGN AND METHODS

Three groups, each composed of 5 male and 5 female Virus Antibody Free CD® rats, were given 0.5, 2.0, or 6.2 mg base/kg of WR242511 by gavage once daily for 14 days. Additionally, one group of 5 male and 5 female rats was given the test article vehicle (1% methylcellulose/0.2% Tween 80) once daily by gavage for 14 days (see Table I, Summary of Experimental Design). Dosing volume, 5 ml/kg, was constant for all groups. One animal in the 6.2 mg base/kg/day dose group (#335) was found dead and necropsied on Day 13 (Day 0 was the first day of dosing). All other animals were sacrificed and necropsied in random order on Day 14. Necropsies were performed according to TRL Standard Operating Procedures. Tissues required by the protocol were examined and fixed in 10% neutral buffered formalin. Tissues required for histopathologic evaluation (see Table II, Protocol-Required Tissues) were trimmed and processed, and slides were prepared in accordance with PAI Standard Operating Procedures. Tissues were then examined by light microscopy.

Microscopic findings for all groups are summarized in the Project Summary Tables (Section II). The mean group severity scores are found in the Severity Summary Tables (Section III). The mean group severity score was determined by dividing the sum of all severity scores for a finding by the number of tissues examined. Microscopic findings in the protocol-required tissues for individual animals are presented in the Tabulated Animal Data Tables (Section IV). The correlation of the necropsy findings and histopathology findings are reported in the Correlation of Gross and Microscopic (Micro) Findings (Section V). The codes used as entries in these tables are explained in the Report Codes Table. Abbreviations used in these tables are explained in the Abbreviation List.

RESULTS AND DISCUSSION

The Results and Discussion section is divided into two parts: Diagnostic Terms and Histopathology Findings. The Diagnostic Terms portion lists and clarifies diagnostic terminology that may be unclear. Terms listed in the Diagnostic Terms portion of this section were not necessarily considered to be test article-related. The Histopathology Findings portion of this section reports the results and provides discussion of the histopathologic evaluation of the tissues.

Diagnostic Terms

The morphologic characteristics of observations and lesions which require comment are presented in subsequent paragraphs to aid in the interpretation of the data.

Liver

Liver necrosis consisted of coagulative necrosis of individual or small clusters of hepatocytes oriented around or along central veins. In these areas, surrounding hepatocytes were sometimes vacuolated, and the organizational pattern of hepatocytes was disrupted. A few mononuclear cells, including macrophages and lymphocytes, were present in these areas.

Focal necrosis in the liver was distinct from liver necrosis described above, and was not associated with the central veins. The foci were large and distinct with defined margins. Affected hepatocytes had undergone coagulative necrosis and were being removed by infiltrating macrophages and neutrophils.

Spleen

Extramedullary hematopoiesis (EMH) in the spleen consisted of increased amounts of myeloid, erythroid, and megakaryocytic cells in the red pulp of the spleen.

Lymphocyte depletion in the spleen consisted of decreased numbers of lymphocytes in the lymphoid follicles.

Histopathology Findings

Potentially treatment-related lesions were found in the liver and spleen.

Liver

Liver necrosis occurred in 3 out of 5 males in the 6.2 mg base/kg/day dose group, with a mean group severity score of 1.00. This change did not occur in males of any other group, and did not occur in any females. The morphologic pattern of liver necrosis was consistent with patterns of liver necrosis known to be associated with exposure to toxic compounds.[1] The occurrence of this lesion only in 60% of the 6.2 mg base/kg/day males and the low (1.00) mean group severity score were considered to be consistent with a mild toxic effect of the test article. For these reasons, liver necrosis was interpreted as a test article-related change.

Focal necrosis of the liver occurred in 1 out of 5 females in each of the 0.5 and 2.0 mg base/kg/day dose groups. In each of these groups, this lesion occurred as a single focus in each affected animal. The mean group severity score for this change in each of the two groups was 0.20. Focal necrosis in the liver is commonly observed in animals and has been associated with infections, parasite migration, and biliary obstruction.[2] As it occurred as a single focus in a single animal in each of the two groups, did not occur in the 6.2 mg base/kg/day (high) dose group, and is a recognized spontaneous lesion in animals, focal necrosis in the liver was interpreted as not related to the test article.

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[1] James A. Popp and Russell C. Cattley, "Hepatobiliary System," Handbook of Toxicologic Pathology, eds. W.M. Haschek and C.G. Rousseaux, (San Diego: Academic Press, Inc., 1991), p.p. 279-314.

[2] W. Roger Kelly, "The Liver and Biliary System," Pathology of Domestic Animals, eds. K.V.F. Jubb, Peter C. Kennedy, and Nigel Palmer, (San Diego: Academic Press, Inc., 1985), p. 255.

Spleen

Extramedullary hematopoiesis (EMH) in the spleen was diagnosed in 3 out of 5 and 2 out of 5 males and in 1 out of 5 and 5 out of 5 females in the 2.0 and 6.2 mg base/kg/day dose groups, respectively. Mean group severity scores for this change were 0.60 and 0.60 in males and 0.20 and 1.80 in females in the 2.0 and 6.2 mg base/kg/day dose groups, respectively. Extramedullary hematopoiesis did not occur in control or 0.5 mg base/kg/day (low) dose groups in either males or females. The occurrence of EMH in the spleen of these rats suggests that there was a demand for increased leukocytes, erythrocytes, or platelets. Though it is difficult to quantify myeloid versus erythroid cells in EMH in tissue section, erythroid cells were more prominent in the EMH than were myeloid cells. This is consistent with the lack of significant inflammation in the tissues examined. For these reasons, EMH in the spleen was interpreted as most likely secondary to anemia.

Depletion of lymphocytes occurred only in animal number 335, which was found dead on Day 13 of the study. This animal was in the 6.2 mg base/kg/day dose group, and had the most severe liver necrosis observed. For these reasons, depletion of splenic lymphocytes in this animal was considered most likely related to generalized toxicity rather than to a direct test article-related effect.

Other Tissues

Several lesions occurred in other tissues examined in this study. These were considered incidental and not to warrant further discussion.

CONCLUSIONS

Under the conditions of this study, administration of WR242511 to rats by gavage for 14 days was associated with necrosis of low severity in the liver in males in the 6.2 mg base/kg/day (high) dose group. As this was the only direct effect of the test article, the no effect level in this study was the 2.0 mg base/kg/day (middle) dose level.

Splenic EMH occurred only in the 2.0 and 6.2 mg base/kg/day dose groups in males and females. The occurrence of splenic EMH was thought to most likely be secondary to anemia.

_____ _____

Michael J. Tomlinson, DVM, Ph.D. Date
Diplomate, ACVP

TABLE I

SUMMARY OF EXPERIMENTAL DESIGN

Treatment Group	Treatment	Dose Level (mg base/kg/day)	Number of Males	Number of Females
1	Vehicle Control*	0	5	5
2	WR242511	0.5	5	5
3	WR242511	2.0	5	5
4	WR242511	6.2	5	5

* Vehicle was 1% methylcellulose/0.2% Tween 80.

TABLE II

PROTOCOL-REQUIRED TISSUES

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

Those tissues marked with an asterisk (*) were examined microscopically for all rats in all groups. The remaining tissues were collected at necropsy, but not processed and examined.

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PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 106

Report Codes Table

A. Codes applying to organs

N	Tissues within normal histological limits
A	Autolysis precluding adequate evaluation
P	Paired organ missing
U	Tissues unsuitable for complete evaluation
S	Tissues not applicable to animal
*	Tissues not required by protocol

B. Codes applying to microscopic diagnoses

1	minimal
2	mild
3	moderate
4	marked
)	focal
]	locally extensive
>	multifocal
P	Present
B	Neoplasm, benign
M	Neoplasm, malignant without metastasis
C	Neoplasm, malignant with metastasis
X	Metastatic site (+)
-	No data entered

HISTOPATHOLOGY TABLES

ABBREVIATION LIST

Cyto - Cytoplasm
Epith - Epithelium
Mbkd - Mg base/kg/day
Tub - Tubule
Vacuo - Vacuolation

SECTION II

PROJECT SUMMARY TABLE

PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 106

Project Summary Table

SUMMARY: Incidence of NEOPLASTIC and NON-NEOPLASTIC Microscopic Findings

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PROJECT ID. NO: TRL106 FATES: Terminal Sacrifice,Natural Death
DAYS : 13-14 SEX: MALE

GROUP:		0.0 mbkd		0.5 mbkd		2.0 mbkd		6.2 mbkd	
NUMBER OF ANIMALS:		5		5		5		5	
		#	%	#	%	#	%	#	%
BRAIN	# Ex	5		5		5		5	
LIVER	# Ex	5		5		5		5	
Necrosis		0	(0)	0	(0)	0	(0)	3	(60)
SPLEEN	# Ex	5		5		5		5	
Extramedullary hematopoiesis		0	(0)	0	(0)	3	(60)	2	(40)
Depletion, lymphocytes		0	(0)	0	(0)	0	(0)	1	(20)
KIDNEY	# Ex	5		5		5		5	
Renal tubule, casts, proteinic		1	(20)	0	(0)	1	(20)	0	(0)
Renal tub, epith, vacuo, cyto		0	(0)	0	(0)	0	(0)	1	(20)
HEART	# Ex	5		5		5		5	
Cardiomyopathy		1	(20)	0	(0)	0	(0)	0	(0)
TESTIS	# Ex	5		5		5		5	
EPIDIDYMIS	# Ex	5		5		5		5	
Inflammation, subacute		1	(20)	0	(0)	0	(0)	0	(0)

PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 106

Project Summary Table

SUMMARY: Incidence of NEOPLASTIC and NON-NEOPLASTIC Microscopic Findings

DRAFT

PROJECT ID. NO: TRL106 FATES: Terminal Sacrifice,Natural Death
DAYS : 13-14 SEX: FEMALE

GROUP:		0.0 mbkd		0.5 mbkd		2.0 mbkd		6.2 mbkd	
NUMBER OF ANIMALS:		5		5		5		5	
		#	%	#	%	#	%	#	%
BRAIN	# Ex	5		5		5		5	
LIVER	# Ex	5		5		5		5	
Necrosis, focal		0	(0)	1	(20)	1	(20)	0	(0)
SPLEEN	# Ex	5		5		5		5	
Extramedullary hematopoiesis		0	(0)	0	(0)	1	(20)	5	(100)
KIDNEY	# Ex	5		5		5		5	
Cortex, interstitium, fibrosis		0	(0)	0	(0)	0	(0)	1	(20)
Nephrocalcinosis		2	(40)	3	(60)	1	(20)	1	(20)
Renal tub, epith, regeneration		0	(0)	1	(20)	0	(0)	1	(20)
HEART	# Ex	5		5		5		5	
Cardiomyopathy		0	(0)	1	(20)	0	(0)	0	(0)
OVARY	# Ex	5		5		5		5	

SECTION III

SEVERITY SUMMARY TABLE

PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 106

Severity Summary Table

DRAFT

PROJECT ID. NO: TRL106
DAYS: 13-14
FATES: Terminal Sacrifice,Natural Death
SEX: MALE

GROUP:		0.0 mbkd		0.5 mbkd		2.0 mbkd		6.2 mbkd	
NUMBER OF ANIMALS:		5		5		5		5	
		#	SEV	#	SEV	#	SEV	#	SEV
BRAIN	# Ex	5		5		5		5	
LIVER	# Ex	5		5		5		5	
Necrosis		0		0		0		3	1.00
SPLEEN	# Ex	5		5		5		5	
Extramedullary hematopoiesis		0		0		3	0.60	2	0.60
Depletion, lymphocytes		0		0		0		1	0.60
KIDNEY	# Ex	5		5		5		5	
Renal tubule, casts, proteinic		1	0.20	0		1	0.20	0	
Renal tub, epith, vacuo, cyto		0		0		0		1	0.40
HEART	# Ex	5		5		5		5	
Cardiomyopathy		1	0.20	0		0		0	
TESTIS	# Ex	5		5		5		5	
EPIDIDYMIS	# Ex	5		5		5		5	
Inflammation, subacute		1	0.20	0		0		0	

* Severity calculated by the number of tissues examined.

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PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 106

Severity Summary Table

DRAFT

PROJECT ID. NO: TRL106 FATES: Terminal Sacrifice,Natural Death
DAYS: 13-14 SEX: FEMALE

GROUP:		0.0 mbkd		0.5 mbkd		2.0 mbkd		6.2 mbkd	
NUMBER OF ANIMALS:		5		5		5		5	
		#	SEV	#	SEV	#	SEV	#	SEV
BRAIN	# Ex	5		5		5		5	
LIVER	# Ex	5		5		5		5	
Necrosis, focal		0		1	0.20	1	0.20	0	
SPLEEN	# Ex	5		5		5		5	
Extramedullary hematopoiesis		0		0		1	0.20	5	1.80
KIDNEY	# Ex	5		5		5		5	
Cortex, interstitium, fibrosis		0		0		0		1	0.20
Nephrocalcinosis		2	0.40	3	0.60	1	0.20	1	0.20
Renal tub, epith, regeneration		0		1	0.20	0		1	0.20
HEART	# Ex	5		5		5		5	
Cardiomyopathy		0		1	0.20	0		0	
OVARY	# Ex	5		5		5		5	

* Severity calculated by the number of tissues examined.

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SECTION IV

TABULATED ANIMAL DATA

Tabulated Animal Data

DRAFT

PROJECT ID: TRL106 GROUP: 0.0 mbkd SEX: MALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID:	301	302	303	304	305
BRAIN	N	N	N	N	N
LIVER	N	N	N	N	N
SPLEEN	N	N	N	N	N
KIDNEY	N	N	N		N
Renal tubule, casts, proteinic	-	-	-	1	-
HEART	N	N	N		N
Cardiomyopathy	-	-	-	1	-
TESTIS	N	N	N	N	N
EPIDIDYMIS	N	N	N	N	
Inflammation, subacute	-	-	-	-	1

Tabulated Animal Data

DRAFT

PROJECT ID: TRL106 GROUP: 0.5 mbkd SEX: MALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID:	311	312	313	314	315
BRAIN	N	N	N	N	N
LIVER	N	N	N	N	N
SPLEEN	N	N	N	N	N
KIDNEY	N	N	N	N	N
HEART	N	N	N	N	N
TESTIS	N	N	N	N	N
EPIDIDYMIS	N	N	N	N	N

Tabulated Animal Data

DRAFT

PROJECT ID: TRL106 GROUP: 2.0 mbkd SEX: MALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID:	321	322	323	324	325
BRAIN	N	N	N	N	N
LIVER	N	N	N	N	N
SPLEEN			N	N	
Extramedullary hematopoiesis	1	1	-	-	1
KIDNEY	N	N	N	N	
Renal tubule, casts, proteinic	-	-	-	-	1
HEART	N	N	N	N	N
TESTIS	N	N	N	N	N
EPIDIDYMIS	N	N	N	N	N

Tabulated Animal Data

DRAFT

PROJECT ID: TRL106 GROUP: 6.2 mbkd SEX: MALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID:	331	332	333	334	335
BRAIN	N	N	N	N	N
LIVER	N	N			
Necrosis	-	-	1	1	3
SPLEEN			N	N	
Extramedullary hematopoiesis	2	1	-	-	-
Depletion, lymphocytes	-	-	-	-	3
KIDNEY	N	N	N	N	
Renal tub, epith, vacuo, cyto	-	-	-	-	2
HEART	N	N	N	N	N
TESTIS	N	N	N	N	N
EPIDIDYMIS	N	N	N	N	N

Tabulated Animal Data

DRAFT

PROJECT ID: TRL106 GROUP: 0.0 mbkd SEX: FEMALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID:	306	307	308	309	310
BRAIN	N	N	N	N	N
LIVER	N	N	N	N	N
SPLEEN	N	N	N	N	N
KIDNEY	N			N	N
Nephrocalcinosis	-	1	1	-	-
HEART	N	N	N	N	N
OVARY	N	N	N	N	N

Tabulated Animal Data

DRAFT

PROJECT ID: TRL106 GROUP: 0.5 mbkd SEX: FEMALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID:	316	317	318	319	320
BRAIN	N	N	N	N	N
LIVER	N	N	N		N
Necrosis, focal	-	-	-	1	-
SPLEEN	N	N	N	N	N
KIDNEY		N			N
Nephrocalcinosis	1	-	1	1	-
Renal tub, epith, regeneration	-	-	1	-	-
HEART	N	N	N	N	
Cardiomyopathy	-	-	-	-	1
OVARY	N	N	N	N	N

Tabulated Animal Data

DRAFT

PROJECT ID: TRL106 GROUP: 2.0 mbkd SEX: FEMALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID:	326	327	328	329	330
BRAIN	N	N	N	N	N
LIVER		N	N	N	N
Necrosis, focal	1	-	-	-	-
SPLEEN		N	N	N	N
Extramedullary hematopoiesis	1	-	-	-	-
KIDNEY	N	N		N	N
Nephrocalcinosis	-	-	1	-	-
HEART	N	N	N	N	N
OVARY	N	N	N	N	N

Tabulated Animal Data

DRAFT

PROJECT ID: TRL106 GROUP: 6.2 mbkd SEX: FEMALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID:	336	337	338	339	340
BRAIN	N	N	N	N	N
LIVER	N	N	N	N	N
SPLEEN					
Extramedullary hematopoiesis	1	2	2	2	2
KIDNEY			N		N
Cortex, interstitium, fibrosis	-	1	-	-	-
Nephrocalcinosis	1	-	-	-	-
Renal tub, epith, regeneration	-	-	-	1	-
HEART	N	N	N	N	N
OVARY	N	N	N	N	N

SECTION V

CORRELATION OF GROSS AND MICROSCOPIC (MICRO) FINDINGS

PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 106

Correlation of Gross & Micro Findings DRAFT

PROJECT ID: TRL106 GROUP: 0.0 mbkd SEX: MALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID: 301 PATHOLOGY ID. NO: TI106-301 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 302 PATHOLOGY ID. NO: TI106-302 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 303 PATHOLOGY ID. NO: TI106-303 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 304 PATHOLOGY ID. NO: TI106-304 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

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PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 106

Correlation of Gross & Micro Findings DRAFT

PROJECT ID: TRL106 GROUP: 0.0 mbkd SEX: MALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID: 305 PATHOLOGY ID. NO: TI106-305 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice

DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

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Correlation of Gross & Micro Findings DRAFT

ANIMAL ID: 311 PATHOLOGY ID. NO: TI106-311 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 312 PATHOLOGY ID. NO: TI106-312 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 313 PATHOLOGY ID. NO: TI106-313 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 314 PATHOLOGY ID. NO: TI106-314 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 106

Correlation of Gross & Micro Findings DRAFT

PROJECT ID: TRL106 GROUP: 0.5 mbkd SEX: MALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID: 315 PATHOLOGY ID. NO: TI106-315 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

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PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 106

Correlation of Gross & Micro Findings DRAFT

PROJECT ID: TRL106 GROUP: 2.0 mbkd SEX: MALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID: 321 PATHOLOGY ID. NO: TI106-321 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 322 PATHOLOGY ID. NO: TI106-322 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 323 PATHOLOGY ID. NO: TI106-323 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 324 PATHOLOGY ID. NO: TI106-324 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 106

Correlation of Gross & Micro Findings DRAFT

PROJECT ID: TRL106 GROUP: 2.0 mbkd SEX: MALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID: 325 PATHOLOGY ID. NO: TI106-325 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice

DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

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PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 106

Correlation of Gross & Micro Findings DRAFT

PROJECT ID: TRL106 GROUP: 6.2 mbkd SEX: MALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID: 331 PATHOLOGY ID. NO: TI106-331 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 332 PATHOLOGY ID. NO: TI106-332 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 333 PATHOLOGY ID. NO: TI106-333 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 334 PATHOLOGY ID. NO: TI106-334 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 106

Correlation of Gross & Micro Findings DRAFT

PROJECT ID: TRL106 GROUP: 6.2 mbkd SEX: MALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID: 335 PATHOLOGY ID. NO: TI106-335 PATHOLOGIST: MJT
ANIMAL FATE: Natural Death

DAYS ON TEST:13

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

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PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 106

Correlation of Gross & Micro Findings DRAFT

PROJECT ID: TRL106 GROUP: 0.0 mbkd SEX: FEMALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID: 306 PATHOLOGY ID. NO: TI106-306 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 307 PATHOLOGY ID. NO: TI106-307 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 308 PATHOLOGY ID. NO: TI106-308 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 309 PATHOLOGY ID. NO: TI106-309 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 106

Correlation of Gross & Micro Findings DRAFT

PROJECT ID: TRL106 GROUP: 0.0 mbkd SEX: FEMALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID: 310 PATHOLOGY ID. NO: TI106-310 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

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Correlation of Gross & Micro Findings DRAFT

ANIMAL ID: 316 PATHOLOGY ID. NO: TI106-316 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 317 PATHOLOGY ID. NO: TI106-317 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 318 PATHOLOGY ID. NO: TI106-318 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 319 PATHOLOGY ID. NO: TI106-319 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

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Correlation of Gross & Micro Findings DRAFT

PROJECT ID: TRL106 GROUP: 0.5 mbkd SEX: FEMALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID: 320 PATHOLOGY ID. NO: TI106-320 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice

DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>SPLEEN - LESION, DIFFUSE, PALE	No corresponding lesion
>LIVER, LEFT LATERAL LOBE - NODULE, SINGLE, SPHERICAL, DARK, HARD, 5 X 4 MM	No corresponding lesion
>LIVER - LESION, MULTIPLE, IRREGULAR, DARK, 2.5 X 0.5 MM	No corresponding lesion

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Correlation of Gross & Micro Findings DRAFT

PROJECT ID: TRL106 GROUP: 2.0 mbkd SEX: FEMALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID: 326 PATHOLOGY ID. NO: TI106-326 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 327 PATHOLOGY ID. NO: TI106-327 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 328 PATHOLOGY ID. NO: TI106-328 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 329 PATHOLOGY ID. NO: TI106-329 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS
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Correlation of Gross & Micro Findings DRAFT

PROJECT ID: TRL106 GROUP: 2.0 mbkd SEX: FEMALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID: 330 PATHOLOGY ID. NO: TI106-330 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

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PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 106

Correlation of Gross & Micro Findings DRAFT

PROJECT ID: TRL106 GROUP: 6.2 mbkd SEX: FEMALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID: 336 PATHOLOGY ID. NO: TI106-336 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 337 PATHOLOGY ID. NO: TI106-337 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 338 PATHOLOGY ID. NO: TI106-338 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 339 PATHOLOGY ID. NO: TI106-339 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 106

Correlation of Gross & Micro Findings DRAFT

PROJECT ID: TRL106 GROUP: 6.2 mbkd SEX: FEMALE
DAYS: 13-14 FATES: Terminal Sacrifice,Natural Death

ANIMAL ID: 340 PATHOLOGY ID. NO: TI106-340 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

13-Aug-1993

SECTION VI

QUALITY ASSURANCE STATEMENT

QUALITY ASSURANCE STATEMENT

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

	Date of Inspection	Phase Inspected	Date Findings Reported to Management and Study Pathologist
*	06/17/93	Tissue Trimming	06/17/93
*	08/09/93	Processing/Embedding	08/09/93
**	07/27/93	Microtomy	07/28/93
*	07/14/93	Staining	07/19/93
*	07/14/93	Coverslipping	07/19/93
*	08/02/93	Labeling	08/02/93
*	06/09/93	Quality Control/Checkout	06/09/93
**	08/12/93	Individual Animal Data	08/16/93
**	08/12/93	Data Entry	08/16/93
**	08/13/93	Computer Validation	08/16/93
**	08/16/93	Draft Pathology Report	08/16/93

*General quarterly phase inspection
**Inspection specific for Study Number

In accordance with the PAI Quality Assurance Division's Standard Operating Procedures, all critical phase inspections are conducted on a random basis quarterly or more frequently. Those general phase inspections listed are the most recent conducted during the period each task associated with this project was performed.

Quality Assurance Unit
PAI Illinois Division

08/16/93
Date

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APPENDIX 10

Protocol and Amendments

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Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-7C
UIC/TRL Study No.: 106

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR242511 IN RATS

1.0 PURPOSE OF THE STUDY:

The purpose of this study is to determine the toxicity of WR242511 in CD® rats following two weeks of daily gavage administration. Results derived from this study will be used to determine dose levels for the "Thirteen Week Oral Toxicity Study of WR242511 in Rats".

2.0 SPONSOR:

2.1	Name:	U.S. Army Medical Research and Development Command
2.2	Address:	Fort Detrick Frederick, MD 21702-5009
2.3	Representative:	George Schieferstein, Ph.D.

3.0 TESTING FACILITY:

3.1	Name:	Toxicology Research Laboratory (TRL)
3.2	Address:	University of Illinois at Chicago (UIC) Department of Pharmacology P.O. Box 6998 Chicago, Illinois 60680
3.3	Study Director:	Barry S. Levine, D.Sc., D.A.B.T.

4.0 DATES:

4.1	Study Initiation Date (see 11.0; Protocol Approval):	12/03/92
4.2	Proposed Initiation of Dosing:	06/24/93
4.3	Proposed Necropsy Dates:	07/08/93
4.4	Proposed Study Completion Date (Draft Study Report):	09/08/93

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5.0 TEST ARTICLE

5.1 Name or Code No: WR242511 Tartrate
Bottle Number will be indicated in the raw data.

5.2 TRL Chemical No: 1720614

5.3 Physical Description: Orange powder

5.4 Stability and Handling of Test Article:

5.4.1 Temperature: -20 to -15°C.

5.4.2 Humidity: Ambient conditions at -20 to -15°C in a freezer.

5.4.3 Light: Protect from light.

5.4.4 Special Requirements: None.

5.5 Special Handling Procedures: Standard safety precautions will be followed including gloves, eye protection, mask, and lab coats.

5.6 Log of Test Articles: The amount, date, identity of person(s) removing aliquots and the purpose for which each aliquot of the test article was removed from the batch will be documented. At termination of the study, all unused test article will be returned to the Sponsor.

6.0 PERSONNEL:

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
Toxicologist	Clyde W. Wheeler, Ph.D.
Pathologist	Michael J. Tomlinson, D.V.M., Ph.D., D.A.C.V.P.
Pathology Support	Ralph M. Bunte, D.V.M., D.A.C.V.P.
Analytical Chemist	Adam Negrusz, Ph.D.
Clinical Veterinarian	James E. Artwohl, D.V.M., M.S., D.A.C.L.A.M.
Veterinarian Support	To be documented in the raw data
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Nancy Dinger, B.S.
Chemistry Specialist	Thomas Tolhurst, B.S.
Clinical Pathology	Maria Lang, A.H.T., C.V.T.
Quality Assurance	Ronald C. Schoenbeck

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7.0 TEST SYSTEM:

7.1 Species: Rat

7.2 Strain: CD® (Virus Antibody Free)

7.3 Number and Sex: 20 Males and 20 Females

7.4 Age of Animals: Approximately 7 weeks old at dosing initiation.

7.5 Weight of Animals: Approximately 225 - 275 g (males) and approximately 150 - 200 g (females) at dosing initiation.

7.6 Source of Animals: Charles River Breeding Laboratories. The specific breeding facility will be documented in the raw data.

7.7 Justification for Selection of Test System: The rat is a standard and accepted rodent species for toxicological studies, and is specified by the Sponsor.

7.8 Procedure for Unique Identification of Test System: Upon arrival, each animal will be given a study-unique quarantine/pretest number. During the test animal selection process, each test animal will be assigned a test animal number unique to it within the population making up the study. This number will appear as an ear tag and will also appear on a cage card visible on the front of each cage. The cage card will additionally contain the study number, test article identification, treatment group number and dose level. Cage cards will be color-coded as a function of treatment group. Raw data records and specimens will also be identified by the unique test animal number.

7.9 Housing: The animals will be housed in an AAALAC-accredited facility. Animals will be singly housed in polycarbonate cages with Anderson-bed-a-cob bedding (Heinold, Kankakee, Illinois) in a temperature (65-78°F) and humidity (approx. 30-70%) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 840 cm area and 20 cm height, is 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 will be routinely transferred to clean cages with fresh bedding once weekly.

7.10 Quarantine Procedure: Animals will be quarantined for approximately one week. During that time, the animals will be observed daily for signs of illness or death, and all unusual observations will be reported to the Study Director, Toxicologist or Clinical Veterinarian. Animals will be examined during quarantine and

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approved for use by the Clinical Veterinarian prior to being placed on test. Any sickly animals will be eliminated prior to the test animal selection process. If a selected animal appears sickly, it will be replaced by a healthy animal prior to initiation of treatment under the direction of the Study Director or Toxicologist. Quarantine release will be documented on the Clinical Veterinarian Log by the veterinarian prior to study initiation.

7.11 Food: Purina Certified Rodent Chow No. 5002 (Ralston Purina Company, St. Louis, MO) will be 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.

7.12 Water: Tap water from an automatic watering system in which the room distribution lines are flushed daily will be provided *ad libitum* from arrival until termination. The water is untreated with additional chlorine or HCl.

7.13 There are no known contaminants in the feed or water which are expected to influence the study. A copy of the feed certification will be kept with the study records. The results of bimonthly comprehensive chemical analyses of Chicago water are documented in files maintained by Quality Assurance.

8.0 EXPERIMENTAL DESIGN:

8.1 Treatment Groups:

Treatment Group	Treatment	Dose Level (mg base/kg/day)[a]	Number of Males	Number of Females
1	Vehicle Control	0	5	5
2	WR242511	0.5	5	5
3	WR242511	2.0	5	5
4	WR242511	6.2	5	5

[a]Dose levels were selected by the Sponsor.

The number of animals/sex/group is necessary for statistical analyses.

If toxicity is not observed after one week of treatment, the mid dose may be escalated above the high dose for the second week of treatment.

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8.2 Frequency and Route of Administration of the Test Articles: The test article will be administered once daily by gavage for at least two weeks. Control animals will receive the test article vehicle. Dosing volume will be 5 ml/kg. The animals will be dosed up to and including the day before their necropsy.

8.3 Justification of Route: The oral route is a convenient and accepted procedure for administering a specific amount of a test article to each animal. It mimics potential human exposure conditions and is specified by the Sponsor.

8.4 Procedure to Control Bias during the Assignment of Animals to Treatment Groups: During the quarantine/pretest period, the animals will be randomized by sex into the groups shown in Section 8.1 using a computer-generated randomization procedure on the basis of body weight.

8.5 Test Article Vehicle: 1% Methylcellulose/0.2% Tween 80.

8.6 Test Article Dosage Form Preparation and Analyses: The stability and homogeneity of the test article/carrier mixture will be determined prior to study start. Fresh dosage formulations will be prepared weekly, if stability data permit, by suspending the appropriate quantity of test article in the vehicle using a mortar and pestle. Sample of dosage formulations (including controls) used at the onset of Weeks 1 and 2 will be analyzed for test article concentration prior to use. Only samples within 10% of their intended concentration will be used.

8.7 Type and Frequency of Observations, Tests, Analyses and Measurements:

8.7.1 Mortality Check: All animals will be observed twice daily, at least six hours apart for moribundity/mortality.

8.7.2 Clinical Signs: All animals will be examined for clinical signs, approximately 1 - 2 hours after dosing.

8.7.3 Clinical Observations: All animals will be subjected to a physical examination including examination of eyes and all orifices in Week -1, on Day 0, and twice weekly thereafter.

8.7.4 Body Weight: Body weights of all animals will be recorded at randomization in Week -1, on Day 0, twice weekly thereafter, and at termination.

8.7.5 Food Consumption: Food consumption for all animals will be measured twice weekly commencing in the latter half of Week -1.

8.7.6 Clinical Pathology: Hematology and clinical chemistry parameters will be measured for all rats on Day 14 (at scheduled necropsy).

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The overnight fasted animals will be anesthetized by carbon dioxide inhalation, and sufficient blood will be collected from the orbital sinus to measure the following parameters. The samples will be processed in the same random order as collected.

Hematology

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

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

Clinical Chemistry

Albumin (A)
Albumin/Globulin (A/G) ratio (calc.)
Alkaline phosphatase
Alanine aminotransferase (ALT/SGPT)
Aspartate aminotransferase (AST/SGOT)
Calcium
Chloride
Cholesterol
Creatinine
Globulin (G) (calc.)
Glucose
Inorganic phosphorus
Potassium
Sodium
Total bile acids
Total protein
Triglycerides
Urea nitrogen (BUN)

8.7.8 Pathology: All animals which die on test or are sacrificed if moribund will be necropsied as soon as possible on the day of death. The surviving animals will be sacrificed and necropsied in random order on Day 14. Euthanasia will be accomplished by carbon dioxide asphyxiation, and an extensive necropsy will be performed under the direction and supervision of the pathologist. Terminal body weights will be collected prior to routine sacrifice. The necropsy procedure will be 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).

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

*Weighed at scheduled necropsy (paired organs will be weighed together).

Those tissues marked with an asterisk (*) will be examined microscopically for all rats in all groups.

8.7.9 Statistical Analyses: For each sex, Analysis of Variance tests will be conducted on body weight, food consumption, hematology, clinical chemistry and organ weight data. Organ weight analysis will consider absolute weights and weights relative to body weight. If a significant F ratio is obtained ($p \leq 0.05$), Dunnett's t test will be used for pair-wise comparisons with the control group. Frequency data such as incidence of mortality, gross necropsy observations and tissues morphology observations will be compared by Fishers Exact Test or Chi-square analyses as necessary.

9.0 RECORDS TO BE MAINTAINED:

All data generated during the conduct study, except those that are generated as direct computer input, shall be recorded directly, promptly, and accurately in ink in bound books with prenumbered pages or on worksheets that shall be bound during or at the conclusion of the nonclinical laboratory study. All appropriate computer and machine output shall be bound during or at the conclusion of the study. All data entries shall be dated on the day of entry and signed or initialed by the person entering the data. Any changes in entries for whatever reason (e.g., to

correct an error or transposition) shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of data input. In computer driven collection systems, the operator responsible for direct input shall be identified at the time of data input. Any changes in computer entries for whatever reason (e.g, to correct an error or transposition) shall be made in such manner so as not to obscure the original entry, if possible, shall indicate the reason for such change, and shall be dated and the responsible individual shall be identified.

All recorded data shall be reviewed, signed, and dated by a knowledgeable person, other than the person making the entry, to assure adherence to procedures and to verify observations.

Upon completion of the study and submission of the final report, all raw data, documentation, specimens, each test article reserves and other materials necessary to reconstruct the study will be stored in the TRL archives maintained by Quality Assurance, unless specified by the Sponsor.

All changes or revisions, and reasons therefore, to this protocol once it is approved shall be documented, signed by the Study Director and Sponsor, dated and maintained with the protocol.

10.0 REGULATORY REQUIREMENTS:

This study will be performed in compliance with the UIC/TRL Quality Assurance Program designed to conform with FDA Good Laboratory Practice Regulations and EPA Good Laboratory Practice Standards. The protocol for this study was approved by the UIC Animal Care Committee.

Will this study be submitted to a regulatory agency? Yes
If so, to which agency(ies)? U.S. Food and Drug Administration
Does the Sponsor request that remaining test articles be returned? Yes
Does the Sponsor request that samples of test article/c arrier mixture(s) be returned? No

11.0 PROTOCOL APPROVAL:

STUDY DIRECTOR: Barry S. Levine
Barry S. Levine, D.Sc., D.A.B.T. — Date: 12/3/92

QUALITY ASSURANCE: Ronald Schoenbeck
Ronald Schoenbeck — Date: 12/7/92

SPONSOR APPROVAL: G Schieferstein
George Schieferstein, Ph.D.
Contracting Officer's
Representative (COR) — Date: 12-8-92

COMMENTS FROM THE COR:

PROTOCOL AMENDMENT DRAFT

Study No.: 106

Title: Two Week Oral Dose Range-Finding Toxicity Study of WR242511 in Rats

1. Page 1 Section 4.0

Change the study dates as follows:

4.2 Proposed Initiation of Dosing: 06/24/93

4.3 Proposed Necropsy Date: 07/08/93

4.4 Proposed Study Completion Date (Draft Study Report): 09/08/93

Reason: Study dates have been finalized.

2. Page 2 Section 5.2

Change the TRL Chemical No. "0930614" to "1720614"

Reason: A different composition of the test article was supplied by the Sponsor (tartrate instead of disulfate which was previously tested and assigned number 0930614).

3. Page 2 Section 6.0

A. Change the Toxicologist from E. Marianna Furedi-Machacek, D.V.M." to "Clyde W. Wheeler, Ph.D."

B. Change the Analytical Chemist form "Ian Tebbett, Ph.D." to "Adam Negrusz, Ph.D."

Reason: Dr. Furedi-Machacek and Dr. Tebbett resigned from UIC.

4. Page 3 Section 7.9

Change "DHEW (NIH) No. 86.23" to "DHHS (NIH) No. 86.23".

Reason: Mistake in protocol.

PROTOCOL AMENDMENT DRAFT

Study No.: 106

Title: Two Week Oral Dose Range-Finding Toxicity Study of WR242511 in Rats

5. Page 4 Section 8.1

A. Change the dose levels to read as follows:

"Low" = "0.5" mg base/kg/day

"Mid" = "2.0" mg base/kg/day

"High" = "6.2" mg base/kg/day

B. Change footnote * to indicate that dose levels were selected by the Sponsor.

Reason: Dose levels have been selected following consultation with the Sponsor.

6. Page 5 Section 8.5

Change Test Article Vehicle from "0.5% Na+carboxymethylcellulose/0.3% Tween 80" to "1% Methylcellulose/0.2% Tween 80".

Reason: Better suspendability was achieved with this vehicle.

7. Page 5 Section 8.6

Change sentence "Samples of dosage formulations (including controls) used in Weeks 1 and 2 will be analyzed for test article concentration prior to use" to "Sample of dosage formulations (including controls) used at the onset of Weeks 1 and 2 will be analyzed for test article concentration prior to use".

Reason: Clarification of protocol since WR242511 dosage formulations are only stable for 48 hours.

8. Page 5 Section 8.7.3

Change "weekly thereafter" to "twice weekly thereafter" regarding clinical observations.

Reason: Mistake in protocol.

PROTOCOL AMENDMENT

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Study No.: 106

Title: Two Week Oral Dose Range-Finding Toxicity Study of WR242511 in Rats

9. Page 5 Section 8.7.5

Change "latter half of Week 1" to "latter half of Week -1" regarding the onset of food consumption measurements.

Reason: Mistake in protocol.

10. Page 6 Section 8.7.6

Change Clinical Chemistry test "Sorbitol dehydrogenase" to "Aspartate aminotransferase (AST/SGOT)".

Reason: The sorbitol dehydrogenase assay is not yet available in the clinical pathology laboratory.

Approvals:

STUDY DIRECTOR: Barry S. Levine, D.Sc. D.A.B.T. 7/7/93 Date

SPONSOR APPROVAL: George Schieferstein, Ph.D. Contracting Officer's Representative (COR) 7/12/93. Date

(ENCL.)

APPENDIX 11

Study Deviations

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR242511 IN RATS

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Study Deviations*

Deviation Type	Specific Deviation	Effect on Study
Protocol	WR242511 tartrate is incorrectly described in the protocol as an orange powder. The tartrate salt of WR242511 is a yellow powder.	None.

*The detailed "Deviation Report" is contained in the raw data which are archive at the University of Illinois at Chicago, Department of Pharmacology, Chicago, Illinois.

The above deviation did not affect the integrity of the study.

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

_____
Date