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Title Page

Study Report for Task Order No. UIC-7D

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR269410 IN RATS

Sponsor: US Army Medical Materiel Development Activity

Test Article: WR269410

Contract No.: DAMD17-92-C-2001

Study Director

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

In-Life Phase Completed On

July 9, 1993

Performing Laboratory

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This study evaluated the toxicity of WR269410 in rats following two weeks of daily oral administration by gavage. Dose levels studied were 0 (vehicle control), 2.0, 6.0, and 18.0 mg/kg/day at study initiation. On Day 7, the mid dose level (6.0 mg/kg/day) was elevated above the high dose to 30 mg/kg/day for the second treatment week due to a lack of significant toxicity at the high dose during the first week of treatment. The primary toxic effect of WR269410 was hemolytic anemia, which was supported by macrocytosis, reticulocytosis, Heinz bodies, splenomegaly and extramedullary hematopoiesis. Females were more sensitive than males to the anemic state. Anemia was seen in males at the two higher doses, but was apparent in all female treatment groups. Methemoglobinemia, the expected pharmacologic effect, was also observed at all three dose levels. As this is the desired pharmacologic effect of WR269410, its occurrence was not considered indicative of toxicity. Cardiomegaly, possibly secondary to the methemoglobinemic and anemic state, was seen only in females at 6.0/30.0 mg/kg/day. 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 dose levels are suggested: 0, 1, 2.5 and 6 mg/kg/day. After consultation with the Sponsor, the following dose levels have been chosen for the three month toxicity study in rats: 0, 1, 3, and 10 mg/kg/day.

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STATEMENT OF COMPLIANCE

To the best of my knowledge, Study No. 112 entitled "Two Week Oral Dose Range-Finding Toxicity Study of WR269410 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.

3/21/94
Date

QUALITY ASSURANCE STATEMENT

STUDY TITLE: TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR269410 IN RATS

STUDY NUMBER: 112

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

INSPECT ON 6/29/93, TO STUDY DIR 6/30/93, TO MGMT 7/2/93
PHASES: TEST ARTICLE PREPARATION

INSPECT ON 7/9/93, TO STUDY DIR 7/12/93, TO MGMT 7/12/93
PHASES: BODY WEIGHT, BLOOD COLLECTION AND CLINICAL PATHOLOGY

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PHASES: ANALYTICAL LABORATORY RAW DATA

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PHASES: ANALYTICAL LABORATORY FINAL REPORT

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PHASES: DRAFT FINAL REPORT

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PHASES: FINAL REPORT

Ronald Schreuhek 3/21/94

QUALITY ASSURANCE **DATE**

Signature Page

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR269410 IN RATS

TRL Chemical No.: 1620614

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

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

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3/21/94
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3/21/94
Date

Study Initiation: December 3, 1992
Dosing Initiation: June 25, 1993
In-Life Completion: July 9, 1993

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APPENDICES

1. SUMMARY

This study evaluated the toxicity of WR269410 in rats following two weeks of daily oral administration by gavage. Dose levels studied were 0 (vehicle control), 2.0, 6.0, and 18.0 mg/kg/day at study initiation. On Day 7, the mid dose level (6.0 mg/kg/day) was elevated above the high dose to 30 mg/kg/day for the second treatment week due to a lack of significant toxicity at the high dose during the first week of treatment. The results are summarized in Table 1.

The primary toxic effect of WR269410 was hemolytic anemia, which was supported by macrocytosis, reticulocytosis, Heinz bodies, splenomegaly and extramedullary hematopoiesis. Females were more sensitive than males to the anemic state. Anemia was seen in males at the two higher doses, but was apparent in all female treatment groups. Methemoglobinemia, the expected pharmacologic effect, was also observed at all three dose levels. As this is the desired pharmacologic effect of WR269410, its occurrence was not considered indicative of toxicity. Cardiomegaly, possibly secondary to the methemoglobinemic and anemic state, was seen only in females at 6.0/30.0 mg/kg/day. 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 dose levels are suggested: 0, 1, 2.5 and 6 mg/kg/day. After consultation with the Sponsor, the following dose levels have been chosen for the three month toxicity study in rats: 0, 1, 3, and 10 mg/kg/day.

2. INTRODUCTION

This study was conducted to determine the toxicity of WR269410 in CD® rats following two weeks of daily gavage administration. The study was conducted in accordance with the specifications of the Sponsor. 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 25, 1993 and the in-life portion was terminated on July 9, 1993.

3. MATERIALS AND METHODS

3.1 Test Article

WR269410 (Bottle Lot No. BM 11565), an off-white powder, was received on May 18, 1993 from Herner and Co.. The chemical name of the test article is p-aminoheptanophenone (PAHP). It was stored at -20 to -15°C and at ambient humidity in the freezer, and was protected from light in an amber bottle.

The Analytical Chemistry Report is contained in Appendix 1. The test article was initially identified by GC-MS and the purity was determined (100%). The purity was re-determined following the completion of the in-life portion of the study. At that time, the purity was 100%. 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 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/kg/day)	Number of Males	Number of Females
1	Vehicle	0	5	5
2	WR269410	2.0	5	5
3	WR269410	*6.0 (Week 1) *30.0 (Week 2)	5	5
4	WR269410	18.0	5	5

*At the discretion of the Study Director, the mid dose was escalated above the high dose to 30.0 mg/kg/day for the second week of treatment.

The initial dose levels were supplied by the Sponsor based on the results of an acute oral toxicity study in rats (UIC/TRL Study No. 104). On Day 7, the mid dose level (6.0 mg/kg/day) was elevated above the high dose to 30 mg/kg/day for the second treatment

week. This was due to a lack of toxicity (body weight, food consumption, clinical signs) during the first week of treatment.

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 weekly. Prior testing indicated that dosing solutions were stable for at least two weeks. 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 administered was calculated as mg/kg/day. All dosage formulations used in Weeks 1 and 2 were analyzed for test article concentration prior to use. 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 25, 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 218 - 256 g (males) and 171 - 203 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 is 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 were sacrificed and necropsied in random order on Day 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/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 solutions used were within 10% of their target concentration.

4.2 Mortality and Clinical Signs/Observations

Summaries of clinical signs and clinical observations 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.

No animals died during the study. Treatment-related daily clinical signs (1 - 2 hrs post-dosing) included rough coat, hunched posture and blue feet. Rough coat was seen in all test 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 males at 18.0 mg/kg/day, in one male receiving 30.0 mg/kg/day, and in one high dose (18.0 mg/kg/day) female. Cyanosis characterized as blue feet was seen in treatment group 3 after the dose level was elevated in Week 2 to 30.0 mg/kg/day and in all animals at 18.0 mg/kg/day.

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.

Significantly decreased body weight gains were apparent in males at 30.0 mg/kg/day during the second week of treatment. Although not statistically significant, slight decreases in body weight gains were also seen in males at 18.0 mg/kg/day (first week of treatment), and in females at 30.0 mg/kg/day during the second week. 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 for males at 18.0 mg/kg/day and at 30.0 mg/kg/day (i.e. second week of treatment). A decrease in food consumption was also observed in females at 30.0 mg/kg/day during the second half of Week 2. Reductions in food consumption were not seen in low dose animals.

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 6. Summaries of hematological tests for males and females are in Tables 13 and 14, respectively. Individual hematology data are in Appendix 7.

Clinical chemistry parameters were not affected by test article treatment. A reduction in glucose levels was seen in low dose females. This finding was considered spurious and not biologically significant.

Significant anemia (decreased RBC count, hemoglobin, and/or hematocrit) was apparent in all dose levels, except for low dose males. Females also appeared to be more sensitive at the higher dose levels. Although significant reductions in RBC count were seen in females at 18.0 and 6.0/30.0 mg/kg/day, their hemoglobin and hematocrit appeared similar to control animals. This apparent contradiction was due to a significant physiologic compensatory response by the bone marrow resulting in severe macrocytosis (approximately 40 -50% increases in MCV for 18.0 and 6.0/30.0 mg/kg/day females), which may have been confounded by significant reticulocytosis. While these macrocytic RBCs contained increased amounts of hemoglobin (increased MCH), they were still hypochromic (decreased MCHC). At the higher doses, RBCs were also anisocytotic (irregularities in size), polychromatic, and poikilocytotic (irregularities in cell shape). In addition to elevated MCV and reticulocytosis, other compensatory responses to the anemic state included elevated numbers of nucleated RBCs and the occurrence of RBCs with Howell-Jolly bodies (immature RBCs with nuclear remnant). Increased numbers of RBCs with Heinz bodies (HB) suggested hemolysis as the mechanism of anemia. Although the mean HB values in females at 6.0/30.0 and 18.0 mg/kg/day were identical (0.1%), due to rounding to one decimal place, the actual means at 6.0/30.0 and 18.0 mg/kg/day were 0.14 and 0.08, respectively. This accounts for the mean value seen at 18.0 mg/kg/day (Table 14) not being significantly different from controls.

Methemoglobinemia, the intended therapeutic effect was seen at three doses. At the lowest dose tested, mean percent methemoglobinemia was approximately 2 - 2.5 in both sexes, whereas it was 0.2 - 0.6 in control animals. As such, significant reductions in RBC counts (approximately 15% in females) occurred at 2.0 mg/kg/day, whereas only a small rise in methemoglobinemia was seen.

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 (% body weight) and absolute splenic weights were seen in both males and females in treatment groups 3 (6.0/30.0 mg/kg/day) and 4 (18.0 mg/kg/day) at necropsy. Although not statistically significant, apparent increases in absolute and relative splenic weights were also seen in low dose females but not males. A significant increase in heart size was also seen in females but

not males at 6.0/30.0 mg/kg/day. This was not seen in any other dose levels. No other organ weights were affected by WR269410-treatment.

4.7 Pathology

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

Splenic extramedullary hematopoiesis (EMH) consisting of increased amounts of hematopoietic cells in the red pulp was observed in animals at 6.0/30.0 and 18.0 mg/kg/day, and in low dose (2.0 mg/kg/day) females. 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 WR269410 in CD® rats following two weeks of daily oral administration. The results are summarized in Table 1. No animals died in this study. Clinical signs of toxicity in WR269410-treated rats were limited to the appearance of rough coat, hunched posture, and cyanosis (blue feet) primarily at the higher dose levels. Decreases in body weight gains were observed in animals which received 30.0 mg/kg/day in the second week of treatment, and possibly in males in Week 1 given 18.0 mg/kg/day. Food consumption was correspondingly decreased in males elevated to 30.0 mg/kg/day and in males at 18.0 mg/kg/day, and possibly in females at the two highest dose levels in the second week of treatment.

Treatment-related anemia was seen in treatment groups 3 (6.0/30.0 mg/kg/day) and 4 (18.0 mg/kg/day) and in low dose (2.0 mg/kg/day) females. At 6.0/30.0 mg/kg/day, RBCs were hypochromic, anisocytotic, poikilocytic and macrocytic, and increased reticulocyte counts, elevated nucleated RBCs and RBCs with Howell-Jolly bodies were seen as a compensatory physiologic response. Splenic extramedullary hematopoiesis supported by splenomegaly was secondary to the anemic state, and was observed in animals at the two highest dose levels and in low dose females. The expected pharmacologic action of WR269410, methemoglobinemia, was observed in animals in all treatment groups. Because the anemia was macrocytic and accompanied by increased number of Heinz bodies and splenomegaly, the anemia was considered hemolytic in origin.

Cardiomegaly without any corresponding histologic lesions was seen in females at 6.0/30.0 mg/kg/day, but not in males at this dose level. Methemoglobinemia and hemolytic anemia may have increased the workload of the heart, resulting in cardiac hypertrophy as a compensatory response. The observed sex difference is consistent with a lesser response in males than in corresponding females to WR269410-induced hemolytic anemia and methemoglobinemia.

In summary, the primary toxic effect of WR269410 was hemolytic anemia, which was supported by macrocytosis, reticulocytosis, Heinz bodies, splenomegaly and extramedullary

hematopoiesis. Females were more sensitive than males to the anemic state. Anemia was seen in males at the two higher doses, but was apparent in all female treatment groups. Methemoglobinemia, the expected pharmacologic effect, was also observed at all three dose levels. As this is the desired pharmacologic effect of WR269410, its occurrence was not considered indicative of toxicity. Cardiomegaly, possibly secondary to the methemoglobinemic and anemic state, was seen only in females at 6.0/30.0 mg/kg/day. 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 dose levels are suggested: 0, 1, 2.5 and 6 mg/kg/day. After consultation with the Sponsor, the following dose levels have been chosen for the three month toxicity study in rats: 0, 1, 3, and 10 mg/kg/day.

6. PERSONNEL

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
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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 W. Taylor St., Chicago, IL 60612-7353.

Table 1

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

Summary of Toxic Responses

Dose (mg/kg/day)	0	2.0	6.0 (Week 1) 30.0 (Week 2)	18.0
Rats/Sex	5	-	5	5
Deaths	-	-	-	-
Body Weight Gain	-	-	↓ (M) Week 2 ↓ (F?) Week 2	↓ (M?)
Food Consumption	-	-	↓ (M) Week 2 ↓ (F) Week 2	↓ (M)
Clinical Observations[a]	RC (M)[d]	RC	RC HP (M) BF	RC HP BF
Hematology[b]	-	↑ METHGB (M) + (F?) ↓ RBC (F) ↓ HGB (F) ↓ HCT (F) ↓ MCHC (F) ↑ RETIC	↑ METHGB ↓ RBC ↓ HGB ↑ MCV ↑ MCH ↓ MCHC ↑ RETIC ↑ NRBC ↑ HB (F)	↑ METHGB ↓ RBC ↓ HGB ↑ MCV ↑ MCH ↓ MCHC ↑ RETIC ↑ NRBC (F?)
Clinical Chemistry	-	-	-	-
Organ Weights	-	↑ Spleen (F?)	↑ Spleen ↑ Heart (F)	↑ Spleen
Histopathology[c]	-	Splenic EMH (F)	Splenic EMH	Splenic EMH
CONCLUSIONS	The primary toxic effect of WR269410 was hemolytic anemia. Toxicity was seen for the males at dose levels of 18.0 and 6.0/30.0 mg/kg/day and for all treatment groups in females. Significant anemia was observed in these animals, and was supported by splenomegaly and splenic EMH. Methemoglobinemia, the pharmacologic effect of WR269410, was apparent at all dose levels. Cardiomegaly, possibly secondary to the methemoglobinemic and anemic state, was seen only in females at 6.0/30.0 mg/kg/day. A no observed toxic effect level was not observed. On the basis of this study, the following dose levels are suggested for the three month toxicity study: 0, 1, 2.5 and 6 mg/kg/day. After consultation with the Sponsor, the following dose levels have been chosen for the three month toxicity study in rats: 0, 1, 3, and 10 mg/kg/day.			

[a]RC = rough coat, HP = hunched posture, BF = blue feet

[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, NRBC = nucleated red blood cells, HB = heinz bodies.

[c]EMH = Extramedullary hematopoiesis.

[d]only noted the first few days of the study

? = Possible marginal effect.

Table 2

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

Dosage Formulation Analyses[a]

Target Concentration (mg/ml)	Day 0	% Target	Day 7	% Target
0	0.00	----	0.00	----
0.4	0.4127 $\pm$ 0.0073	103.2	0.3949 $\pm$ 0.0042	98.7
1.2	1.1691 $\pm$ 0.0031	97.4	1.2163 $\pm$ 0.0072	101.4
3.6	3.7198 $\pm$ 0.0064	97.1	3.6759 $\pm$ 0.0044	102.1
6.0	----	----	6.1084 $\pm$ 0.0157	101.8

[a]Mean $\pm$ standard deviation for triplicate runs.

Table 3

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

SUMMARY OF CLINICAL SIGNS

STUDY: 112 SEX: MALE

DOSE:(mg/kg)	0	2.0	6.0/30.0	18.0
GROUP:	1-M	2-M	3-M	4-M
Scheduled Sacrifice	5	5	5	5
Hunched Posture	0	0	2	3
Rough Coat	2	5	5	5
Blue Feet	0	0	5	5
Total Number of Animals	5	5	5	5

Table 4

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR269410 IN RATS

SUMMARY OF CLINICAL SIGNS

STUDY: 112 SEX: FEMALE

DOSE:(mg/kg)	0	2.0	6.0/30.0	18.0
GROUP:	1-F	2-F	3-F	4-F
Scheduled Sacrifice	5	5	5	5
Hunched Posture	0	0	0	1
Rough Coat	0	2	4	5
Blue Feet	0	0	5	5
Total Number of Animals	5	5	5	5

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR269410 IN RATS

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 112 SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1-M	2.0 2-M	6.0/30.0 3-M	18.0 4-M
DAY -4	MEAN	207.3	208.4	206.2	207.5
	S.D.	9.86	9.56	8.31	10.43
	N	5	5	5	5
DAY 0	MEAN	241.4	238.1	236.3	234.3
	S.D.	9.12	10.10	8.18	13.86
	N	5	5	5	5
DAY 3	MEAN	262.6	256.7	254.6	248.7
	S.D.	8.14	12.32	6.76	18.65
	N	5	5	5	5
DAY 7	MEAN	295.1	285.7	286.9	272.9
	S.D.	6.77	12.93	7.39	26.14
	N	5	5	5	5
Day 11	MEAN	316.6	301.4	299.6	291.3
	S.D.	9.30	13.57	4.47	29.98
	N	5	5	5	5
DAY 13	MEAN	330.7	314.8	308.6	304.5
	S.D.	11.27	14.04	4.62	32.45
	N	5	5	5	5

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

Analysis of Variance using DUNNETT'S Procedure

Table 6

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR269410 IN RATS

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 112 SEX: MALE

PERIOD[a]	DOSE: (mg/kg) / GROUP:	0 1-M	2.0 2-M	6.0/30.0 3-M	18.0 4-M
DAY 3[b]	MEAN	21.2	18.6	18.3	14.3
	S.D.	3.25	6.34	3.77	5.07
	N	5	5	5	5
DAY 7	MEAN	32.5	28.9	32.3	24.3
	S.D.	5.37	4.28	3.53	8.46
	N	5	5	5	5
Day 11	MEAN	21.5	15.7	12.7*	18.3
	S.D.	4.75	4.63	3.12	4.67
	N	5	5	5	5
DAY 13	MEAN	14.2	13.4	9.0*	13.2
	S.D.	2.65	2.18	0.89	3.28
	N	5	5	5	5
TOTAL GAIN	MEAN	89.3	76.7	72.3	70.1
	S.D.	13.05	11.89	6.75	19.94
	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

Table 7

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR269410 IN RATS

SUMMARY OF BODY WEIGHTS (Grams)

STUDY: 112 SEX: FEMALE

PERIOD	DOSE: (mg/kg) / GROUP:	0 1-F	2.0 2-F	6.0/30.0 3-F	18.0 4-F
DAY -4	MEAN	166.0	168.1	166.6	165.6
	S.D.	8.37	8.45	7.74	8.03
	N	5	5	5	5
DAY 0	MEAN	182.9	186.5	183.3	184.3
	S.D.	8.45	9.22	7.52	6.52
	N	5	5	5	5
DAY 3	MEAN	188.0	198.6	191.3	188.4
	S.D.	6.44	9.55	10.24	6.76
	N	5	5	5	5
DAY 7	MEAN	203.1	215.0	207.8	203.7
	S.D.	8.39	9.87	9.66	10.84
	N	5	5	5	5
Day 11	MEAN	213.7	220.8	215.1	216.5
	S.D.	9.25	10.41	11.82	9.19
	N	5	5	5	5
DAY 13	MEAN	223.8	227.3	217.9	219.6
	S.D.	11.28	9.76	12.16	11.33
	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 WR269410 IN RATS

SUMMARY OF WEIGHT GAINS (Grams)

STUDY: 112 SEX: FEMALE

PERIOD[a]	DOSE: (mg/kg) GROUP:	0 1-F	2.0 2-F	6.0/30.0 3-F	18.0 4-F
DAY 3[b]	MEAN	5.1	12.1	8.0	4.0
	S.D.	3.87	5.60	4.68	2.41
	N	5	5	5	5
DAY 7	MEAN	15.1	16.5	16.5	15.4
	S.D.	5.08	1.79	1.47	5.27
	N	5	5	5	5
Day 11	MEAN	10.6	5.8	7.4	12.8
	S.D.	1.99	7.69	4.27	2.10
	N	5	5	5	5
DAY 13	MEAN	10.1	6.5	2.8	3.1
	S.D.	7.05	3.82	8.28	5.88
	N	5	5	5	5
TOTAL GAIN	MEAN	40.9	40.8	34.7	35.3
	S.D.	5.48	3.62	8.60	5.68
	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

Table 9

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR269410 IN RATS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 112 SEX: MALE

PERIOD[a]	DOSE:(mg/kg) GROUP:	0 1-M	2.0 2-M	6.0/30.0 3-M	18.0 4-M
DAY 0[b]	INTAKE (g)	20.2	20.3	19.5	18.5
	S.D.	1.09	1.15	1.25	2.48
	N	4	5	5	5
DAY 3	INTAKE (g)	23.1	22.8	21.6	19.9*
	S.D.	0.74	1.55	1.20	2.61
	N	5	5	5	5
DAY 7	INTAKE (g)	23.8	22.0	22.3	19.6**
	S.D.	1.29	1.15	1.07	2.34
	N	5	5	5	5
DAY 11	INTAKE (g)	26.8	23.9	21.2*	22.0*
	S.D.	2.58	3.30	0.83	3.18
	N	5	5	5	5
DAY 13	INTAKE (g)	23.4	22.3	17.5**	20.4
	S.D.	1.22	1.74	1.81	2.78
	N	5	5	5	5

* 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 -4

Table 10

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR269410 IN RATS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 112 SEX: FEMALE

PERIOD [a]	DOSE:(mg/kg) GROUP:	0 1-F	2.0 2-F	6.0/30.0 3-F	18.0 4-F
DAY 0 [b]	INTAKE (g)	15.4	15.7	16.4	15.3
	S.D.	1.04	1.57	1.65	0.53
	N	5	5	5	5
DAY 3	INTAKE (g)	16.7	18.6	18.1	14.3
	S.D.	0.96	1.68	2.78	1.47
	N	5	5	5	5
DAY 7	INTAKE (g)	16.7	17.7	16.1	14.1
	S.D.	1.21	1.18	3.79	1.49
	N	5	5	5	5
DAY 11	INTAKE (g)	20.0	18.5	18.2	19.2
	S.D.	2.04	3.05	2.88	2.94
	N	5	5	5	5
DAY 13	INTAKE (g)	17.3	16.5	11.3*	14.5
	S.D.	2.18	1.77	3.92	3.82
	N	5	5	5	5

* 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 -4

Table 11

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: DAY 14

STUDY IO: 112 SEX: MALE

ANALYSIS OF VARIANCE FOLLOWEO 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/kg/day									
MEAN	70	12.4	0.47	142	6.18	113	11.0	10.5	139
SD	51.1	1.84	0.017	1.3	0.517	2.9	0.38	0.63	16.4
N	5	5	5	5	5	5	5	5	5
Group: 2-M : 2.0 mg/kg/day									
MEAN	51	15.4	0.51	141	6.09	112	10.7	10.4	133
SD	11.7	3.35	0.048	1.5	0.250	3.6	0.32	0.23	7.3
N	5	5	5	5	5	5	5	5	5
Group: 3-M : 6.0 mg/kg/day (Day 0 - 6)/30.0 mg/kg/day (Day 7 - 13)									
MEAN	47	12.8	0.53	142	5.84	115	10.8	10.8	121
SD	3.2	1.73	0.027	1.6	0.331	3.8	0.34	0.74	17.0
N	5	5	5	5	5	5	5	5	5
Group: 4-M : 18.0 mg/kg/day									
MEAN	55	14.4	0.53	143	6.22	113	11.0	10.0	122
SD	31.2	2.39	0.044	0.5	0.476	3.3	0.44	1.02	16.5
N	5	5	5	5	5	5	5	5	5

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: DAY 14

STUDY ID: 112 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/kg/day									
MEAN	60	105	7.3	4.1	3.2	1.30	43.2	231	56
SD	6.7	17.5	0.34	0.30	0.27	0.172	18.52	53.8	7.1
N	5	5	5	5	5	5	5	5	5
Group: 2-M : 2.0 mg/kg/day									
MEAN	57	107	7.5	3.9	3.6	1.11	76.7	271	68
SD	8.9	12.6	0.34	0.11	0.30	0.093	36.18	50.6	10.5
N	5	5	5	5	5	5	5	5	5
Group: 3-M : 6.0 mg/kg/day (Day 0 - 6)/30.0 mg/kg/day (Day 7 - 13)									
MEAN	68	119	7.5	4.1	3.5	1.18	70.5	216	60
SD	9.6	16.3	0.26	0.17	0.30	0.136	32.20	38.2	5.0
N	5	5	5	5	5	5	5	5	5
Group: 4-M : 18.0 mg/kg/day									
MEAN	65	120	7.4	4.1	3.3	1.24	57.6	303	56
SD	9.2	29.3	0.36	0.09	0.28	0.073	13.64	125.4	17.0
N	5	5	5	5	5	5	5	5	5

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: DAY 14

STUDY IO: 112 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/kg/day									
MEAN	55	104	7.7	3.9	3.8	1.09	30.7	210	57
SD	9.7	10.1	0.43	0.66	0.77	0.308	10.79	39.1	18.3
N	5	5	5	5	5	5	5	5	5
Group: 2-F : 2.0 mg/kg/day									
MEAN	57	108	7.7	4.3	3.4	1.25	29.5	193	50
SD	12.6	29.1	0.16	0.20	0.13	0.103	19.97	32.6	11.3
N	5	5	5	5	5	5	5	5	5
Group: 3-F : 6.0 mg/kg/day (Day 0 - 6)/30.0 mg/kg/day (Oay 7 - 13)									
MEAN	78	133	7.9	4.4	3.5	1.24	54.0	158	55
SO	22.7	36.0	0.46	0.21	0.27	0.056	15.54	43.4	4.5
N	5	5	5	5	5	5	5	5	5
Group: 4-F : 18.0 mg/kg/day									
MEAN	54	121	8.0	4.6	3.4	1.34	43.1	196	64
SD	15.1	22.4	0.65	0.50	0.19	0.100	20.24	32.3	10.9
N	5	5	5	5	5	5	5	5	5

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: DAY 14

STUDY ID: 112 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/kg/day									
MEAN	50	14.4	0.53	143	5.90	113	11.1	10.3	154
SD	6.7	2.51	0.040	2.5	0.540	5.7	0.70	1.06	17.7
N	5	5	5	5	5	5	5	5	5
Group: 2-F : 2.0 mg/kg/day									
MEAN	52	14.3	0.51	142	5.81	110	11.0	10.1	118**
SD	6.4	2.01	0.033	0.9	0.521	1.7	0.29	0.94	13.9
N	5	5	5	5	5	5	5	5	5
Group: 3-F : 6.0 mg/kg/day (Day 0 - 6)/30.0 mg/kg/day (Day 7 - 13)									
MEAN	71	14.3	0.56	142	6.27	114	11.0	10.8	136
SD	31.4	3.50	0.040	1.6	0.836	2.3	0.34	0.95	17.6
N	5	5	5	5	5	5	5	5	5
Group: 4-F : 18.0 mg/kg/day									
MEAN	65	12.8	0.56	143	6.20	113	11.2	10.3	132
SD	30.9	1.80	0.055	3.6	1.051	3.4	0.84	1.11	14.1
N	5	5	5	5	5	5	5	5	5

**-Significant Difference from Control P < .01

Table 13

TWO WEEK ORAL RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

SUMMARY OF HEMATOLOGICAL TESTS
PERIOD: DAY 14

STUDY ID: 112 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/kg/day									
MEAN	7.38	16.2	45.4	61.6	22.0	35.6	0.9	0	0.0
SD	0.419	0.37	0.70	2.56	0.78	0.28	0.36	0.4	0.00
N	5	5	5	5	5	5	5	5	5
Group: 2-M : 2.0 mg/kg/day									
MEAN	7.25	15.8	44.0	60.8	21.9	36.0	1.5	0	0.0
SD	0.353	0.30	0.80	1.92	0.65	0.15	0.62	0.4	0.00
N	5	5	5	5	5	5	5	5	5
Group: 3-M : 6.0 mg/kg/day (Day 0 - 6)/30.0 mg/kg/day (Day 7-13)									
MEAN	6.22**	14.8**	44.6	71.7**	23.7**	33.1**	6.4**	1*	0.0
SD	0.214	0.25	0.70	3.19	0.69	0.65	3.69	1.1	0.04
N	5	5	5	5	5	5	5	5	5
Group: 4-M : 18.0 mg/kg/day									
MEAN	5.94**	14.9**	44.4	75.0**	25.1**	33.4**	6.0*	0	0.0
SD	0.385	0.62	1.34	3.44	0.92	0.80	3.46	0.4	0.00
N	5	5	5	5	5	5	5	5	5

WBC corrected for NRBC = or > 10

**-Significant Difference from Control P < .01

*-Significant Difference from Control P < .05

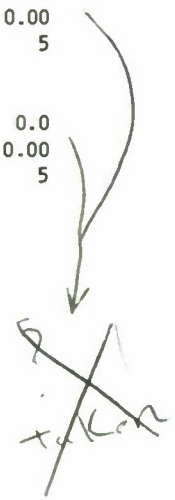
TWO WEEK ORAL RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

SUMMARY OF HEMATOLOGICAL TESTS
PERIOD: DAY 14

STUDY ID: 112 SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	%METHGB	PLT	WBC	M. Neutrop	I. Neutrop	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/kg/day									
MEAN	0.6	1160	16.3	1.1	0.7	14.0	0.4	0.2	0.0
SD	0.29	74.9	2.83	0.25	0.49	2.93	0.29	0.09	0.00
N	5	5	5	5	5	5	5	5	5
Group: 2-M : 2.0 mg/kg/day									
MEAN	2.0**	1229	15.6	2.0	0.5	12.3	0.6	0.2	0.0
SD	0.48	95.3	3.61	0.82	0.36	3.10	0.26	0.30	0.00
N	5	5	5	5	5	5	5	5	5
Group: 3-M : 6.0 mg/kg/day (Day 0 - 6)/30.0 mg/kg/day (Day 7-13)									
MEAN	7.8**	1271	18.5	2.0	0.8	14.8	0.9	0.0	0.0
SD	0.80	105.4	6.13	0.87	0.49	4.32	0.57	0.09	0.00
N	5	5	5	5	5	5	5	5	5
Group: 4-M : 18.0 mg/kg/day									
MEAN	4.7**	1242	16.6	1.5	0.7	13.8	0.5	0.1	0.0
SD	0.38	119.1	2.91	0.88	0.54	1.95	0.40	0.08	0.00
N	5	5	5	5	5	5	5	5	5



WBC corrected for NRBC = or > 10

**-Significant Difference from Control P < .01

TWO WEEK ORAL RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

SUMMARY OF HEMATOLOGICAL TESTS
PERIOD: DAY 14

STUDY ID: 112 SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	%METHGB	PLT	WBC	M. Neutrop	I. Neutrop	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/kg/day									
MEAN	0.2	1110	13.8	2.7	0.1	10.5	0.4	0.1	0.0
SD	0.34	122.2	3.01	0.99	0.17	2.82	0.24	0.13	0.00
N	5	5	5	5	5	5	5	5	5
Group: 2-F : 2.0 mg/kg/day									
MEAN	2.5	1267	13.9	2.4	0.3	10.7	0.4	0.1	0.0
SD	1.40	102.7	2.84	1.28	0.27	1.55	0.27	0.11	0.00
N	5	5	5	5	5	5	5	5	5
Group: 3-F : 6.0 mg/kg/day (Day 0-6)/30.0 mg/kg/day (Day 7-13)									
MEAN	14.1**	1360	14.1	2.3	0.5	10.7	0.6	0.1	0.0
SD	12.45	321.1	2.51	0.82	0.24	1.83	0.37	0.09	0.00
N	5	5	5	5	5	5	5	5	5
Group: 4-F : 18.0 mg/kg day									
MEAN	7.3	1198	12.7	1.6	0.5	10.2	0.4	0.0	0.0
SD	2.53	67.3	2.93	0.69	0.51	2.65	0.23	0.04	0.00
N	5	5	5	5	5	5	5	5	5

WBC corrected for NRBC = or > 10

**-Significant Difference from Control P < .01

Table 15

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

ORGAN WEIGHT SUMMARY (% BODY WEIGHT)

STUDY: 112
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	0.648	0.643	0.663	0.691
	SD	0.0181	0.0316	0.0073	0.0565
	N	5	5	5	5
HEART (% BODY WEIGHT)					
	MEAN	0.375	0.386	0.392	0.405
	SD	0.0269	0.0050	0.0093	0.0250
	N	5	5	5	5
KIDNEYS (% BODY WEIGHT)					
	MEAN	0.990	1.002	0.918	0.893
	SD	0.0150	0.1023	0.0540	0.0896
	N	5	5	5	5
LIVER (% BODY WEIGHT)					
	MEAN	4.067	4.094	3.833	3.835
	SD	0.2414	0.3008	0.2032	0.4065
	N	5	5	5	5
SPLEEN (% BODY WEIGHT)					
	MEAN	0.200	0.206	0.542**	0.407**
	SD	0.0201	0.0276	0.0586	0.0788
	N	5	5	5	5
TESTES (% BODY WEIGHT)					
	MEAN	1.233	1.309	1.333	1.341
	SD	0.0706	0.1189	0.0893	0.1596
	N	5	5	5	5

(1)-0 mg/kg
(2)-2.0 mg/kg
(3)-6.0 mg/kg / 30.0 mg/kg
(4)-18.0 mg/kg
** - Significant difference P<.01

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR269410 IN RATS

ORGAN WEIGHT SUMMARY

STUDY: 112
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	307.1	293.2	289.1	285.1
	SD	7.59	13.23	5.50	30.66
	N	5	5	5	5
BRAIN (G)	MEAN	1.987	1.881	1.917	1.957
	SD	0.0449	0.0610	0.0521	0.0726
	N	5	5	5	5
HEART (G)	MEAN	1.151	1.132	1.135	1.155
	SD	0.0953	0.0602	0.0425	0.1578
	N	5	5	5	5
KIDNEYS (G)	MEAN	3.041	2.939	2.653	2.564
	SD	0.0550	0.3718	0.1706	0.5151
	N	5	5	5	5
LIVER (G)	MEAN	12.498	12.026	11.084	11.010
	SD	0.9963	1.3397	0.7059	2.2338
	N	5	5	5	5
SPLEEN (G)	MEAN	0.614	0.605	1.565**	1.178**
	SD	0.0563	0.0832	0.1532	0.3601
	N	5	5	5	5
TESTES (G)	MEAN	3.783	3.826	3.854	3.795
	SD	0.1445	0.2237	0.2680	0.3402
	N	5	5	5	5

(1)-0 mg/kg
(2)-2.0 mg/kg
(3)-6.0 mg/kg / 30.0 mg/kg
(4)-18.0 mg/kg
** - Significant difference P<.01

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR269410 IN RATS

ORGAN WEIGHT SUMMARY (% BODY WEIGHT)

STUDY: 112
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	0.904	0.900	0.919	0.920
	SD	0.0364	0.0631	0.0389	0.0520
	N	5	5	5	5
HEART (% BODY WEIGHT)					
	MEAN	0.445	0.444	0.573*	0.481
	SD	0.0333	0.0367	0.1164	0.0335
	N	5	5	5	5
KIDNEYS (% BODY WEIGHT)					
	MEAN	0.999	0.965	0.948	0.998
	SD	0.1293	0.0749	0.0316	0.0555
	N	5	5	5	5
LIVER (% BODY WEIGHT)					
	MEAN	4.450	4.278	4.345	4.401
	SD	0.4382	0.1716	0.3634	0.2534
	N	5	5	5	5
OVARY (% BODY WEIGHT)					
	MEAN	0.065	0.053	0.061	0.055
	SD	0.0207	0.0142	0.0112	0.0083
	N	5	5	5	5
SPLEEN (% BODY WEIGHT)					
	MEAN	0.290	0.436	0.969**	0.722**
	SD	0.0405	0.1174	0.1034	0.1178
	N	5	5	5	5

(5)-0 mg/kg
(6)-2.0 mg/kg
(7)-6.0 mg/kg / 30.0 mg/kg
(8)-18.0 mg/kg
* - Significant difference P<.05
** - Significant difference P<.01

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR269410 IN RATS

ORGAN WEIGHT SUMMARY

STUDY: 112
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	205.3	210.7	201.9	201.8
	SD	11.17	8.08	9.94	9.82
	N	5	5	5	5
BRAIN (G)					
	MEAN	1.855	1.893	1.854	1.853
	SD	0.1108	0.0707	0.0766	0.0553
	N	5	5	5	5
HEART (G)					
	MEAN	0.912	0.935	1.165	0.971
	SD	0.0423	0.0759	0.2951	0.0821
	N	5	5	5	5
KIDNEYS (G)					
	MEAN	2.050	2.031	1.914	2.011
	SD	0.3023	0.1460	0.1013	0.0675
	N	5	5	5	5
LIVER (G)					
	MEAN	9.126	9.017	8.792	8.881
	SD	0.9490	0.5582	1.0414	0.6446
	N	5	5	5	5
OVARY (G)					
	MEAN	0.133	0.112	0.123	0.111
	SD	0.0355	0.0297	0.0206	0.0214
	N	5	5	5	5
SPLEEN (G)					
	MEAN	0.597	0.915	1.963**	1.465**
	SD	0.1027	0.2257	0.2894	0.2984
	N	5	5	5	5

(5)-0 mg/kg
(6)-2.0 mg/kg
(7)-6.0 mg/kg / 30.0 mg/kg
(8)-18.0 mg/kg
** - Significant difference P<.01

Table 19

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

Summary of Microscopic Lesions[a]

		Dose (mg base/kg/day)			
ORGAN - lesion	Sex	0	2.0	6.0 (Week 1) 30.0 (Week 2)	18.0
Spleen - Extramedullary hematopoiesis	M	0/5 (0.00)	0/5 (0.00)	5/5 (1.60)	5/5 (1.80)
	F	0/5 (0.00)	4/5 (1.00)	5/5 (2.60)	5/5 (2.00)

[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.

APPENDIX 1

Analytical Chemistry Methodology and Dosage Formulation Analysis

PURITY, IDENTITY AND SAMPLES ANALYSIS IN 1% METHYLCELLULOSE AND 0.2% TWEEN 80 OF p-AMINOHEPTANOPHENONE (WR269410). STUDY NO. 112

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 17, 1993

APPROVED: AUGUST 17, 1993
DR. EUGENE F. WOODS, Ph.D.

OBJECTIVE

The objective of this study was to confirm the initial identity and establish the purity of WR269410 and to develop the analytical method for dosage formulation analysis.

WR269410 samples were submitted for analysis June 22 and June 29, 1993. Results are found on pages 10 and 11.

In low and in high concentrations WR269410 is stable for two weeks (<10% loss). This will be reported with the longer term toxicological studies.

EXPERIMENTAL

The subject sample - WR269410 was supplied by the Toxicology Research Laboratory and stored at -20^{0}C when it was not analyzed.

Description

A fine white 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 WR269410 prepared in mobile phase. The sample was found with maximal absorptivity observed at 230 nm and 312 nm.

ANALYTICAL METHOD

Reagents

Subject sample (WR269410) was supplied by the Toxicology Research Laboratory. HPLC grade methanol, acetonitrile and acetic acid glacial were purchased from Fisher Scientific, 1-heptanosulfonate sodium salt from Regis. HPLC grade water was supplied through a Millipore, MILLI-Q Reagent Water System which was fed with distilled water.

Standards

A 1.0 mg/ml of WR269410 stock solution was prepared by weighing 100 mg of WR269410 into 100 ml volumetric flask. The content was dissolved in and the volume brought to mark with mobile phase. Calibration standards solutions were prepared in mobile phase using 1.0 mg/ml WR269410 stock solution as follows.

Volume Transferred (ml)	Flask Volume (ml)	Final Concentration (µg/ml)
1.0	100	10.0
2.0	100	20.0
4.0	100	40.0
6.0	100	60.0
8.0	100	80.0
10.0	100	100.0

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

Controls

Control A (9 mg/ml), control B (50 mg/ml), and control C (110 mg/ml) were prepared by weighing 900 mg, 5000 mg and 11000 mg respectively of WR269410 into three 100 ml volumetric flasks, dissolved in and diluted to mark with mobile phase. Aliquots of 1.5 ml of each control were transferred to individually labelled screw-capped vials, sealed and stored at -20°C until analyzed.

Analytical Procedure

One set of WR269410 calibration standards and three vials of each stock control solutions were removed from a -20°C freezer to warm up prior to samples analysis. Working control solutions were prepared as follows. Control A - 1 ml of stock solution was transferred to a 25 ml volumetric flask and diluted to mark with mobile phase, 5 ml then were then transferred to a 25 ml volumetric flask and diluted to mark with mobile phase. Control B - 1 ml of stock was transferred to a 25 ml volumetric flask and diluted to mark with mobile phase. One milliliter was then transferred to another 25 ml volumetric flask and diluted to mark with mobile phase. Control C - 1 ml of stock solution was transferred to 100 ml volumetric flask and diluted to mark with mobile phase. One milliliter was then transferred to a 25 ml volumetric flask and diluted to mark with mobile phase. 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, WR269410 was monitored at 254 nm.

PURITY

HPLC System

Solvent Delivery System:	Perkin-Elmer Series 3B Pump
Injector:	Rheodyne 7125 with 20 ul sample loop
Analytical Column:	uBondapak C18, 300 mm x 3.9 mm (Waters)
Detector:	Kratos Spectroflow 773 UV Detector, 0.010 AUFS, 230nm and 312nm
Integrator:	LCI-100 Perkin-Elmer Integrator
Mobile Phase:	60% of acetonitrile and 40% of 0.01 M heptanosulfonate sodium salt in 0.1% (v/v) acetic acid (in water), flow 1.5 ml/minute

Procedure

Six solutions of WR269410 were prepared as follows. Twenty five mg of WR269410 sample was weighed into a 25 ml volumetric flask. The sample was dissolved in and the volume brought to mark with mobile phase. A 20 ul aliquot of each solution was immediately chromatographed at 230 nm and next at 312 nm. The same procedure was used for initial and following sample of WR269410.

Results

Typical chromatograms are shown in Figure II and III. The initial and following purity studies of WR269410 show that there are no UV absorbing impurities (230 nm, 312 nm) and from this point of view the substance is 100% pure.

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-1 with a 3 micron film thickness.

GC Parameters: injector temp. 250°C, oven temp. 70°C initial, 280°C final, 20°C/minute ramp, carrier gas - helium, flow rate 2 ml/minute, split ratio 10:1

Procedure

Subject sample (WR269410) was submitted from the Toxicology Research Laboratory. The sample was dissolved in methanol to a concentration of 1 ug/ml and a 2 ul aliquot was injected on the column. The MSD scanned from 40 amu to 400 amu at a rate of 1 scan per second.

Results - GS-MS

The mass spectrum indicates a molecular ion m/e 205 which is in agreement with the WR269410 molecular weight. Major fragments of the sample are m/e 41, 65, 92, 120, 135, 148.

Figure IV shows the mass spectrum of the initial WR269410 sample.

FIGURE I

ULTRAVIOLET SPECTRUM OF WR269410

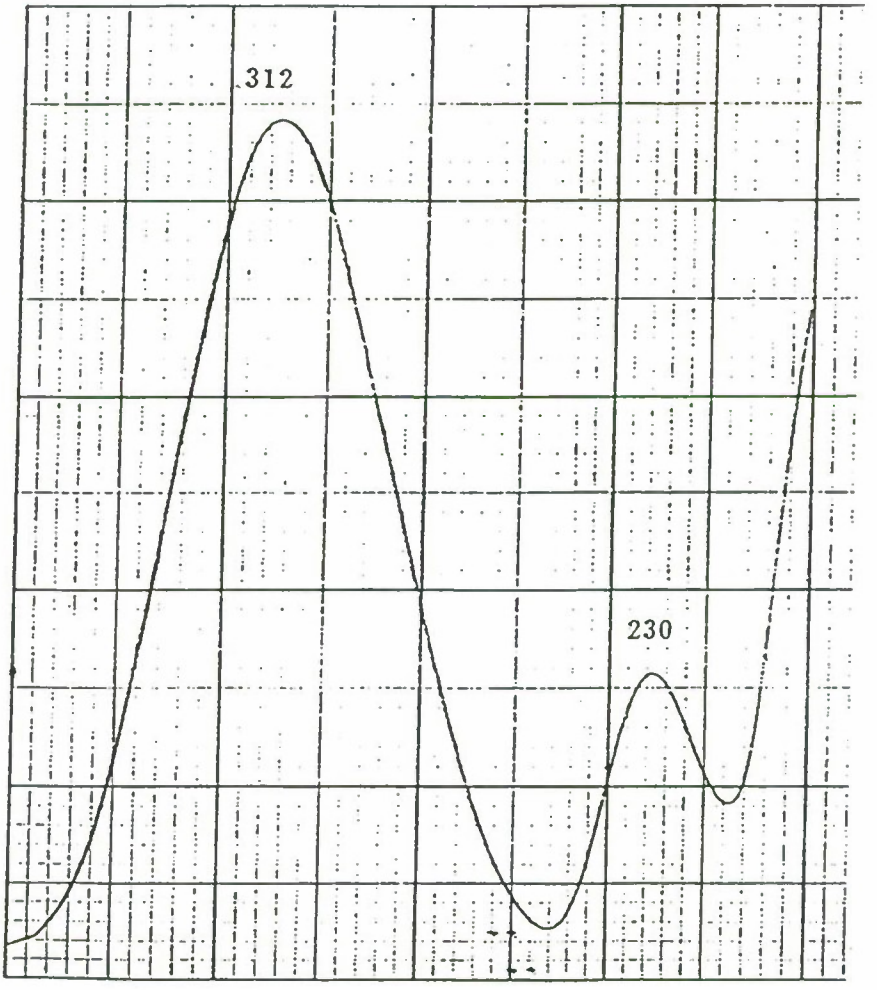
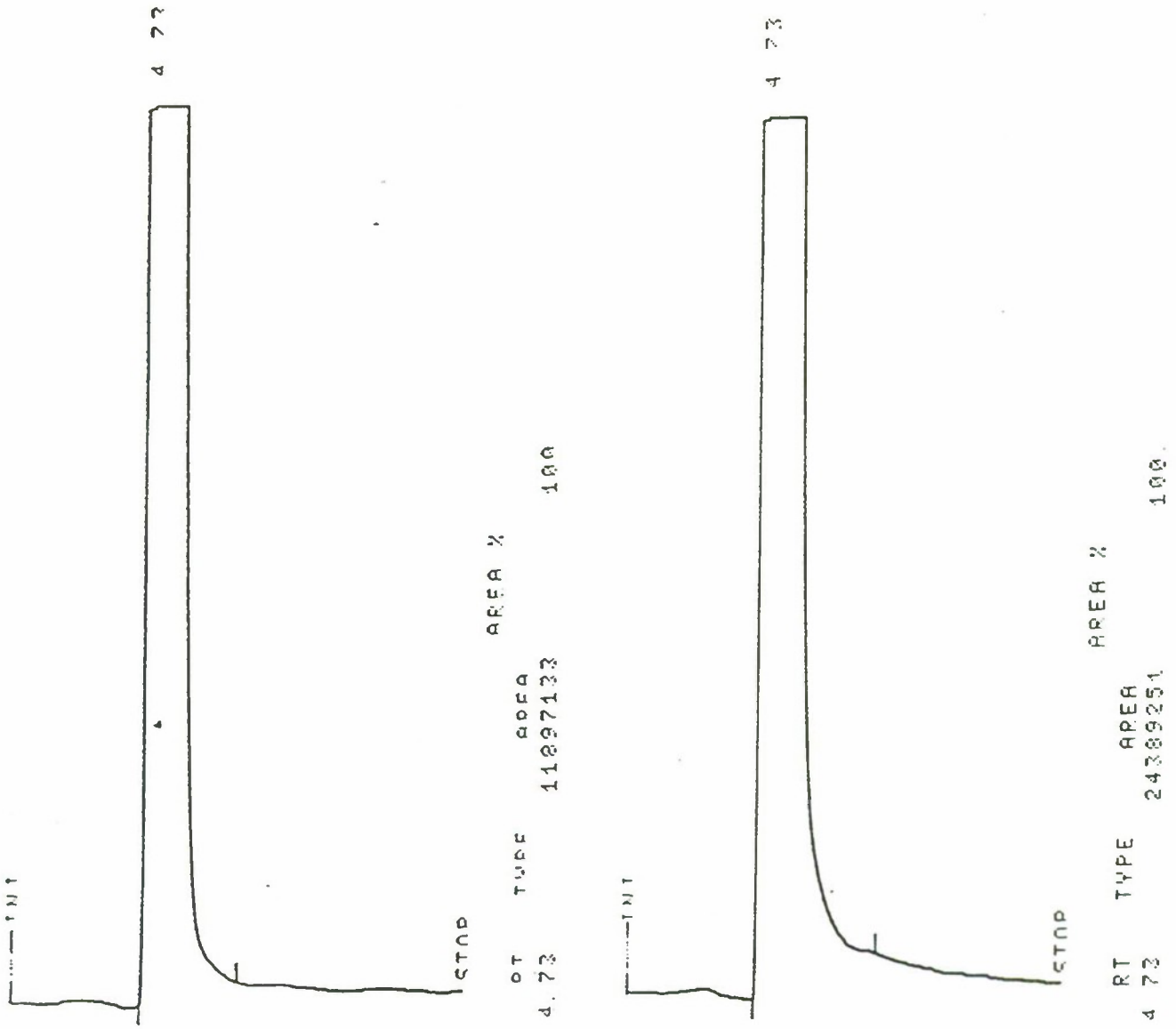


FIGURE II

CHROMATOGRAMS OF WR269410 AT 230 NM (A) AND 312 NM (B), CONCENTRATION 1 MG/ML INITIAL SAMPLE



A B

FIGURE III

CHROMATOGRAMS OF WR269410 AT 230 NM (A) AND 312 NM (B), CONCENTRATION 1 MG/ML FOLLOWING SAMPLE

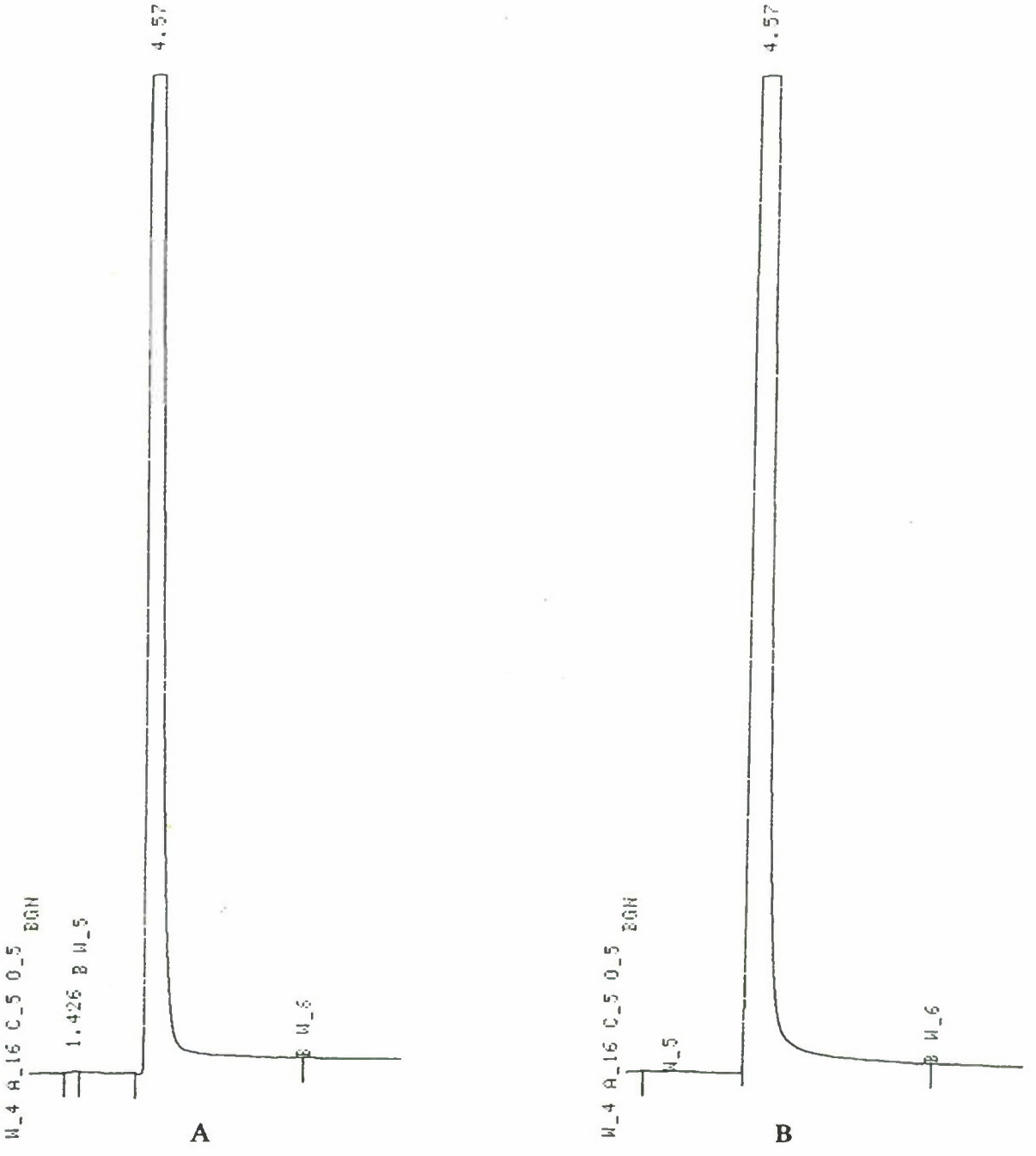
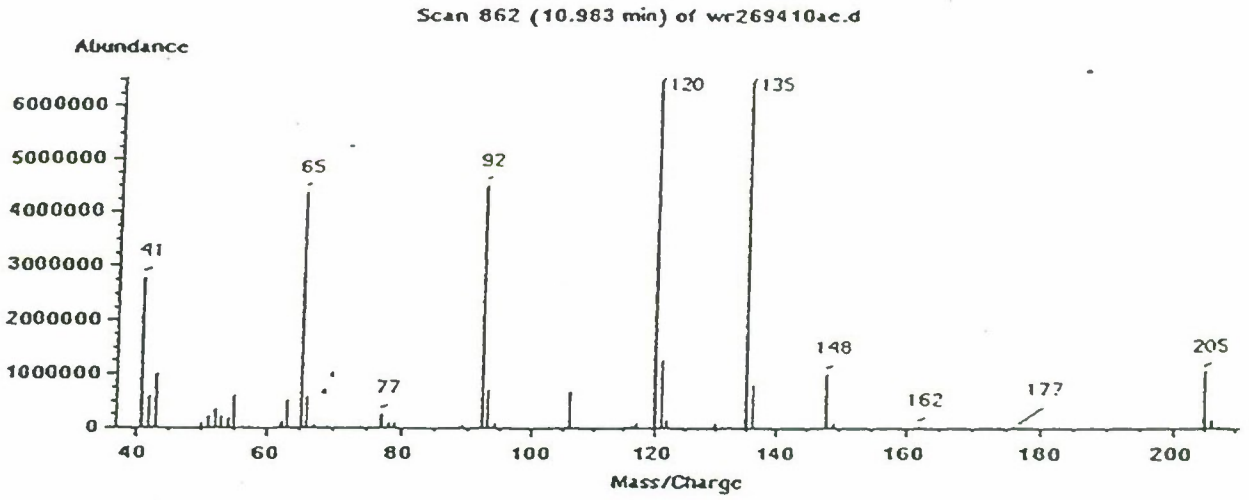


FIGURE IV

MASS SPECTRUM OF INITIAL WR269410 SAMPLE



MEMO

DATE: June 22, 1993

TO: Dr. Barry S. Levine

FROM: Adam Negrusz
Forensic Toxicology Laboratory
College of Pharmacy

RE: WR269410 samples submitted for analysis June 22, 1993.

WR269410 Concentration
(mg/ml)

Sample Identification	Mean (± SD)
PINK (0.4)	0.4127 ± 0.0073
BLUE (1.2)	1.1691 ± 0.0031
BROWN (3.6)	3.7198 ± 0.0064

MEMO

DATE: June 29, 1993

TO: Dr. Barry S. Levine

FROM: Adam Negrusz
Forensic Toxicology Laboratory
College of Pharmacy

RE: WR269410 samples submitted for analysis June 29, 1993.

WR269410 Concentration (mg/ml)

Sample Identification	Mean (± SD)
PINK (0.4)	0.3949 ± 0.0042
BLUE (1.2)	1.2163 ± 0.0072
BROWN (3.6)	3.6759 ± 0.0044
PINK WITH BLACK DOT (6.0)	6.1084 ± 0.0157

APPENDIX 2

Clinical Pathology Methodology

HEMATOLOGY

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
Measured with a Co-oximeter (Instrumentation Laboratory Model 282).

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

HEMATOLOGY TEST DIRECTORY

STUDY: 112

NO.	ABBR. UNITS	DESCRIPTION PRECISION	CALCULATED	OPERAND A	OPERAND B	---LOWER LIMIT--- MALE	FEMALE	---UPPER LIMIT--- MALE	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 112 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
24.	CR	Creanation
25.	IP	Increased Platelets

(END OF REPORT) 17-SEP-1993

STUDY 112 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) 17-SEP-1993

CLINICAL CHEMISTRY

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.

Creatinine

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

Total Protein

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

Albumin

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

Calcium

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
J. Clin. Chem. Clin. Biochem., 21, 731, 1983

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

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

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.

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

CLINICAL CHEMISTRY TEST DIRECTORY

STUDY: 112

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.	AST U/L	Aspartate Aminotransferase Integer	NO			50	50	160	160
3.	TP g/dL	Total Protein 0.0	NO			5.3	5.3	8.5	8.5
4.	ALB g/dL	Albumin 0.0	NO			3.4	3.4	5.6	5.6
5.	TBA mg/dL	Total Bile Acid 0.0	NO			0.0	0.0	100.0	100.0
6.	ALKP U/L	Alkaline Phosphatase Integer	NO			60	60	300	300
7.	CHOL mg/dL	Cholesterol Integer	NO			25	25	100	100
8.	TRY mg/dL	Triglycerides Integer	NO			25	25	100	100
9.	BUN mg/dL	Blood Urea Nitrogen 0.0	NO			7.0	7.0	22.0	22.0
10.	CREA mg/dL	Creatinine 0.00	NO			0.40	0.40	0.80	0.80
11.	NA mmol/L	Sodium Integer	NO			140	140	148	148
12.	K mmol/L	Potassium 0.00	NO			5.00	5.00	7.00	7.00
13.	CL mEq/L	Chloride Integer	NO			95.0	95.0	112.0	112.0
14.	CA mg/dL	Calcium 0.0	NO			9.5	9.5	12.0	12.0
15.	IP mg/dL	Inorganic Phosphorus 0.0	NO			9.5	9.5	12.0	12.0

CLINICAL CHEMISTRY TEST DIRECTORY

STUDY: 112

NO.	ABBR. / UNITS	DESCRIPTION / PRECISION	CALCULATED	OPERAND A	OPERAND B	---LOWER LIMIT--- MALE	FEMALE	---UPPER LIMIT--- MALE	FEMALE
16.	GLU mg/dL	Glucose Integer	NO			80	80	150	150
17.	GLOB g/dL	Globulin 0.0	Operand A - Operand B	TP	ALB	2.0	2.0	4.5	4.5
18.	A/G -	A/G Ratio 0.00	Operand A / Operand B	ALB	GLOB	1.00	1.00	2.00	2.00

(END OF REPORT) 08-SEP-1993

APPENDIX 3

Individual Observations

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL OBSERVATIONS

STUDY: 112 GROUP: 1-M SEX: MALE
DAY 0-DAY 14 DOSE: 0(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
961	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14
962	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14
963	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14
964	Normal			DAY 0-DAY 1
	Normal			DAY 3-DAY 13
	Rough Coat			DAY 2
	Scheduled Sacrifice			DAY 14
965	Normal			DAY 0-DAY 1
	Normal			DAY 3-DAY 13
	Rough Coat			DAY 2
	Scheduled Sacrifice			DAY 14

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL OBSERVATIONS

STUDY: 112 GROUP: 2-M SEX: MALE
DAY 0-DAY 14 DOSE: 2.0(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
971	Normal			DAY 0
	Normal			DAY 3-DAY 13
	Rough Coat			DAY 1-DAY 2
	Scheduled Sacrifice			DAY 14
972	Normal			DAY 0-DAY 1
	Normal			DAY 3-DAY 13
	Rough Coat			DAY 2
	Scheduled Sacrifice			DAY 14
973	Normal			DAY 0-DAY 1
	Normal			DAY 3-DAY 13
	Rough Coat			DAY 2
	Scheduled Sacrifice			DAY 14
974	Normal			DAY 0
	Normal			DAY 2-DAY 7
	Normal			DAY 9-DAY 13
	Rough Coat			DAY 1
	Rough Coat			DAY 8
	Scheduled Sacrifice			DAY 14
975	Normal			DAY 0
	Normal			DAY 3-DAY 13
	Rough Coat			DAY 1-DAY 2
	Scheduled Sacrifice			DAY 14

INDIVIDUAL OBSERVATIONS

STUDY: 112 GROUP: 3-M SEX: MALE
DAY 0-DAY 14 DOSE: 6.0 /30.0 (mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
981	Blue Feet			DAY 9-DAY 13
	Normal			DAY 0-DAY 1
	Normal			DAY 3-DAY 8
	Rough Coat			DAY 2
	Scheduled Sacrifice			DAY 14
982	Blue Feet			DAY 7
	Blue Feet			DAY 9-DAY 13
	Hunched Posture			DAY 2
	Normal			DAY 0-DAY 1
	Normal			DAY 3-Day 6
	Normal			DAY 8
	Rough Coat			DAY 2
	Scheduled Sacrifice			DAY 14
983	Blue Feet			DAY 9-DAY 13
	Hunched Posture			DAY 2
	Normal			DAY 0
	Normal			DAY 4-DAY 8
	Rough Coat			DAY 1-DAY 3
	Rough Coat			Day 11-DAY 13
	Scheduled Sacrifice			DAY 14
984	Blue Feet			DAY 9
	Blue Feet			Day 12-DAY 13
	Normal			DAY 0
	Normal			DAY 3-DAY 7
	Rough Coat			DAY 1-DAY 2
	Rough Coat			DAY 8
	Rough Coat			DAY 10-DAY 13
	Scheduled Sacrifice			DAY 14
985	Blue Feet			DAY 9-DAY 13
	Normal			DAY 0-DAY 1
	Normal			DAY 3-DAY 8
	Rough Coat			DAY 2
	Scheduled Sacrifice			DAY 14

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL OBSERVATIONS

STUDY: 112 GROUP: 4-M SEX: MALE
DAY 0-DAY 14 DOSE: 18.0(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
991	Blue Feet			Day 5-DAY 7
	Blue Feet			DAY 9-DAY 10
	Blue Feet			Day 12-DAY 13
	Hunched Posture			DAY 7
	Normal			DAY 0
	Normal			DAY 3-DAY 4
	Normal			Day 11
	Rough Coat			DAY 1-DAY 2
	Rough Coat			DAY 7-DAY 8
	Scheduled Sacrifice			DAY 14
992	Blue Feet			Day 5-DAY 7
	Blue Feet			DAY 9-DAY 13
	Normal			DAY 0
	Normal			DAY 4
	Normal			DAY 8
	Rough Coat			DAY 1-DAY 3
	Rough Coat			Day 5-DAY 7
	Scheduled Sacrifice			DAY 14
993	Blue Feet			DAY 3
	Blue Feet			Day 6-DAY 7
	Blue Feet			DAY 9-Day 11
	Blue Feet			DAY 13
	Hunched Posture			DAY 2
	Normal			DAY 0
	Normal			Day 12
	Rough Coat			DAY 1-Day 5
	Rough Coat			DAY 7-DAY 8
	Rough Coat			DAY 13
	Scheduled Sacrifice			DAY 14
994	Blue Feet			DAY 3
	Blue Feet			Day 5-DAY 7
	Blue Feet			Day 11-DAY 13
	Normal			DAY 0
	Normal			DAY 4
	Normal			DAY 8-DAY 10
	Rough Coat			DAY 1-DAY 2
	Scheduled Sacrifice			DAY 14

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL OBSERVATIONS

STUDY: 112 GROUP: 4-M SEX: MALE
DAY 0-DAY 14 DOSE: 18.0(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
995	Blue Feet			DAY 3
	Blue Feet			Day 5-DAY 7
	Blue Feet			DAY 9-DAY 13
	Hunched Posture			DAY 2
	Normal			DAY 0
	Normal			DAY 4
	Normal			DAY 8
	Rough Coat			DAY 1-DAY 3
	Scheduled Sacrifice			DAY 14

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL OBSERVATIONS

STUDY: 112 GROUP: 1-F SEX: FEMALE
DAY 0-DAY 14 DOSE: 0(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
966	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14
967	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14
968	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14
969	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14
970	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14

INDIVIDUAL OBSERVATIONS

STUDY: 112 GROUP: 2-F SEX: FEMALE
DAY 0-DAY 14 DOSE: 2.0(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
976	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14
977	Normal			DAY 0
	Normal			DAY 2-DAY 13
	Rough Coat			DAY 1
	Scheduled Sacrifice			DAY 14
978	Normal			DAY 0-DAY 1
	Normal			DAY 3-DAY 13
	Rough Coat			DAY 2
	Scheduled Sacrifice			DAY 14
979	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14
980	Normal			DAY 0-DAY 13
	Scheduled Sacrifice			DAY 14

INDIVIDUAL OBSERVATIONS

STUDY: 112 GROUP: 3-F SEX: FEMALE
DAY 0-DAY 14 DOSE: 6.0/30.0 (mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
986	Blue Feet			DAY 9-DAY 13
	Normal			DAY 0
	Normal			DAY 4-DAY 8
	Rough Coat			DAY 1-DAY 3
	Rough Coat			Day 11
	Scheduled Sacrifice			DAY 14
987	Blue Feet			DAY 9-DAY 13
	Normal			DAY 0-DAY 8
	Scheduled Sacrifice			DAY 14
988	Blue Feet			DAY 7
	Blue Feet			DAY 9-DAY 13
	Normal			DAY 0
	Normal			DAY 3
	Normal			Day 5-Day 6
	Normal			DAY 8
	Rough Coat			DAY 1-DAY 2
	Rough Coat			DAY 4
	Scheduled Sacrifice			DAY 14
989	Blue Feet			DAY 7
	Blue Feet			DAY 9-Day 12
	Normal			DAY 0-DAY 1
	Normal			DAY 3-Day 6
	Normal			DAY 8
	Normal			DAY 13
	Rough Coat			DAY 2
	Scheduled Sacrifice			DAY 14
990	Blue Feet			DAY 7
	Blue Feet			DAY 9-DAY 13
	Normal			DAY 0
	Normal			DAY 3-Day 6
	Normal			DAY 8
	Rough Coat			DAY 1-DAY 2
	Scheduled Sacrifice			DAY 14

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL OBSERVATIONS

STUDY: 112 GROUP: 4-F SEX: FEMALE
DAY 0-DAY 14 DOSE: 18.0(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
996	Blue Feet			DAY 3-DAY 7
	Blue Feet			DAY 9-DAY 13
	Normal			DAY 0
	Normal			DAY 8
	Rough Coat			DAY 1-DAY 3
	Rough Coat			Day 5-DAY 7
	Rough Coat			Day 11
	Scheduled Sacrifice			DAY 14
997	Blue Feet			DAY 3-DAY 7
	Blue Feet			DAY 9-DAY 13
	Hunched Posture			DAY 7
	Normal			DAY 0
	Normal			DAY 8
	Rough Coat			DAY 1-DAY 2
	Rough Coat			DAY 7
	Rough Coat			Day 11
	Scheduled Sacrifice			DAY 14
998	Blue Feet			Day 5-DAY 7
	Blue Feet			DAY 9-DAY 13
	Normal			DAY 0
	Normal			DAY 4
	Normal			DAY 8
	Rough Coat			DAY 1-DAY 2
	Rough Coat			Day 6
	Rough Coat			Day 11
	Scheduled Sacrifice			DAY 14
999	Blue Feet			DAY 3-DAY 7
	Blue Feet			Day 11-Day 12
	Normal			DAY 0
	Normal			DAY 8-DAY 10
	Normal			DAY 13
	Rough Coat			DAY 1-DAY 2
	Scheduled Sacrifice			DAY 14

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL OBSERVATIONS

STUDY: 112 GROUP: 4-F SEX: FEMALE
DAY 0-DAY 14 DOSE: 18.0(mg/kg)

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
1000	Blue Feet			DAY 3-DAY 7
	Blue Feet			Day 11-Day 12
	Normal			DAY 0
	Normal			DAY 8-DAY 10
	Normal			DAY 13
	Rough Coat			DAY 1-DAY 2
	Rough Coat			DAY 7
	Scheduled Sacrifice			DAY 14

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 112 SEX: MALE

PERIOD	DOSE:(mg/kg) / GROUP:	0 1-M	2.0 2-M	6.0 3-M	18.0 4-M
DAY 0					
	No. Observed	5	5	5	5
	Normal	5 100%	5 100%	5 100%	5 100%
DAY 1					
	No. Observed	5	5	5	5
	Normal	5 100%	2 40%	3 60%	0
	Rough Coat	0	3 60%	2 40%	5 100%
DAY 2					
	No. Observed	5	5	5	5
	Normal	3 60%	1 20%	0	0
	Hunched Posture	0	0	2 40%	2 40%
	Rough Coat	2 40%	4 80%	5 100%	5 100%
DAY 3					
	No. Observed	5	5	5	5
	Normal	5 100%	5 100%	4 80%	1 20%
	Rough Coat	0	0	1 20%	3 60%
	Blue Feet	0	0	0	3 60%
DAY 4					
	No. Observed	5	5	5	5
	Normal	5 100%	5 100%	5 100%	4 80%
	Rough Coat	0	0	0	1 20%
DAY 5					
	No. Observed	5	5	5	5
	Normal	5 100%	5 100%	5 100%	0
	Rough Coat	0	0	0	2 40%
	Blue Feet	0	0	0	4 80%
DAY 6					
	No. Observed	5	5	5	5
	Normal	5 100%	5 100%	5 100%	0
	Rough Coat	0	0	0	1 20%
	Blue Feet	0	0	0	5 100%
DAY 7					
	No. Observed	5	5	5	5

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 112 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	2.0 2-M	6.0 3-M	18.0 4-M
	Normal	5 100%	5 100%	4 80%	0
	Hunched Posture	0	0	0	1 20%
	Rough Coat	0	0	0	3 60%
	Blue Feet	0	0	1 20%	5 100%
DAY 8					
	No. Observed	5	5	5	5
	Normal	5 100%	4 80%	4 80%	3 60%
	Rough Coat	0	1 20%	1 20%	2 40%
DAY 9					
	No. Observed	5	5	5	5
	Normal	5 100%	5 100%	0	1 20%
	Blue Feet	0	0	5 100%	4 80%
DAY 10					
	No. Observed	5	5	5	5
	Normal	5 100%	5 100%	0	1 20%
	Rough Coat	0	0	1 20%	0
	Blue Feet	0	0	4 80%	4 80%
OAY 11					
	No. Observed	5	5	5	5
	Normal	5 100%	5 100%	0	1 20%
	Rough Coat	0	0	2 40%	0
	Blue Feet	0	0	4 80%	4 80%
DAY 12					
	No. Observed	5	5	5	5
	Normal	5 100%	5 100%	0	1 20%
	Rough Coat	0	0	2 40%	0
	Blue Feet	0	0	5 100%	4 80%
DAY 13					
	No. Observed	5	5	5	5
	Normal	5 100%	5 100%	0	0
	Rough Coat	0	0	2 40%	1 20%
	Blue Feet	0	0	5 100%	5 100%
DAY 14					
	No. Observed	5	5	5	5

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 112 SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	2.0 2-M	6.0 3-M	18.0 4-M
Scheduled Sacrifice		5 100%	5 100%	5 100%	5 100%

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 112 SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	2.0 2-F	6.0 3-F	18.0 4-F
DAY 0					
No. Observed		5	5	5	5
Normal		5 100%	5 100%	5 100%	5 100%
DAY 1					
No. Observed		5	5	5	5
Normal		5 100%	4 80%	2 40%	0
Rough Coat		0	1 20%	3 60%	5 100%
DAY 2					
No. Observed		5	5	5	5
Normal		5 100%	4 80%	1 20%	0
Rough Coat		0	1 20%	4 80%	5 100%
DAY 3					
No. Observed		5	5	5	4
Normal		5 100%	5 100%	4 80%	0
Rough Coat		0	0	1 20%	1 25%
Blue Feet		0	0	0	4 100%
DAY 4					
No. Observed		5	5	5	5
Normal		5 100%	5 100%	4 80%	1 20%
Rough Coat		0	0	1 20%	0
Blue Feet		0	0	0	4 80%
DAY 5					
No. Observed		5	5	5	5
Normal		5 100%	5 100%	5 100%	0
Rough Coat		0	0	0	1 20%
Blue Feet		0	0	0	5 100%
DAY 6					
No. Observed		5	5	5	5
Normal		5 100%	5 100%	5 100%	0
Rough Coat		0	0	0	2 40%
Blue Feet		0	0	0	5 100%
DAY 7					
No. Observed		5	5	5	5

SUMMARY OF OBSERVATION INCIDENCE

STUDY: 112 SEX: FEMALE

PERIOD	DOSE:(mg/kg) / GROUP:	0 1-F	2.0 2-F	6.0 3-F	18.0 4-F
	Normal	5 100%	5 100%	2 40%	0
	Hunched Posture	0	0	0	1 20%
	Rough Coat	0	0	0	3 60%
	Blue Feet	0	0	3 60%	5 100%
DAY 8					
	No. Observed	5	5	5	5
	Normal	5 100%	5 100%	5 100%	5 100%
DAY 9					
	No. Observed	5	5	5	5
	Normal	5 100%	5 100%	0	2 40%
	Blue Feet	0	0	5 100%	3 60%
DAY 10					
	No. Observed	5	5	5	5
	Normal	5 100%	5 100%	0	2 40%
	Blue Feet	0	0	5 100%	3 60%
DAY 11					
	No. Observed	5	5	5	5
	Normal	5 100%	5 100%	0	0
	Rough Coat	0	0	1 20%	3 60%
	Blue Feet	0	0	5 100%	5 100%
DAY 12					
	No. Observed	5	5	5	5
	Normal	5 100%	5 100%	0	0
	Blue Feet	0	0	5 100%	5 100%
DAY 13					
	No. Observed	5	5	5	5
	Normal	5 100%	5 100%	1 20%	2 40%
	Blue Feet	0	0	4 80%	3 60%
DAY 14					
	No. Observed	5	5	5	5
	Scheduled Sacrifice	5 100%	5 100%	5 100%	5 100%

APPENDIX 4

Individual Body Weights and Body Weight Gains

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 112 GROUP: 1-M SEX: MALE
DOSE: 0(mg/kg)

ANIMAL #	DAY -4	DAY 0	DAY 3	DAY 7	Day 11	DAY 13
961	211.2	247.8	268.7	306.1	330.5	346.5
962	221.9	252.6	269.2	294.9	310.1	320.4
963	202.0	241.8	266.9	295.1	318.6	333.2
964	205.2	233.9	257.2	290.9	317.4	334.4
965	196.0	230.9	250.9	288.4	306.3	319.2
MEAN	207.3	241.4	262.6	295.1	316.6	330.7
S.D.	9.86	9.12	8.14	6.77	9.30	11.27
N	5	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 112 GROUP: 2-M SEX: MALE
DOSE: 2.0(mg/kg)

ANIMAL #	DAY -4	DAY 0	DAY 3	DAY 7	Day 11	DAY 13
971	220.2	247.9	266.0	289.8	297.9	313.3
972	195.9	224.0	239.0	266.1	284.0	296.4
973	215.0	246.4	258.9	286.0	300.9	316.0
974	207.3	240.3	269.4	302.0	321.9	335.8
975	203.4	231.8	250.3	284.4	302.3	312.4
MEAN	208.4	238.1	256.7	285.7	301.4	314.8
S.D.	9.56	10.10	12.32	12.93	13.57	14.04
N	5	5	5	5	5	5

--: Data Unavailable

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 112 GROUP: 3-M SEX: MALE
DOSE: 6.0 /30.0 (mg/kg)

ANIMAL #	DAY -4	DAY 0	DAY 3	DAY 7	Day 11	DAY 13
981	209.4	235.5	251.4	282.2	295.4	305.6
982	217.4	244.4	257.3	284.1	298.6	306.8
983	194.5	222.8	244.3	278.9	295.5	303.6
984	204.6	239.0	258.7	292.6	302.9	312.4
985	205.1	239.7	261.1	296.5	305.4	314.4
MEAN	206.2	236.3	254.6	286.9	299.6	308.6
S.D.	8.31	8.18	6.76	7.39	4.47	4.62
N	5	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 112 GROUP: 4-M SEX: MALE
DOSE: 18.0(mg/kg)

ANIMAL #	DAY -4	DAY 0	DAY 3	DAY 7	Day 11	DAY 13
991	218.5	256.0	278.3	313.8	336.0	353.5
992	193.6	217.9	228.0	247.7	259.4	273.2
993	203.1	234.9	251.3	282.4	305.5	320.3
994	205.1	229.0	240.5	257.0	275.6	285.1
995	217.3	233.9	245.2	263.8	279.8	290.2
MEAN	207.5	234.3	248.7	272.9	291.3	304.5
S.D.	10.43	13.86	18.65	26.14	29.98	32.45
N	5	5	5	5	5	5

--: Data Unavailable

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 112 GROUP: 1-M SEX: MALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 3[b]	DAY 7	DAY 11	DAY 13	TOTAL GAIN
961	20.9	37.4	24.4	16.0	98.7
962	16.6	25.7	15.2	10.3	67.8
963	25.1	28.2	23.5	14.6	91.4
964	23.3	33.7	26.5	17.0	100.5
965	20.0	37.5	17.9	12.9	88.3
MEAN	21.2	32.5	21.5	14.2	89.3
S.D.	3.25	5.37	4.75	2.65	13.05
N	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 0

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 112 GROUP: 2-M SEX: MALE
DOSE: 2.0 (mg/kg)

ANIMAL #	DAY 3[b]	DAY 7	DAY 11	DAY 13	TOTAL GAIN
971	18.1	23.8	8.1	15.4	65.4
972	15.0	27.1	17.9	12.4	72.4
973	12.5	27.1	14.9	15.1	69.6
974	29.1	32.6	19.9	13.9	95.5
975	18.5	34.1	17.9	10.1	80.6
MEAN	18.6	28.9	15.7	13.4	76.7
S.D.	6.34	4.28	4.63	2.18	11.89
N	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 0

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 112 GROUP: 3-M SEX: MALE
DOSE: 6.0 /30.0 (mg/kg)

ANIMAL #	DAY 3[b]	DAY 7	DAY 11	DAY 13	TOTAL GAIN
981	15.9	30.8	13.2	10.2	70.1
982	12.9	26.8	14.5	8.2	62.4
983	21.5	34.6	16.6	8.1	80.8
984	19.7	33.9	10.3	9.5	73.4
985	21.4	35.4	8.9	9.0	74.7
MEAN	18.3	32.3	12.7	9.0	72.3
S.D.	3.77	3.53	3.12	0.89	6.75
N	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 0

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 112 GROUP: 4-M SEX: MALE
DOSE: 18.0(mg/kg)

ANIMAL #	DAY 3[b]	DAY 7	DAY 11	DAY 13	TOTAL GAIN
991	22.3	35.5	22.2	17.5	97.5
992	10.1	19.7	11.7	13.8	55.3
993	16.4	31.1	23.1	14.8	85.4
994	11.5	16.5	18.6	9.5	56.1
995	11.3	18.6	16.0	10.4	56.3
MEAN	14.3	24.3	18.3	13.2	70.1
S.D.	5.07	8.46	4.67	3.28	19.94
N	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 0

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 112 GROUP: 1-F SEX: FEMALE
DOSE: 0(mg/kg)

ANIMAL #	DAY -4	DAY 0	DAY 3	DAY 7	Day 11	DAY 13
966	174.1	190.3	190.3	198.7	211.1	228.1
967	153.5	171.4	177.4	192.5	200.0	209.7
968	164.1	186.1	193.0	215.1	225.4	236.7
969	164.9	176.6	186.6	203.7	216.0	214.5
970	173.3	189.9	192.6	205.4	216.0	230.0
MEAN	166.0	182.9	188.0	203.1	213.7	223.8
S.D.	8.37	8.45	6.44	8.39	9.25	11.28
N	5	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 112 GROUP: 2-F SEX: FEMALE
DOSE: 2.0(mg/kg)

ANIMAL #	DAY -4	DAY 0	DAY 3	DAY 7	Day 11	DAY 13
976	178.6	202.8	212.1	227.0	239.1	243.8
977	156.7	181.2	185.5	200.3	215.5	226.1
978	173.2	184.7	197.0	214.5	213.4	221.8
979	168.5	182.4	201.1	220.1	218.2	226.2
980	163.7	181.4	197.1	213.2	217.8	218.6
MEAN	168.1	186.5	198.6	215.0	220.8	227.3
S.D.	8.45	9.22	9.55	9.87	10.41	9.76
N	5	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 112 GROUP: 3-F SEX: FEMALE
DOSE: 6.0/30.0 (mg/kg)

ANIMAL #	DAY -4	DAY 0	DAY 3	DAY 7	Day 11	DAY 13
986	171.8	188.8	202.0	216.9	231.4	223.4
987	157.9	172.5	181.7	197.7	204.6	212.7
988	161.9	178.9	179.3	196.9	202.9	199.0
989	164.5	185.3	194.4	212.8	215.8	226.9
990	177.1	190.8	199.0	214.5	220.9	227.7
MEAN	166.6	183.3	191.3	207.8	215.1	217.9
S.D.	7.74	7.52	10.24	9.66	11.82	12.16
N	5	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 112 GROUP: 4-F SEX: FEMALE
DOSE: 18.0(mg/kg)

ANIMAL #	DAY -4	DAY 0	DAY 3	DAY 7	Day 11	DAY 13
996	158.7	182.2	189.6	209.7	221.9	218.0
997	155.8	177.3	178.5	190.4	205.7	203.7
998	167.7	180.5	185.9	198.6	213.2	218.6
999	174.2	193.7	196.8	218.7	229.3	235.4
1000	171.6	188.0	191.0	201.2	212.3	222.4
MEAN	165.6	184.3	188.4	203.7	216.5	219.6
S.D.	8.03	6.52	6.76	10.84	9.19	11.33
N	5	5	5	5	5	5

--: Data Unavailable

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 112 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 3[b]	DAY 7	DAY 11	DAY 13	TOTAL GAIN
966	0.0	8.4	12.4	17.0	37.8
967	6.0	15.1	7.5	9.7	38.3
968	6.9	22.1	10.3	11.3	50.6
969	10.0	17.1	12.3	-1.5	37.9
970	2.7	12.8	10.6	14.0	40.1
MEAN	5.1	15.1	10.6	10.1	40.9
S.D.	3.87	5.08	1.99	7.05	5.48
N	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 0

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 112 GROUP: 2-F SEX: FEMALE
DOSE: 2.0 (mg/kg)

ANIMAL #	DAY 3[b]	DAY 7	DAY 11	DAY 13	TOTAL GAIN
976	9.3	14.9	12.1	4.7	41.0
977	4.3	14.8	15.2	10.6	44.9
978	12.3	17.5	-1.1	8.4	37.1
979	18.7	19.0	-1.9	8.0	43.8
980	15.7	16.1	4.6	0.8	37.2
MEAN	12.1	16.5	5.8	6.5	40.8
S.D.	5.60	1.79	7.69	3.82	3.62
N	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 0

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 112 GROUP: 3-F SEX: FEMALE
DOSE: 6.0/30.0 (mg/kg)

ANIMAL #	DAY 3[b]	DAY 7	DAY 11	DAY 13	TOTAL GAIN
986	13.2	14.9	14.5	-8.0	34.6
987	9.2	16.0	6.9	8.1	40.2
988	0.4	17.6	6.0	-3.9	20.1
989	9.1	18.4	3.0	11.1	41.6
990	8.2	15.5	6.4	6.8	36.9
MEAN	8.0	16.5	7.4	2.8	34.7
S.D.	4.68	1.47	4.27	8.28	8.60
N	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 0

INDIVIDUAL WEIGHT GAIN (Grams)[a]

STUDY: 112 GROUP: 4-F SEX: FEMALE
DOSE: 18.0(mg/kg)

ANIMAL #	DAY 3[b]	DAY 7	DAY 11	DAY 13	TOTAL GAIN
996	7.4	20.1	12.2	-3.9	35.8
997	1.2	11.9	15.3	-2.0	26.4
998	5.4	12.7	14.6	5.4	38.1
999	3.1	21.9	10.6	6.1	41.7
1000	3.0	10.2	11.1	10.1	34.4
MEAN	4.0	15.4	12.8	3.1	35.3
S.D.	2.41	5.27	2.10	5.88	5.68
N	5	5	5	5	5

--: Data Unavailable

a = Successive periods
b = Baseline is Day 0

APPENDIX 5

Individual Food Consumption Data

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 112 GROUP: 1-M SEX: MALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 0[b]	DAY 3	DAY 7	DAY 11	DAY 13
961	--	22.9	25.8	27.7	24.7
962	21.2	22.9	22.7	24.9	21.6
963	21.0	24.1	23.3	25.1	24.3
964	18.9	22.1	22.8	25.2	23.1
965	19.7	23.4	24.3	30.9	23.1
MEAN	20.2	23.1	23.8	26.8	23.4
S.D.	1.09	0.74	1.29	2.58	1.22
N	4	5	5	5	5

--: Data Unavailable

a = Successive Periods
b = Food was weighed in on Day -4

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 112 GROUP: 2-M SEX: MALE
DOSE: 2.0 (mg/kg)

ANIMAL #	DAY 0[b]	DAY 3	DAY 7	DAY 11	DAY 13
971	19.8	24.2	21.5	21.3	23.0
972	18.7	20.6	21.2	22.7	20.7
973	21.3	22.0	21.0	22.2	22.5
974	21.5	24.2	23.8	29.6	24.7
975	20.2	23.2	22.4	23.9	20.5
MEAN	20.3	22.8	22.0	23.9	22.3
S.D.	1.15	1.55	1.15	3.30	1.74
N	5	5	5	5	5

--: Data Unavailable

a = Successive Periods
b = Food was weighed in on Day -4

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 112 GROUP: 3-M SEX: MALE
DOSE: 6.0/30.0 (mg/kg)

ANIMAL #	DAY 0[b]	DAY 3	DAY 7	DAY 11	DAY 13
981	17.5	19.8	21.2	20.6	19.8
982	20.3	21.5	21.9	21.5	18.2
983	18.9	21.4	21.7	22.0	18.2
984	20.4	22.3	23.1	20.1	15.7
985	20.2	23.0	23.8	21.9	15.6
MEAN	19.5	21.6	22.3	21.2	17.5
S.D.	1.25	1.20	1.07	0.83	1.81
N	5	5	5	5	5

--: Data Unavailable

a = Successive Periods
b = Food was weighed in on Day -4

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 112 GROUP: 4-M SEX: MALE
DOSE: 18.0 (mg/kg)

ANIMAL #	DAY 0[b]	DAY 3	DAY 7	DAY 11	DAY 13
991	22.2	24.3	23.7	26.8	24.4
992	17.6	18.1	18.2	20.4	18.5
993	19.4	20.3	19.5	23.7	22.3
994	17.6	18.3	18.8	19.6	18.0
995	15.6	18.5	18.0	19.5	19.0
MEAN	18.5	19.9	19.6	22.0	20.4
S.D.	2.48	2.61	2.34	3.18	2.78
N	5	5	5	5	5

--: Data Unavailable

a = Successive Periods
b = Food was weighed in on Day -4

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 112 GROUP: 1-F SEX: FEMALE
DOSE: 0(mg/kg)

ANIMAL #	DAY 0[b]	DAY 3	DAY 7	DAY 11	DAY 13
966	15.5	16.8	16.5	19.5	18.2
967	15.0	15.5	15.6	18.1	16.5
968	16.2	18.1	18.7	21.4	20.1
969	13.8	17.0	16.7	22.7	14.2
970	16.4	16.3	15.9	18.1	17.7
MEAN	15.4	16.7	16.7	20.0	17.3
S.D.	1.04	0.96	1.21	2.04	2.18
N	5	5	5	5	5

--: Data Unavailable

a = Successive Periods
b = Food was weighed in on Day -4

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 112 GROUP: 2-F SEX: FEMALE
DOSE: 2.0 (mg/kg)

ANIMAL #	DAY 0[b]	DAY 3	DAY 7	DAY 11	DAY 13
976	17.9	21.0	19.8	22.8	18.9
977	15.9	16.9	17.1	18.5	17.2
978	13.5	18.2	17.3	14.8	14.2
979	15.4	19.5	17.6	16.7	15.5
980	15.8	17.3	16.9	19.8	16.6
MEAN	15.7	18.6	17.7	18.5	16.5
S.D.	1.57	1.68	1.18	3.05	1.77
N	5	5	5	5	5

--: Data Unavailable

a = Successive Periods
b = Food was weighed in on Day -4

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 112 GROUP: 3-F SEX: FEMALE
DOSE: 6.0/30.0 (mg/kg)

ANIMAL #	DAY 0[b]	DAY 3	DAY 7	DAY 11	DAY 13
986	17.5	21.7	19.2	22.6	10.6
987	15.4	18.3	9.7	19.8	17.4
988	14.9	14.2	15.9	16.3	7.3
989	18.8	19.4	18.1	16.1	8.8
990	15.6	17.1	17.8	16.4	12.5
MEAN	16.4	18.1	16.1	18.2	11.3
S.D.	1.65	2.78	3.79	2.88	3.92
N	5	5	5	5	5

--: Data Unavailable

a = Successive Periods
b = Food was weighed in on Day -4

INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)[a]

STUDY: 112 GROUP: 4-F SEX: FEMALE
DOSE: 18.0(mg/kg)

ANIMAL #	DAY 0[b]	DAY 3	DAY 7	DAY 11	DAY 13
996	15.6	16.8	15.7	18.6	15.7
997	14.8	13.5	12.2	24.3	8.0
998	14.8	14.5	13.0	17.9	14.8
999	16.0	13.1	15.3	18.7	16.2
1000	15.1	13.8	14.4	16.7	17.9
MEAN	15.3	14.3	14.1	19.2	14.5
S.D.	0.53	1.47	1.49	2.94	3.82
N	5	5	5	5	5

--: Data Unavailable

a = Successive Periods
b = Food was weighed in on Day -4

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 112 GROUP: 1-M SEX: MALE
DOSE: 0 (mg/kg)

ANIMAL #	DAY 0[b]	DAY 3	DAY 7	DAY 11	DAY 13
961	--	68.7	103.3	110.8	49.4
962	84.8	68.8	90.9	99.4	43.2
963	83.9	72.2	93.1	100.5	48.5
964	75.4	66.4	91.1	100.8	46.2
965	78.6	70.1	97.2	123.6	46.1
MEAN	80.7	69.2	95.1	107.0	46.7
S.D.	4.46	2.12	5.23	10.35	2.42
N	4	5	5	5	5

--: Data Unavailable

a = Successive Periods
b = Food was weighed in on Day -4

INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 112 GROUP: 2-M SEX: MALE
DOSE: 2.0 (mg/kg)[b]

ANIMAL #	DAY 0	DAY 3	DAY 7	DAY 11	DAY 13
971	79.0	72.5	85.8	85.2	46.0
972	74.9	61.9	84.6	90.7	41.4
973	85.3	66.1	83.9	88.7	45.0
974	85.8	72.7	95.3	118.4	49.3
975	80.8	69.7	89.5	95.7	41.0
MEAN	81.2	68.6	87.8	95.7	44.5
S.D.	4.55	4.59	4.71	13.22	3.44
N	5	5	5	5	5

--: Data Unavailable

a = Successive Periods
b = Food was weighed in on Day -4

INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 112 GROUP: 3-M SEX: MALE
DOSE: 6.0/30.0 (mg/kg)

ANIMAL #	DAY 0[b]	DAY 3	DAY 7	DAY 11	DAY 13
981	70.0	59.5	84.9	82.3	39.6
982	81.2	64.5	87.4	86.1	36.3
983	75.5	64.3	86.6	87.8	36.3
984	81.4	66.8	92.5	80.4	31.4
985	80.7	68.9	95.2	87.7	31.1
MEAN	77.8	64.8	89.3	84.9	34.9
S.D.	4.98	3.51	4.34	3.34	3.63
N	5	5	5	5	5

--: Data Unavailable

a = Successive Periods
b = Food was weighed in on Day -4

INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 112 GROUP: 4-M SEX: MALE
DOSE: 18.0 (mg/kg)

ANIMAL #	DAY 0[b]	DAY 3	DAY 7	DAY 11	DAY 13
991	88.9	73.0	94.8	107.0	48.8
992	70.3	54.4	72.8	81.5	37.0
993	77.4	61.0	78.1	94.7	44.5
994	70.3	54.8	75.2	78.2	36.0
995	62.5	55.5	72.1	78.0	38.0
MEAN	73.9	59.7	78.6	87.9	40.9
S.D.	9.91	7.88	9.36	12.69	5.55
N	5	5	5	5	5

--: Data Unavailable

a = Successive Periods
b = Food was weighed in on Day -4

INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 112 GROUP: 1-F SEX: FEMALE
DOSE:[b] 0(mg/kg)

ANIMAL #	DAY 0	DAY 3	DAY 7	DAY 11	DAY 13
966	61.9	50.3	66.0	77.8	36.3
967	59.9	46.6	62.4	72.2	32.9
968	64.6	54.4	74.8	85.7	40.2
969	55.1	51.0	66.7	90.7	28.3
970	65.4	48.9	63.4	72.5	35.4
MEAN	61.4	50.2	66.7	79.8	34.6
S.D.	4.14	2.87	4.89	8.20	4.40
N	5	5	5	5	5

--: Data Unavailable

a = Successive Periods
b = Food was weighed in on Day -4

INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 112 GROUP: 2-F SEX: FEMALE
DOSE: 2.0(mg/kg)

ANIMAL #	DAY 0[b]	DAY 3	DAY 7	DAY 11	DAY 13
976	71.7	63.1	79.2	91.3	37.8
977	63.4	50.7	68.2	74.0	34.4
978	54.1	54.7	69.0	59.1	28.4
979	61.6	58.4	70.3	66.7	31.0
980	63.0	51.9	67.4	79.2	33.1
MEAN	62.8	55.8	70.8	74.1	32.9
S.D.	6.26	5.06	4.81	12.26	3.54
N	5	5	5	5	5

--: Data Unavailable

a = Successive Periods
b = Food was weighed in on Day -4

INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 112 GROUP: 3-F SEX: FEMALE
DOSE:[b] 6.0/30.0 (mg/kg)

ANIMAL #	DAY 0	DAY 3	DAY 7	DAY 11	DAY 13
986	69.8	65.1	76.7	90.2	21.2
987	61.4	54.8	38.6	79.0	34.8
988	59.4	42.5	63.5	65.1	14.5
989	75.0	58.3	72.3	64.3	17.6
990	62.2	51.3	71.3	65.4	25.0
MEAN	65.6	54.4	64.5	72.8	22.6
S.D.	6.59	8.38	15.23	11.48	7.86
N	5	5	5	5	5

--: Data Unavailable

a = Successive Periods
b = Food was weighed in on Day -4

INDIVIDUAL FOOD CONSUMPTION (Grams)[a]

STUDY: 112 GROUP: 4-F SEX: FEMALE
DOSE: 18.0 (mg/kg)

ANIMAL #	DAY 0[b]	DAY 3	DAY 7	DAY 11	DAY 13
996	62.4	50.3	62.7	74.2	31.3
997	59.2	40.5	48.9	97.1	16.0
998	59.0	43.5	52.1	71.6	29.6
999	64.1	39.3	61.1	74.9	32.3
1000	60.2	41.3	57.5	66.8	35.7
MEAN	61.0	43.0	56.5	76.9	29.0
S.D.	2.20	4.37	5.87	11.72	7.59
N	5	5	5	5	5

--: Data Unavailable

a = Successive Periods
b = Food was weighed in on Day -4

APPENDIX 6

Individual Clinical Chemistry Data

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

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

STUDY ID: 112 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/kg/day								
961	61	101	7.5	4.6	2.9	1.59	32.3	224
962	64	121	7.7	4.1	3.6	1.14	53.2	222
963	63	90	6.8	3.8	3.0	1.27	38.3	179
964	48	126	7.3	4.0	3.3	1.21	22.4	209
965	63	88	7.4	4.2	3.2	1.31	69.6	322
MEAN	60	105	7.3	4.1	3.2	1.30	43.2	231
SD	6.7	17.5	0.34	0.30	0.27	0.172	18.52	53.8
N	5	5	5	5	5	5	5	5
GROUP: 2-M:2.0 mg/kg/day								
971	48	89	7.8	3.9	3.9	1.00	40.7	248
972	47	118	6.9	3.8	3.1	1.23	66.6	243
973	60	108	7.6	3.9	3.7	1.05	63.9	304
974	65	100	7.5	3.9	3.6	1.08	137.3	218
975	65	119	7.6	4.1	3.5	1.17	75.1	342
MEAN	57	107	7.5	3.9	3.6	1.11	76.7	271
SD	8.9	12.6	0.34	0.11	0.30	0.093	36.18	50.6
N	5	5	5	5	5	5	5	5
GROUP: 3-M:6.0 mg/kg/day (Day 0 - 6)/30.0 mg/kg/day (Day 7 - 13)								
981	79	119	7.6	4.2	3.4	1.24	94.4	274
982	56	112	7.6	3.8	3.8	1.00	65.1	224
983	66	118	7.1	4.1	3.0	1.37	39.7	212
984	64	102	7.5	4.0	3.5	1.14	41.2	170
985	77	146	7.8	4.2	3.6	1.17	112.2	199
MEAN	68	119	7.5	4.1	3.5	1.18	70.5	216
SD	9.6	16.3	0.26	0.17	0.30	0.136	32.20	38.2
N	5	5	5	5	5	5	5	5
GROUP: 4-M:18.0 mg/kg/day								
991	70	112	8.0	4.2	3.8	1.11	74.6	242
992	76	154	7.3	4.1	3.2	1.28	57.8	245
993	65	99	7.2	4.0	3.2	1.25	51.8	339
994	51	87	7.2	4.0	3.2	1.25	65.1	184
995	65	146	7.1	4.0	3.1	1.29	38.5	504
MEAN	65	120	7.4	4.1	3.3	1.24	57.6	303
SD	9.2	29.3	0.36	0.09	0.28	0.073	13.64	125.4
N	5	5	5	5	5	5	5	5

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

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

STUDY ID: 112 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/kg/day								
961	50	156	14.5	0.47	143	5.56	108	11.6
962	54	49	13.5	0.46	140	6.35	115	11.0
963	64	29	12.9	0.50	141	6.17	115	10.6
964	48	40	10.4	0.46	143	6.94	114	10.8
965	62	74	10.5	0.46	142	5.90	113	10.8
MEAN	56	70	12.4	0.47	142	6.18	113	11.0
SD	7.1	51.1	1.84	0.017	1.3	0.517	2.9	0.38
N	5	5	5	5	5	5	5	5
GROUP: 2-M:2.0 mg/kg/day								
971	67	60	15.5	0.44	142	5.98	112	10.9
972	54	39	11.7	0.51	139	6.40	117	10.4
973	62	53	20.6	0.56	141	5.89	112	10.4
974	76	40	15.9	0.48	142	6.31	107	10.5
975	80	65	13.4	0.54	143	5.86	110	11.1
MEAN	68	51	15.4	0.51	141	6.09	112	10.7
SD	10.5	11.7	3.35	0.048	1.5	0.250	3.6	0.32
N	5	5	5	5	5	5	5	5
GROUP: 3-M:6.0 mg/kg/day (Day 0 - 6)/30.0 mg/kg/day (Day 7 - 13)								
981	59	50	14.8	0.51	144	5.73	114	11.3
982	61	49	13.8	0.53	141	6.25	117	11.1
983	60	49	10.7	0.52	141	5.37	118	10.6
984	66	43	13.4	0.50	143	6.03	109	10.7
985	52	44	11.3	0.57	140	5.82	118	10.5
MEAN	60	47	12.8	0.53	142	5.84	115	10.8
SD	5.0	3.2	1.73	0.027	1.6	0.331	3.8	0.34
N	5	5	5	5	5	5	5	5
GROUP: 4-M:18.0 mg/kg/day								
991	81	84	10.9	0.53	143	5.61	112	11.6
992	58	50	17.1	0.61	143	6.79	116	11.3
993	62	9	13.2	0.51	143	6.48	116	10.6
994	43	84	14.9	0.52	144	6.36	108	11.0
995	38	46	15.7	0.50	144	5.87	113	10.6
MEAN	56	55	14.4	0.53	143	6.22	113	11.0
SD	17.0	31.2	2.39	0.044	0.5	0.476	3.3	0.44
N	5	5	5	5	5	5	5	5

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

STUDY ID: 112 SEX: MALE

ANIMAL ID	IP mg/dL	GLU mg/dL
GROUP: 1-M:0 mg/kg/day		
961	9.7	137
962	10.5	166
963	11.1	138
964	11.2	132
965	10.2	122
MEAN	10.5	139
SD	0.63	16.4
N	5	5
GROUP: 2-M:2.0 mg/kg/day		
971	10.5	127
972	10.1	126
973	10.7	142
974	10.5	130
975	10.3	139
MEAN	10.4	133
SD	0.23	7.3
N	5	5
GROUP: 3-M:6.0 mg/kg/day (Day 0 - 6)/30.0 mg/kg/day (Day 7 - 13)		
981	11.4	100
982	10.5	126
983	10.3	125
984	10.1	111
985	11.8	145
MEAN	10.8	121
SD	0.74	17.0
N	5	5
GROUP: 4-M:18.0 mg/kg/day		
991	9.7	118
992	11.8	151
993	9.4	114
994	9.7	114
995	9.4	112
MEAN	10.0	122
SD	1.02	16.5
N	5	5

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

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

STUDY ID: 112 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/kg/day								
966	68	102	7.6	3.9	3.7	1.05	40.7	193
967	44	98	8.3	4.7	3.6	1.31	34.6	158
968	62	109	7.2	4.0	3.2	1.25	18.0	243
969	54	119	8.0	2.9	5.1	0.57	20.3	200
970	49	93	7.5	4.2	3.3	1.27	39.7	254
MEAN	55	104	7.7	3.9	3.8	1.09	30.7	210
SD	9.7	10.1	0.43	0.66	0.77	0.308	10.79	39.1
N	5	5	5	5	5	5	5	5
GROUP: 2-F:2.0 mg/kg/day								
976	59	96	7.7	4.5	3.2	1.41	20.0	236
977	66	111	7.6	4.1	3.5	1.17	24.6	206
978	59	95	7.7	4.2	3.5	1.20	20.0	150
979	35	82	8.0	4.5	3.5	1.29	17.8	200
980	65	157	7.6	4.1	3.5	1.17	64.9	175
MEAN	57	108	7.7	4.3	3.4	1.25	29.5	193
SD	12.6	29.1	0.16	0.20	0.13	0.103	19.97	32.6
N	5	5	5	5	5	5	5	5
GROUP: 3-F:6.0 mg/kg/day (Day 0 - 6)/30.0 mg/kg/day (Day 7 - 13)								
986	53	114	7.9	4.4	3.5	1.26	46.1	168
987	70	97	7.6	4.2	3.4	1.24	35.1	217
988	113	183	7.4	4.2	3.2	1.31	60.4	117
989	68	113	8.6	4.7	3.9	1.21	52.0	113
990	85	158	8.0	4.3	3.7	1.16	76.4	174
MEAN	78	133	7.9	4.4	3.5	1.24	54.0	158
SD	22.7	36.0	0.46	0.21	0.27	0.056	15.54	43.4
N	5	5	5	5	5	5	5	5
GROUP: 4-F:18.0 mg/kg/day								
996	81	140	8.8	5.3	3.5	1.51	38.1	174
997	49	106	8.2	4.6	3.6	1.28	21.2	182
998	48	142	7.9	4.5	3.4	1.32	70.5	207
999	48	90	7.0	3.9	3.1	1.26	56.6	170
1000	45	126	7.9	4.5	3.4	1.32	28.9	248
MEAN	54	121	8.0	4.6	3.4	1.34	43.1	196
SD	15.1	22.4	0.65	0.50	0.19	0.100	20.24	32.3
N	5	5	5	5	5	5	5	5

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

STUDY ID: 112 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/kg/day								
966	88	50	17.2	0.55	139	5.54	118	10.3
967	43	59	13.3	0.57	145	6.61	108	12.2
968	47	51	12.0	0.47	142	6.26	118	10.8
969	48	40	12.5	0.51	145	5.27	106	11.0
970	60	50	17.0	0.55	143	5.81	115	11.0
MEAN	57	50	14.4	0.53	143	5.90	113	11.1
SD	18.3	6.7	2.51	0.040	2.5	0.540	5.7	0.70
N	5	5	5	5	5	5	5	5
GROUP: 2-F:2.0 mg/kg/day								
976	41	47	16.9	0.55	141	5.19	110	10.6
977	65	61	12.8	0.52	142	6.52	109	11.2
978	50	50	12.8	0.48	143	5.66	111	10.8
979	37	56	12.9	0.47	143	5.55	109	11.1
980	56	46	16.0	0.52	143	6.14	113	11.3
MEAN	50	52	14.3	0.51	142	5.81	110	11.0
SD	11.3	6.4	2.01	0.033	0.9	0.521	1.7	0.29
N	5	5	5	5	5	5	5	5
GROUP: 3-F:6.0 mg/kg/day (Day 0 - 6)/30.0 mg/kg/day (Day 7 - 13)								
986	55	52	14.0	0.60	143	5.43	114	11.3
987	56	37	10.1	0.50	141	5.72	112	10.8
988	59	59	12.4	0.54	140	6.17	116	10.8
989	56	97	15.6	0.55	143	6.45	112	10.8
990	47	111	19.4	0.59	144	7.59	117	11.5
MEAN	55	71	14.3	0.56	142	6.27	114	11.0
SD	4.5	31.4	3.50	0.040	1.6	0.836	2.3	0.34
N	5	5	5	5	5	5	5	5
GROUP: 4-F:18.0 mg/kg/day								
996	57	119	14.5	0.65	148	7.82	109	12.6
997	54	49	14.2	0.55	144	6.69	114	11.2
998	79	62	13.7	0.55	142	5.65	111	10.8
999	59	44	11.1	0.50	139	5.46	118	10.5
1000	73	51	10.7	0.55	140	5.36	114	10.7
MEAN	64	65	12.8	0.56	143	6.20	113	11.2
SD	10.9	30.9	1.80	0.055	3.6	1.051	3.4	0.84
N	5	5	5	5	5	5	5	5

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

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

STUDY ID: 112 SEX: FEMALE

ANIMAL ID	IP mg/dL	GLU mg/dL
GROUP: 1-F:0 mg/kg/day		
966	9.7	154
967	11.4	177
968	11.1	144
969	8.8	131
970	10.5	164
MEAN	10.3	154
SD	1.06	17.7
N	5	5
GROUP: 2-F:2.0 mg/kg/day		
976	10.0	125
977	9.5	128
978	9.6	112
979	9.5	97
980	11.7	130
MEAN	10.1	118
SD	0.94	13.9
N	5	5
GROUP: 3-F:6.0 mg/kg/day (Day 0 - 6)/30.0 mg/kg/day (Day 7 - 13)		
986	10.5	106
987	9.3	141
988	11.2	150
989	11.1	134
990	11.8	147
MEAN	10.8	136
SD	0.95	17.6
N	5	5
GROUP: 4-F:18.0 mg/kg/day		
996	11.7	117
997	10.2	140
998	10.4	120
999	10.5	134
1000	8.6	151
MEAN	10.3	132
SD	1.11	14.1
N	5	5

APPENDIX 7

Individual Hematology Data

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: DAY 14

STUDY ID: 112 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/kg/day								
961	7.12	16.2	45.4	63.8	22.8	35.7	1.0	0
962	8.13	16.8	46.5	57.2	20.7	36.1	0.5	0
963	7.21	15.9	44.8	62.1	22.1	35.5	0.6	0
964	7.23	15.9	44.8	62.0	22.0	35.5	1.3	0
965	7.23	16.1	45.5	62.9	22.3	35.4	1.2	1
MEAN	7.38	16.2	45.4	61.6	22.0	35.6	0.9	0
SD	0.419	0.37	0.70	2.56	0.78	0.28	0.36	0.4
N	5	5	5	5	5	5	5	5
GROUP: 2-M:2.0 mg/kg/day								
971	7.68	16.2	44.9	58.5	21.1	36.1	2.5	0
972	6.80	15.4	42.8	62.9	22.6	36.0	1.2	1
973	7.39	16.0	44.3	59.9	21.7	36.1	0.9	0
974	6.99	15.7	43.8	62.7	22.5	35.8	1.7	0
975	7.40	15.9	44.4	60.0	21.5	35.8	1.3	0
MEAN	7.25	15.8	44.0	60.8	21.9	36.0	1.5	0
SD	0.353	0.30	0.80	1.92	0.65	0.15	0.62	0.4
N	5	5	5	5	5	5	5	5
GROUP: 3-M:6.0 mg/kg/day (Day 0 - 6)/30.0 mg/kg/day (Day 7-13)								
981	5.88	14.5	45.3	77.0	24.7	32.0	9.4	1
982	6.44	15.0	45.1	70.0	23.3	33.3	9.0	2
983	6.16	14.8	44.5	72.2	24.0	33.3	4.6	1
984	6.29	15.0	44.5	70.7	23.8	33.7	8.4	0
985	6.32	14.5	43.5	68.8	22.9	33.3	0.8	3
MEAN	6.22	14.8	44.6	71.7	23.7	33.1	6.4	1
SD	0.214	0.25	0.70	3.19	0.69	0.65	3.69	1.1
N	5	5	5	5	5	5	5	5
GROUP: 4-M:18.0 mg/kg/day								
991	5.59	14.0	43.6	78.0	25.0	32.1	7.9	0
992	6.25	15.0	44.1	70.6	24.0	34.0	7.2	0
993	5.54	14.6	43.7	78.9	26.4	33.4	9.4	0
994	5.90	15.0	44.0	74.6	25.4	34.1	5.0	0
995	6.40	15.7	46.8	73.1	24.5	33.5	0.5	1
MEAN	5.94	14.9	44.4	75.0	25.1	33.4	6.0	0
SD	0.385	0.62	1.34	3.44	0.92	0.80	3.46	0.4
N	5	5	5	5	5	5	5	5

WBC corrected for NRBC = or > 10

TWO WEEK ORAL RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: DAY 14

STUDY ID: 112 SEX: MALE

ANIMAL ID	HB %	%METHGB %	PLT 10^3/ccm	WBC 10^3/cmm	M. Neutrop 10^3/cmm	I. Neutrop 10^3/cmm	Lymphocyte 10^3/cmm	Monocytes 10^3/cmm
GROUP: 1-M:0 mg/kg/day								
961	0.0	0.6	1114	18.0	1.1	0.2	15.8	0.7
962	0.0	0.4	1103	17.8	0.9	1.1	15.5	0.2
963	0.0	1.1	1134	17.3	0.9	0.9	14.9	0.5
964	0.0	0.4	1163	11.3	1.5	0.2	8.8	0.6
965	0.0	0.6	1288	17.2	1.0	1.2	15.0	0.0
MEAN	0.0	0.6	1160	16.3	1.1	0.7	14.0	0.4
SD	0.00	0.29	74.9	2.83	0.25	0.49	2.93	0.29
N	5	5	5	5	5	5	5	5
GROUP: 2-M:2.0 mg/kg/day								
971	0.0	1.2	1143	18.3	2.7	0.0	14.1	0.7
972	0.0	2.4	1130	9.3	1.4	0.7	7.1	0.2
973	0.0	1.9	1301	17.3	1.6	0.2	15.1	0.5
974	0.0	2.3	1223	17.1	3.1	0.5	12.8	0.7
975	0.0	2.1	1347	15.8	1.3	0.9	12.5	0.9
MEAN	0.0	2.0	1229	15.6	2.0	0.5	12.3	0.6
SD	0.00	0.48	95.3	3.61	0.82	0.36	3.10	0.26
N	5	5	5	5	5	5	5	5
GROUP: 3-M:6.0 mg/kg/day (Day 0 - 6)/30.0 mg/kg/day (Day 7-13)								
981	0.1	9.1	1149	28.5	3.4	1.4	21.9	1.7
982	0.0	7.2	1407	17.5	2.1	0.5	13.7	1.1
983	0.0	7.4	1318	19.1	1.7	1.3	15.3	0.8
984	0.0	7.9	1301	12.9	1.2	0.5	10.8	0.4
985	0.0	7.2	1182	14.3	1.4	0.4	12.2	0.3
MEAN	0.0	7.8	1271	18.5	2.0	0.8	14.8	0.9
SD	0.04	0.80	105.4	6.13	0.87	0.49	4.32	0.57
N	5	5	5	5	5	5	5	5
GROUP: 4-M:18.0 mg/kg/day								
991	0.0	4.4	1425	19.8	1.8	1.6	16.2	0.0
992	0.0	4.6	1236	18.3	2.6	0.7	14.3	0.7
993	0.0	4.4	1222	14.5	0.6	0.6	13.1	0.1
994	0.0	5.3	1238	12.7	0.6	0.1	10.9	0.9
995	0.0	4.9	1091	17.7	1.9	0.7	14.3	0.7
MEAN	0.0	4.7	1242	16.6	1.5	0.7	13.8	0.5
SD	0.00	0.38	119.1	2.91	0.88	0.54	1.95	0.40
N	5	5	5	5	5	5	5	5

WBC corrected for NRBC = or > 10

TWO WEEK ORAL RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: DAY 14

STUDY ID: 112 SEX: MALE

ANIMAL ID	Eosinophil 10^3/cmm	Basophils 10^3/cmm
GROUP: 1-M:0 mg/kg/day		
961	0.2	0.0
962	0.2	0.0
963	0.2	0.0
964	0.2	0.0
965	0.0	0.0
MEAN	0.2	0.0
SD	0.09	0.00
N	5	5
GROUP: 2-M:2.0 mg/kg/day		
971	0.7	0.0
972	0.0	0.0
973	0.0	0.0
974	0.0	0.0
975	0.2	0.0
MEAN	0.2	0.0
SD	0.30	0.00
N	5	5
GROUP: 3-M:6.0 mg/kg/day (Day 0 - 6)/30.0 mg/kg/day (Day 7-13)		
981	0.0	0.0
982	0.2	0.0
983	0.0	0.0
984	0.0	0.0
985	0.0	0.0
MEAN	0.0	0.0
SD	0.09	0.00
N	5	5
GROUP: 4-M:18.0 mg/kg/day		
991	0.2	0.0
992	0.0	0.0
993	0.1	0.0
994	0.1	0.0
995	0.0	0.0
MEAN	0.1	0.0
SD	0.08	0.00
N	5	5

WBC corrected for NRBC = or > 10

TWO WEEK ORAL RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: DAY 14

STUDY ID: 112 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/kg/day								
966	7.07	16.0	42.8	60.5	22.6	37.4	0.6	0
967	6.75	16.1	42.9	63.6	23.9	37.5	0.5	0
968	6.91	15.4	42.3	61.2	22.3	36.4	0.6	0
969	7.33	16.4	43.6	59.5	22.4	37.6	0.7	0
970	6.79	15.4	40.5	59.6	22.7	38.0	1.2	0
MEAN	6.97	15.9	42.4	60.9	22.8	37.4	0.7	0
SD	0.237	0.44	1.17	1.67	0.65	0.59	0.28	0.0
N	5	5	5	5	5	5	5	5
GROUP: 2-F:2.0 mg/kg/day								
976	6.06	13.7	38.5	63.5	22.6	35.6	3.3	1
977	7.01	15.3	40.9	58.3	21.8	37.4	3.5	0
978	5.63	12.4	34.6	61.5	22.0	35.8	5.1	0
979	5.57	12.7	36.2	65.0	22.8	35.1	6.7	0
980	5.33	12.5	36.6	68.7	23.5	34.2	5.7	4
MEAN	5.92	13.3	37.4	63.4	22.5	35.6	4.9	1
SD	0.664	1.22	2.42	3.88	0.68	1.17	1.45	1.7
N	5	5	5	5	5	5	5	5
GROUP: 3-F:6.0 mg/kg/day (Day 0-6)/30.0 mg/kg/day (Day 7-13)								
986	4.97	13.1	43.1	86.7	26.4	30.4	17.0	6
987	4.91	12.8	41.2	83.9	26.1	31.1	18.7	2
988	4.41	13.2	42.8	97.1	29.9	30.8	13.7	4
989	4.38	13.1	42.4	96.8	29.9	30.9	9.9	10
990	4.12	12.0	39.6	96.1	29.1	30.3	20.8	19
MEAN	4.56	12.8	41.8	92.1	28.3	30.7	16.0	8
SD	0.367	0.49	1.44	6.31	1.88	0.34	4.30	6.7
N	5	5	5	5	5	5	5	5
GROUP: 4-F:18.0 mg/kg day								
996	5.81	15.4	45.3	78.0	26.5	34.0	10.6	1
997	5.84	16.2	48.5	83.0	27.7	33.4	7.5	2
998	5.05	14.7	45.0	89.1	29.1	32.7	11.5	2
999	4.63	13.3	40.6	87.7	28.7	32.8	9.1	9
1000	5.59	16.0	47.5	85.0	28.6	33.7	8.2	3
MEAN	5.38	15.1	45.4	84.6	28.1	33.3	9.4	3
SD	0.527	1.17	3.05	4.36	1.04	0.56	1.66	3.2
N	5	5	5	5	5	5	5	5

WBC corrected for NRBC = or > 10

TWO WEEK ORAL RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: DAY 14

STUDY ID: 112 SEX: FEMALE

ANIMAL ID	HB %	%METHGB %	PLT 10^3/ccm	WBC 10^3/cmm	M. Neutrop 10^3/cmm	I. Neutrop 10^3/cmm	Lymphocyte 10^3/cmm	Monocytes 10^3/cmm
GROUP: 1-F:0 mg/kg/day								
966	0.0	0.8	1211	9.6	2.8	0.4	6.2	0.2
967	0.0	0.1	932	14.8	1.5	0.0	12.6	0.7
968	0.0	0.1	1160	12.9	1.9	0.0	10.3	0.5
969	0.0	0.0	1210	17.9	3.8	0.2	13.4	0.5
970	0.0	0.0	1037	13.9	3.5	0.1	9.9	0.1
MEAN	0.0	0.2	1110	13.8	2.7	0.1	10.5	0.4
SD	0.00	0.34	122.2	3.01	0.99	0.17	2.82	0.24
N	5	5	5	5	5	5	5	5
GROUP: 2-F:2.0 mg/kg/day								
976	0.0	1.7	1098	12.9	2.1	0.1	10.2	0.5
977	0.0	1.5	1333	15.4	3.5	0.3	10.8	0.6
978	0.0	3.5	1362	18.1	4.0	0.7	13.2	0.0
979	0.0	1.4	1259	11.0	1.4	0.0	9.1	0.4
980	0.0	4.5	1281	12.2	1.1	0.4	10.0	0.7
MEAN	0.0	2.5	1267	13.9	2.4	0.3	10.7	0.4
SD	0.00	1.40	102.7	2.84	1.28	0.27	1.55	0.27
N	5	5	5	5	5	5	5	5
GROUP: 3-F:6.0 mg/kg/day (Day 0-6)/30.0 mg/kg/day (Day 7-13)								
986	0.1	9.5	1039	15.8	2.2	0.9	12.0	0.5
987	0.0	5.7	1359	10.8	1.7	0.6	8.1	0.3
988	0.1	13.8	1042	13.5	2.3	0.4	10.5	0.3
989	0.2	6.0	1722	13.2	1.5	0.4	10.0	1.2
990	0.3	35.6	1638	17.3	3.6	0.3	12.8	0.5
MEAN	0.1	14.1	1360	14.1	2.3	0.5	10.7	0.6
SD	0.11	12.45	321.1	2.51	0.82	0.24	1.83	0.37
N	5	5	5	5	5	5	5	5
GROUP: 4-F:18.0 mg/kg day								
996	0.2	5.8	1179	17.9	1.4	1.3	14.9	0.4
997	0.0	5.2	1219	11.3	0.9	0.2	9.5	0.7
998	0.1	9.5	1267	11.1	1.7	0.3	8.5	0.6
999	0.0	10.6	1234	12.2	2.7	0.0	9.4	0.1
1000	0.1	5.5	1092	11.1	1.2	0.6	8.8	0.4
MEAN	0.1	7.3	1198	12.7	1.6	0.5	10.2	0.4
SD	0.08	2.53	67.3	2.93	0.69	0.51	2.65	0.23
N	5	5	5	5	5	5	5	5

WBC corrected for NRBC = or > 10

INDIVIDUAL ANIMAL HEMATOLOGY REPORT BY GROUP
PERIOD: DAY 14

STUDY ID: 112 SEX: FEMALE

ANIMAL ID	Eosinophil 10^3/cmm	Basophils 10^3/cmm
GROUP: 1-F:0 mg/kg/day		
966	0.0	0.0
967	0.0	0.0
968	0.1	0.0
969	0.0	0.0
970	0.3	0.0
MEAN	0.1	0.0
SD	0.13	0.00
N	5	5
GROUP: 2-F:2.0 mg/kg/day		
976	0.0	0.0
977	0.2	0.0
978	0.2	0.0
979	0.0	0.0
980	0.0	0.0
MEAN	0.1	0.0
SD	0.11	0.00
N	5	5
GROUP: 3-F:6.0 mg/kg/day (Day 0-6)/30.0 mg/kg/day (Day 7-13)		
986	0.2	0.0
987	0.0	0.0
988	0.0	0.0
989	0.1	0.0
990	0.0	0.0
MEAN	0.1	0.0
SD	0.09	0.00
N	5	5
GROUP: 4-F:18.0 mg/kg day		
996	0.0	0.0
997	0.0	0.0
998	0.0	0.0
999	0.0	0.0
1000	0.1	0.0
MEAN	0.0	0.0
SD	0.04	0.00
N	5	5

WBC corrected for NRBC = or > 10

TWO WEEK ORAL RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

WHITE DIFFERENTIAL COUNTS

STUDY ID: 112

GROUP: 1-M : 0 mg/kg/day SEX: MALE

ANIMAL ID		DAY 14 REL	DAY 14 ABS
961	Nucleated Red Cells	0	
	M. Neutrophils	6	1.1
	I. Neutrophils	1	0.2
	Lymphocytes	88	15.8
	Monocytes	4	0.7
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		18.0
962	Nucleated Red Cells	0	
	M. Neutrophils	5	0.9
	I. Neutrophils	6	1.1
	Lymphocytes	87	15.5
	Monocytes	1	0.2
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.8
963	Nucleated Red Cells	0	
	M. Neutrophils	5	0.9
	I. Neutrophils	5	0.9
	Lymphocytes	86	14.9
	Monocytes	3	0.5
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.3
964	Nucleated Red Cells	0	
	M. Neutrophils	13	1.5
	I. Neutrophils	2	0.2
	Lymphocytes	78	8.8
	Monocytes	5	0.6
	Eosinophils	2	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		11.3
965	Nucleated Red Cells	1	
	M. Neutrophils	6	1.0
	I. Neutrophils	7	1.2
	Lymphocytes	87	15.0
	Monocytes	0	0.0
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.2

NRBC Corrected After-10

TWO WEEK ORAL RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

WHITE DIFFERENTIAL COUNTS

STUDY ID: 112

GROUP: 2-M : 2.0 mg/kg/day SEX: MALE

ANIMAL ID		DAY 14 REL	DAY 14 ABS
971	Nucleated Red Cells	0	
	M. Neutrophils	15	2.7
	I. Neutrophils	0	0.0
	Lymphocytes	77	14.1
	Monocytes	4	0.7
	Eosinophils	4	0.7
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		18.3
972	Nucleated Red Cells	1	
	M. Neutrophils	15	1.4
	I. Neutrophils	7	0.7
	Lymphocytes	76	7.1
	Monocytes	2	0.2
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		9.3
973	Nucleated Red Cells	0	
	M. Neutrophils	9	1.6
	I. Neutrophils	1	0.2
	Lymphocytes	87	15.1
	Monocytes	3	0.5
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.3
974	Nucleated Red Cells	0	
	M. Neutrophils	18	3.1
	I. Neutrophils	3	0.5
	Lymphocytes	75	12.8
	Monocytes	4	0.7
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.1
975	Nucleated Red Cells	0	
	M. Neutrophils	8	1.3
	I. Neutrophils	6	0.9
	Lymphocytes	79	12.5
	Monocytes	6	0.9
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		15.8

NRBC Corrected After-10

TWO WEEK ORAL RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

WHITE DIFFERENTIAL COUNTS

STUDY ID: 112

GROUP: 3-M : 6.0 mg/kg/day (Day 0 - 6)/30.0 mg/kg/day (Day 7-13) SEX: MALE

ANIMAL ID		DAY 14 REL	DAY 14 ABS
981	Nucleated Red Cells	1	
	M. Neutrophils	12	3.4
	I. Neutrophils	5	1.4
	Lymphocytes	77	21.9
	Monocytes	6	1.7
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		28.5
982	Nucleated Red Cells	2	
	M. Neutrophils	12	2.1
	I. Neutrophils	3	0.5
	Lymphocytes	78	13.7
	Monocytes	6	1.1
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.5
983	Nucleated Red Cells	1	
	M. Neutrophils	9	1.7
	I. Neutrophils	7	1.3
	Lymphocytes	80	15.3
	Monocytes	4	0.8
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		19.1
984	Nucleated Red Cells	0	
	M. Neutrophils	9	1.2
	I. Neutrophils	4	0.5
	Lymphocytes	84	10.8
	Monocytes	3	0.4
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		12.9
985	Nucleated Red Cells	3	
	M. Neutrophils	10	1.4
	I. Neutrophils	3	0.4
	Lymphocytes	85	12.2
	Monocytes	2	0.3
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		14.3

NRBC Corrected After-10

TWO WEEK ORAL RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

WHITE DIFFERENTIAL COUNTS

STUDY ID: 112

GROUP: 4-M : 18.0 mg/kg/day SEX: MALE

ANIMAL ID		DAY 14 REL	DAY 14 ABS
991	Nucleated Red Cells	0	
	M. Neutrophils	9	1.8
	I. Neutrophils	8	1.6
	Lymphocytes	82	16.2
	Monocytes	0	0.0
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		19.8
992	Nucleated Red Cells	0	
	M. Neutrophils	14	2.6
	I. Neutrophils	4	0.7
	Lymphocytes	78	14.3
	Monocytes	4	0.7
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		18.3
993	Nucleated Red Cells	0	
	M. Neutrophils	4	0.6
	I. Neutrophils	4	0.6
	Lymphocytes	90	13.1
	Monocytes	1	0.1
	Eosinophils	1	0.1
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		14.5
994	Nucleated Red Cells	0	
	M. Neutrophils	5	0.6
	I. Neutrophils	1	0.1
	Lymphocytes	86	10.9
	Monocytes	7	0.9
	Eosinophils	1	0.1
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		12.7
995	Nucleated Red Cells	1	
	M. Neutrophils	11	1.9
	I. Neutrophils	4	0.7
	Lymphocytes	81	14.3
	Monocytes	4	0.7
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.7

NRBC Corrected After-10

TWO WEEK ORAL RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

WHITE DIFFERENTIAL COUNTS

STUDY ID: 112

GROUP: 1-F : 0 mg/kg/day SEX: FEMALE

ANIMAL ID		DAY 14 REL	DAY 14 ABS
966	Nucleated Red Cells	0	
	M. Neutrophils	29	2.8
	I. Neutrophils	4	0.4
	Lymphocytes	65	6.2
	Monocytes	2	0.2
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		9.6
967	Nucleated Red Cells	0	
	M. Neutrophils	10	1.5
	I. Neutrophils	0	0.0
	Lymphocytes	85	12.6
	Monocytes	5	0.7
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		14.8
968	Nucleated Red Cells	0	
	M. Neutrophils	15	1.9
	I. Neutrophils	0	0.0
	Lymphocytes	80	10.3
	Monocytes	4	0.5
	Eosinophils	1	0.1
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		12.9
969	Nucleated Red Cells	0	
	M. Neutrophils	21	3.8
	I. Neutrophils	1	0.2
	Lymphocytes	75	13.4
	Monocytes	3	0.5
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.9
970	Nucleated Red Cells	0	
	M. Neutrophils	25	3.5
	I. Neutrophils	1	0.1
	Lymphocytes	71	9.9
	Monocytes	1	0.1
	Eosinophils	2	0.3
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		13.9

NRBC Corrected After-10

WHITE DIFFERENTIAL COUNTS

STUDY ID: 112

GROUP: 2-F : 2.0 mg/kg/day SEX: FEMALE

ANIMAL ID		DAY 14 REL	DAY 14 ABS
976	Nucleated Red Cells	1	
	M. Neutrophils	16	2.1
	I. Neutrophils	1	0.1
	Lymphocytes	79	10.2
	Monocytes	4	0.5
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		12.9
977	Nucleated Red Cells	0	
	M. Neutrophils	23	3.5
	I. Neutrophils	2	0.3
	Lymphocytes	70	10.8
	Monocytes	4	0.6
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		15.4
978	Nucleated Red Cells	0	
	M. Neutrophils	22	4.0
	I. Neutrophils	4	0.7
	Lymphocytes	73	13.2
	Monocytes	0	0.0
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		18.1
979	Nucleated Red Cells	0	
	M. Neutrophils	13	1.4
	I. Neutrophils	0	0.0
	Lymphocytes	83	9.1
	Monocytes	4	0.4
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		11.0
980	Nucleated Red Cells	4	
	M. Neutrophils	9	1.1
	I. Neutrophils	3	0.4
	Lymphocytes	82	10.0
	Monocytes	6	0.7
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		12.2

NRBC Corrected After-10

TWO WEEK ORAL RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

WHITE DIFFERENTIAL COUNTS

STUDY ID: 112

GROUP: 3-F : 6.0 mg/kg/day (Day 0-6)/30.0 mg/kg/day (Day 7-13) SEX: FEMALE

ANIMAL ID		DAY 14 REL	DAY 14 ABS
986	Nucleated Red Cells	6	
	M. Neutrophils	14	2.2
	I. Neutrophils	6	0.9
	Lymphocytes	76	12.0
	Monocytes	3	0.5
	Eosinophils	1	0.2
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		15.8
987	Nucleated Red Cells	2	
	M. Neutrophils	16	1.7
	I. Neutrophils	6	0.6
	Lymphocytes	75	8.1
	Monocytes	3	0.3
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		10.8
988	Nucleated Red Cells	4	
	M. Neutrophils	17	2.3
	I. Neutrophils	3	0.4
	Lymphocytes	78	10.5
	Monocytes	2	0.3
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		13.5
989	Nucleated Red Cells	10	
	M. Neutrophils	11	1.5
	I. Neutrophils	3	0.4
	Lymphocytes	76	10.0
	Monocytes	9	1.2
	Eosinophils	1	0.1
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		13.2
990	Nucleated Red Cells	19	
	M. Neutrophils	21	3.6
	I. Neutrophils	2	0.3
	Lymphocytes	74	12.8
	Monocytes	3	0.5
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.3

NRBC Corrected After-10

WHITE DIFFERENTIAL COUNTS

STUDY IO: 112

GROUP: 4-F : 18.0 mg/kg day

SEX: FEMALE

ANIMAL IO		DAY 14 REL	DAY 14 ABS
996	Nucleated Red Cells	1	
	M. Neutrophils	8	1.4
	I. Neutrophils	7	1.3
	Lymphocytes	83	14.9
	Monocytes	2	0.4
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		17.9
997	Nucleated Red Cells	2	
	M. Neutrophils	8	0.9
	I. Neutrophils	2	0.2
	Lymphocytes	84	9.5
	Monocytes	6	0.7
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		11.3
998	Nucleated Red Cells	2	
	M. Neutrophils	15	1.7
	I. Neutrophils	3	0.3
	Lymphocytes	77	8.5
	Monocytes	5	0.6
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		11.1
999	Nucleated Red Cells	9	
	M. Neutrophils	22	2.7
	I. Neutrophils	0	0.0
	Lymphocytes	77	9.4
	Monocytes	1	0.1
	Eosinophils	0	0.0
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		12.2
1000	Nucleated Red Cells	3	
	M. Neutrophils	11	1.2
	I. Neutrophils	5	0.6
	Lymphocytes	79	8.8
	Monocytes	4	0.4
	Eosinophils	1	0.1
	Basophils	0	0.0
	Atypical Lymphocytes	0	0.0
	WBC		11.1

NRBC Corrected After-10

TWO WEEK ORAL RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

MORPHOLOGY OBSERVATIONS

STUDY ID: 112 SEX: MALE

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

ANIMAL ID	DAY 14
961	Anisocytosis,Slight
962	Anisocytosis,Slight
963	Anisocytosis,Slight
964	Anisocytosis,Slight; Poikilocytes,Slight
965	Anisocytosis,Slight

MORPHOLOGY OBSERVATIONS

STUDY ID: 112 SEX: MALE

GROUP: 2-M : 2.0 mg/kg/day

ANIMAL ID	DAY 14
971	Anisocytosis,Slight
972	Anisocytosis,Slight
973	Normal Red Blood Cells
974	Anisocytosis,Slight; Poikilocytes,Slight
975	Anisocytosis,Slight

MORPHOLOGY OBSERVATIONS

STUDY ID: 112 SEX: MALE

GROUP: 3-M : 6.0 mg/kg/day (Day 0 - 6)/30.0 mg/kg/day (Day 7-13)

ANIMAL ID	DAY 14
981	Crenation,Moderate; Polychromasia,Slight Poikilocytes, Moderate;Target Cells,Slight; Anisocytosis, Moderate
982	Polychromasia,Slight Poikilocytes,Slight; Anisocytosis, Moderate
983	Polychromasia,Slight Poikilocytes, Moderate; Anisocytosis, Moderate
984	Clumped Platelets, Slight;Polychromasia Slight;Poikilocytes, Moderate; Anisocytosis,Mod. to Marked
985	Clumped Platelets, Marked;Polychromasia Slight;Poikilocytes, Moderate;Target Cells,Slight; Anisocytosis,Mod. to Marked

TWO WEEK ORAL RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

MORPHOLOGY OBSERVATIONS

STUDY ID: 112 SEX: MALE

GROUP: 4-M : 18.0 mg/kg/day

ANIMAL ID	DAY 14
991	Target Cells,Slight; Anisocytosis,Slight
992	Polychromasia,Slight Poikilocytes,Slight; Anisocytosis, Moderate
993	Poikilocytes,Slight; Anisocytosis, Moderate
994	Polychromasia,Slight Poikilocytes,Slight; Anisocytosis, Moderate
995	Polychromasia,Slight Anisocytosis,Slight

TWO WEEK ORAL RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

MORPHOLOGY OBSERVATIONS

STUDY ID: 112 SEX: FEMALE

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

ANIMAL ID	DAY 14
966	Anisocytosis,Slight
967	Anisocytosis,Slight; Poikilocytes,Slight
968	Anisocytosis,Slight; Poikilocytes,Slight
969	Normal Red Blood Cells
970	Anisocytosis,Slight

MORPHOLOGY OBSERVATIONS

STUDY ID: 112 SEX: FEMALE

GROUP: 2-F : 2.0 mg/kg/day

ANIMAL ID	DAY 14
976	Anisocytosis, Moderate; Polychromasia,Slight
977	Anisocytosis,Slight
978	Anisocytosis,Slight; Polychromasia,Slight
979	Anisocytosis,Slight; Polychromasia,Slight Poikilocytes,Slight
980	Polychromasia, Moderate; Poikilocytes,Slight; Anisocytosis,Mod. to Marked

TWO WEEK ORAL RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

MORPHOLOGY OBSERVATIONS

STUDY ID: 112 SEX: FEMALE

GROUP: 3-F : 6.0 mg/kg/day (Day 0-6)/30.0 mg/kg/day (Day 7-13)

ANIMAL ID	DAY 14
986	Clumped Platelets, Mod. to Marked; Crenation,Moderate; Polychromasia,Slight Poikilocytes, Moderate; Anisocytosis,Mod. to Marked
987	Clumped Platelets, Slight;Polychromasia Slight;Poikilocytes, Moderate; Anisocytosis,Mod. to Marked
988	Clumped Platelets, Moderate; Polychromasia, Moderate; Poikilocytes, Moderate; Anisocytosis,Mod. to Marked
989	Increased Platelets, Moderate; Polychromasia, Moderate; Poikilocytes, Moderate; Anisocytosis,Mod. to Marked;Howell-Jolly Bodies,Mod. to Marked
990	Increased Platelets, Moderate; Polychromasia, Moderate; Poikilocytes, Moderate; Anisocytosis,Mod. to Marked;Howell-Jolly Bodies,Moderate

MORPHOLOGY OBSERVATIONS

STUDY ID: 112 SEX: FEMALE

GROUP: 4-F : 18.0 mg/kg day

ANIMAL ID	DAY 14
996	Polychromasia,Slight Poikilocytes,Slight; Anisocytosis, Moderate
997	Howell-Jolly Bodies, Moderate; Polychromasia,Slight Poikilocytes,Slight; Anisocytosis,Slight
998	Polychromasia,Slight Anisocytosis, Moderate
999	Polychromasia,Slight Poikilocytes,Slight; Anisocytosis, Moderate
1000	Poikilocytes,Slight; Anisocytosis, Moderate

APPENDIX 8

Individual Organ Weights

INDIVIDUAL ORGAN WEIGHTS

STUDY: 112
SEX: MALE

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

ANIMAL ID: / BALANCE NO.:	961	962	963	964	965
BODY WEIGHT (G)	319.5	303.9	307.9	304.6	299.4
BRAIN (G)	2.018	2.008	2.003	1.908	2.000
% BODY WEIGHT	0.632	0.661	0.651	0.626	0.668
HEART (G)	1.254	1.254	1.081	1.107	1.060
% BODY WEIGHT	0.392	0.413	0.351	0.363	0.354
KIDNEYS (G)	3.113	3.003	3.082	2.982	3.024
% BODY WEIGHT	0.974	0.988	1.001	0.979	1.010
LIVER (G)	13.953	11.403	12.461	12.884	11.788
% BODY WEIGHT	4.367	3.752	4.047	4.230	3.937
SPLEEN (G)	0.542	0.614	0.694	0.634	0.588
% BODY WEIGHT	0.170	0.202	0.225	0.208	0.196
TESTES (G)	3.611	3.704	3.911	3.737	3.954
% BODY WEIGHT	1.130	1.219	1.270	1.227	1.321

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 112
SEX: MALE

GROUP: 2-M - 2.0 mg/kg
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	971	972	973	974	975
BODY WEIGHT (G)	291.9	273.9	295.6	311.1	293.4
BRAIN (G)	1.937	1.826	1.821	1.871	1.952
% BODY WEIGHT	0.664	0.667	0.616	0.601	0.665
HEART (G)	1.105	1.058	1.145	1.222	1.132
% BODY WEIGHT	0.379	0.386	0.387	0.393	0.386
KIDNEYS (G)	3.108	2.785	2.676	3.511	2.616
% BODY WEIGHT	1.065	1.017	0.905	1.129	0.892
LIVER (G)	12.604	10.516	11.436	14.024	11.552
% BODY WEIGHT	4.318	3.839	3.869	4.508	3.937
SPLEEN (G)	0.737	0.513	0.619	0.568	0.590
% BODY WEIGHT	0.252	0.187	0.209	0.183	0.201
TESTES (G)	3.898	4.029	4.001	3.704	3.497
% BODY WEIGHT	1.335	1.471	1.354	1.191	1.192

INDIVIDUAL ORGAN WEIGHTS

STUDY: 112
SEX: MALE

GROUP: 3-M - 6.0 mg/kg (Days 0 - 6)/30.0 mg/kg (Days 7 - 13)
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	981	982	983	984	985
BODY WEIGHT (G)	284.3	284.4	286.8	293.6	296.2
BRAIN (G)	1.865	1.874	1.903	1.983	1.959
% BODY WEIGHT	0.656	0.659	0.664	0.675	0.661
HEART (G)	1.094	1.096	1.135	1.196	1.152
% BODY WEIGHT	0.385	0.385	0.396	0.407	0.389
KIDNEYS (G)	2.594	2.530	2.772	2.483	2.887
% BODY WEIGHT	0.912	0.890	0.967	0.846	0.975
LIVER (G)	10.603	11.034	10.858	10.618	12.305
% BODY WEIGHT	3.730	3.880	3.786	3.616	4.154
SPLEEN (G)	1.578	1.811	1.416	1.460	1.560
% BODY WEIGHT	0.555	0.637	0.494	0.497	0.527
TESTES (G)	3.472	4.068	3.806	4.149	3.775
% BODY WEIGHT	1.221	1.430	1.327	1.413	1.274

INDIVIDUAL ORGAN WEIGHTS

STUDY: 112
SEX: MALE

GROUP: 4-M - 18.0 mg/kg
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	991	992	993	994	995
BODY WEIGHT (G)	332.7	255.6	297.5	270.0	269.5
BRAIN (G)	2.084	1.938	1.899	1.934	1.930
% BODY WEIGHT	0.626	0.758	0.638	0.716	0.716
HEART (G)	1.327	1.023	1.323	1.090	1.013
% BODY WEIGHT	0.399	0.400	0.445	0.404	0.376
KIDNEYS (G)	3.304	2.019	2.817	2.178	2.502
% BODY WEIGHT	0.993	0.790	0.947	0.807	0.928
LIVER (G)	13.938	9.466	12.904	9.512	9.229
% BODY WEIGHT	4.189	3.703	4.337	3.523	3.424
SPLEEN (G)	1.730	0.950	1.360	0.904	0.946
% BODY WEIGHT	0.520	0.372	0.457	0.335	0.351
TESTES (G)	4.053	3.440	3.408	4.078	3.996
% BODY WEIGHT	1.218	1.346	1.146	1.510	1.483

INDIVIDUAL ORGAN WEIGHTS

STUDY: 112
SEX: FEMALE

GROUP: 1-f - 0 mg/kg
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	966	967	968	969	970
BODY WEIGHT (G)	206.3	189.1	218.3	200.6	212.0
BRAIN (G)	1.987	1.729	1.926	1.754	1.879
% BODY WEIGHT	0.963	0.914	0.882	0.874	0.886
HEART (G)	0.940	0.931	0.883	0.853	0.953
% BODY WEIGHT	0.456	0.492	0.404	0.425	0.450
KIDNEYS (G)	2.108	2.008	2.529	1.872	1.735
% BODY WEIGHT	1.022	1.062	1.158	0.933	0.818
LIVER (G)	10.658	8.241	9.277	8.984	8.471
% BODY WEIGHT	5.166	4.358	4.250	4.479	3.996
OVARY (G)	0.114	0.174	0.127	0.162	0.087
% BODY WEIGHT	0.055	0.092	0.058	0.081	0.041
SPLEEN (G)	0.608	0.448	0.594	0.595	0.738
% BODY WEIGHT	0.295	0.237	0.272	0.297	0.348

TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS

INDIVIDUAL ORGAN WEIGHTS

STUDY: 112
SEX: FEMALE

GROUP: 2-f - 2.0 mg/kg
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	976	977	978	979	980
BODY WEIGHT (G)	223.3	208.8	201.7	212.7	207.0
BRAIN (G)	1.798	1.891	1.980	1.939	1.857
% BODY WEIGHT	0.805	0.906	0.982	0.912	0.897
HEART (G)	0.918	0.865	0.864	1.024	1.005
% BODY WEIGHT	0.411	0.414	0.428	0.481	0.486
KIDNEYS (G)	2.086	2.219	2.064	1.955	1.831
% BODY WEIGHT	0.934	1.063	1.023	0.919	0.885
LIVER (G)	9.657	9.378	8.201	8.816	9.035
% BODY WEIGHT	4.325	4.491	4.066	4.145	4.365
OVARY (G)	0.094	0.151	0.105	0.134	0.078
% BODY WEIGHT	0.042	0.072	0.052	0.063	0.038
SPLEEN (G)	0.787	0.605	1.102	0.929	1.152
% BODY WEIGHT	0.352	0.290	0.546	0.437	0.557

INDIVIDUAL ORGAN WEIGHTS

STUDY: 112
SEX: FEMALE

GROUP: 3-F - 6.0 mg/kg (Days 0 - 6)/30.0 mg/kg (Days 7 - 13)
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	986	987	988	989	990
BODY WEIGHT (G)	210.5	196.1	191.4	197.3	214.4
BRAIN (G)	1.961	1.866	1.827	1.749	1.866
% BODY WEIGHT	0.932	0.952	0.955	0.886	0.870
HEART (G)	1.309	0.993	0.933	0.972	1.620
% BODY WEIGHT	0.622	0.506	0.487	0.493	0.756
KIDNEYS (G)	2.010	1.959	1.765	1.856	1.979
% BODY WEIGHT	0.955	0.999	0.922	0.941	0.923
LIVER (G)	9.328	8.924	7.099	8.736	9.871
% BODY WEIGHT	4.431	4.551	3.709	4.428	4.604
OVARY (G)	0.121	0.144	0.098	0.143	0.108
% BODY WEIGHT	0.057	0.073	0.051	0.072	0.050
SPLEEN (G)	2.394	1.781	1.782	1.727	2.129
% BODY WEIGHT	1.137	0.908	0.931	0.875	0.993

INDIVIDUAL ORGAN WEIGHTS

STUDY: 112
SEX: FEMALE

GROUP: 4-F - 18.0 mg/kg
ALL FATES ALL DAYS ALL BALANCES

ANIMAL ID: / BALANCE NO.:	996	997	998	999	1000
BODY WEIGHT (G)	207.8	187.6	200.4	213.7	199.6
BRAIN (G)	1.782	1.868	1.888	1.916	1.811
% BODY WEIGHT	0.858	0.996	0.942	0.897	0.907
HEART (G)	0.910	0.912	1.042	1.077	0.912
% BODY WEIGHT	0.438	0.486	0.520	0.504	0.457
KIDNEYS (G)	2.064	2.054	1.952	2.061	1.924
% BODY WEIGHT	0.993	1.095	0.974	0.964	0.964
LIVER (G)	9.977	8.302	8.780	8.792	8.553
% BODY WEIGHT	4.801	4.425	4.381	4.114	4.285
OVARY (G)	0.123	0.084	0.118	0.136	0.094
% BODY WEIGHT	0.059	0.045	0.059	0.064	0.047
SPLEEN (G)	1.510	1.021	1.398	1.846	1.551
% BODY WEIGHT	0.727	0.544	0.698	0.864	0.777

APPENDIX 9

Pathology Report

FINAL PATHOLOGY REPORT FOR TRL STUDY NUMBER 112 TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR269410 IN RATS

PREPARED
BY
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CHICAGO, IL 60680

MARCH 10, 1994

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SECTION I

PATHOLOGY NARRATIVE

FINAL PATHOLOGY REPORT

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR269410 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 WR269410 in Rats," TRL Study Number 112.

EXPERIMENTAL DESIGN AND METHODS

Three groups, each composed of 5 male and 5 female Virus Antibody Free CD® rats, were given WR269410 by gavage once daily for 14 days. Dose levels in group 2 (2.0 mg/kg/day) and group 4 (18.0 mg/kg/day) were constant for the 14 day dosing period. Group 3 was given 6.0 mg/kg/day of WR269410 for the first week. As no signs of toxicity were observed after one week of treatment, in compliance with the protocol, the dosage was escalated to 30.0 mg/kg/day for the second week of dosing. 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. All 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 scores were 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.

Spleen

Extramedullary hematopoiesis (EMH) in the spleen consisted of increased amounts of hematopoietic cells in the red pulp of the spleen.

Liver

Foci of necrosis in the liver were large and distinct with defined margins. Affected hepatocytes had undergone coagulative necrosis and were being removed by infiltrating macrophages and neutrophils.

Histopathology Findings

Spleen

Extramedullary hematopoiesis (EMH) in the spleen was diagnosed in 0 out of 5, 5 out of 5, and 5 out of 5 males and in 4 out of 5, 5 out of 5, and 5 out of 5 females in groups 2, 3, and 4, respectively. Mean group severity scores for this change were 0.00, 1.60, and 1.80 in males, and 1.00, 2.60, and 2.00 in females in groups 2, 3, and 4, respectively. Extramedullary hematopoiesis did not occur in the control (group 1) males or females. Both incidence and mean group severity scores for this change were considered consistent with a dose-related response, inasmuch as group 3 was escalated from 6.0 to 30.0 mg/kg/day during the second week of dosing. The occurrence of EMH in the spleen of these rats suggests that there was a demand for increased blood cells. 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, and suggests that the EMH may have occurred in response to anemia. For these reasons, EMH in the spleen was interpreted as most likely secondary to increased erythrocyte destruction that may or may not have caused clinical anemia.

Liver

Focal necrosis in the liver occurred in 1 out of 5 group 4 males and in 1 out of 5, 3 out of 5, 0 out of 5, and 1 out of 5 females in groups 1 (control), 2, 3, and 4, respectively. Severity scores were minimal in all affected animals, regardless of treatment group, as the necrosis occurred as a single focus in all affected animals. As it occurred as a single focus in each affected animal, did not occur in a dose-related incidence, and is a recognized spontaneous lesion in animals, focal necrosis in the liver was interpreted as not related to the test article.

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 WR269410 to rats by gavage for 14 days was associated with EMH in the spleen.

The incidence and/or mean group severity scores for this change were generally dose-related in both sexes. The occurrence of splenic EMH was thought to most likely be secondary to increased erythrocyte destruction. There were no changes identified that were considered direct toxic effects of the test article.

Michael J. Tomlinson

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

March 10, 1994
Date

TABLE I

SUMMARY OF EXPERIMENTAL DESIGN

Treatment Group	Treatment	Dose Level (mg/kg/day)	Number of Males	Number of Females
1	Vehicle Control*	0	5	5
2	WR269410	2.0	5	5
3	WR269410	6.0/30.0**	5	5
4	WR269410	18.0	5	5

* Vehicle was 1% methylcellulose/0.2% Tween 80.
** Dose was 6.0 mg/kg/day for the first week of dosing and 30.0 mg/kg/day for the second week of dosing.

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.

PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

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

Infiltr - Infiltrate

SECTION II

PROJECT SUMMARY TABLE

PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

Project Summary Table

SUMMARY: Incidence of NEOPLASTIC and NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: TRL112 FATES: Terminal Sacrifice
DAYS : 14 SEX: MALE

GROUP:		Group 1		Group 2		Group 3		Group 4	
NUMBER OF ANIMALS:		5		5		5		5	
		#	%	#	%	#	%	#	%
BRAIN	# Ex	5		5		5		5	
LIVER	# Ex	5		5		5		5	
Focal necrosis		0	(0)	0	(0)	0	(0)	1	(20)
Periportal, infiltr, cellular		1	(20)	0	(0)	1	(20)	0	(0)
SPLEEN	# Ex	5		5		5		5	
Extramedullary hematopoiesis		0	(0)	0	(0)	5	(100)	5	(100)
KIDNEY	# Ex	5		5		5		5	
Cortex, cyst		1	(20)	0	(0)	0	(0)	0	(0)
Infiltrate, cellular		0	(0)	2	(40)	0	(0)	0	(0)
Pelvis, dilatation		1	(20)	0	(0)	0	(0)	0	(0)
HEART	# Ex	5		5		5		5	
TESTIS	# Ex	5		5		5		5	
EPIDIDYMIS	# Ex	5		5		5		5	

25-Aug-1993

PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

Project Summary Table

SUMMARY: Incidence of NEOPLASTIC and NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: TRL112 FATES: Terminal Sacrifice
DAYS : 14 SEX: FEMALE

GROUP:		Group 1		Group 2		Group 3		Group 4	
NUMBER OF ANIMALS:		5		5		5		5	
		#	%	#	%	#	%	#	%
BRAIN	# Ex	5		5		5		5	
LIVER	# Ex	5		5		5		5	
Focal necrosis		1	(20)	3	(60)	0	(0)	1	(20)
Multinucleated hepatocyte		0	(0)	0	(0)	1	(20)	0	(0)
SPLEEN	# Ex	5		5		5		5	
Extramedullary hematopoiesis		0	(0)	4	(80)	5	(100)	5	(100)
KIDNEY	# Ex	5		5		5		5	
Cortex, infarct		0	(0)	0	(0)	2	(40)	0	(0)
Nephrocalcinosis		3	(60)	4	(80)	3	(60)	3	(60)
HEART	# Ex	5		5		5		5	
OVARY	# Ex	5		5		5		5	

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SECTION III

SEVERITY SUMMARY TABLE

PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

Severity Summary Table

PROJECT ID. NO: TRL112 FATES: Terminal Sacrifice
DAYS: 14 SEX: MALE

GROUP:		Group 1		Group 2		Group 3		Group 4	
NUMBER OF ANIMALS:		5		5		5		5	
		#	SEV	#	SEV	#	SEV	#	SEV
BRAIN	# Ex	5		5		5		5	
LIVER	# Ex	5		5		5		5	
Focal necrosis		0		0		0		1	0.20
Periportal, infiltr, cellular		1	0.20	0		1	0.20	0	
SPLEEN	# Ex	5		5		5		5	
Extramedullary hematopoiesis		0		0		5	1.60	5	1.80
KIDNEY	# Ex	5		5		5		5	
Infiltrate, cellular		0		2	0.40	0		0	
Pelvis, dilatation		1	0.40	0		0		0	
HEART	# Ex	5		5		5		5	
TESTIS	# Ex	5		5		5		5	
EPIDIDYMIS	# Ex	5		5		5		5	

* Severity calculated by the number of tissues examined.

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PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

Severity Summary Table

PROJECT ID. NO: TRL112 FATES: Terminal Sacrifice
DAYS: 14 SEX: FEMALE

GROUP:		Group 1		Group 2		Group 3		Group 4	
NUMBER OF ANIMALS:		5		5		5		5	
		#	SEV	#	SEV	#	SEV	#	SEV
BRAIN	# Ex	5		5		5		5	
LIVER	# Ex	5		5		5		5	
Focal necrosis		1	0.20	3	0.60	0		1	0.20
Multinucleated hepatocyte		0		0		1	0.20	0	
SPLEEN	# Ex	5		5		5		5	
Extramedullary hematopoiesis		0		4	1.00	5	2.60	5	2.00
KIDNEY	# Ex	5		5		5		5	
Cortex, infarct		0		0		2	0.40	0	
Nephrocalcinosis		3	0.60	4	0.80	3	0.60	3	0.80
HEART	# Ex	5		5		5		5	
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

PROJECT ID: TRL112 GROUP: Group 1 SEX: MALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID:	0961	0962	0963	0964	0965
BRAIN	N	N	N	N	N
LIVER	N	N	N	N	
Periportal, infiltr, cellular	-	-	-	-	1
SPLEEN	N	N	N	N	N
KIDNEY	N	N	N	N	
Cortex, cyst	-	-	-	-	P
Pelvis, dilatation	-	-	-	-	2
HEART	N	N	N	N	N
TESTIS	N	N	N	N	N
EPIDIDYMIS	N	N	N	N	N

Tabulated Animal Data

PROJECT ID: TRL112 GROUP: Group 2 SEX: MALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID:	0971	0972	0973	0974	0975
BRAIN	N	N	N	N	N
LIVER	N	N	N	N	N
SPLEEN	N	N	N	N	N
KIDNEY	N	N			N
Infiltrate, cellular	-	-	1	1	-
HEART	N	N	N	N	N
TESTIS	N	N	N	N	N
EPIDIDYMIS	N	N	N	N	N

Tabulated Animal Data

PROJECT ID: TRL112 GROUP: Group 3 SEX: MALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID:	0981	0982	0983	0984	0985
BRAIN	N	N	N	N	N
LIVER	N		N	N	N
Periportal, infiltr, cellular	-	1	-	-	-
SPLEEN					
Extramedullary hematopoiesis	1	2	2	1	2
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

PROJECT ID: TRL112 GROUP: Group 4 SEX: MALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID:	0991	0992	0993	0994	0995
BRAIN	N	N	N	N	N
LIVER	N	N		N	N
Focal necrosis	-	-	1	-	-
SPLEEN					
Extramedullary hematopoiesis	2	1	2	2	2
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

PROJECT ID: TRL112 GROUP: Group 1 SEX: FEMALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID:	0966	0967	0968	0969	0970
BRAIN	N	N	N	N	N
LIVER		N	N	N	N
Focal necrosis	1	-	-	-	-
SPLEEN	N	N	N	N	N
KIDNEY	N			N	
Nephrocalcinosis	-	1	1	-	1
HEART	N	N	N	N	N
OVARY	N	N	N	N	N

Tabulated Animal Data

PROJECT ID: TRL112 GROUP: Group 2 SEX: FEMALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID:	0976	0977	0978	0979	0980
BRAIN	N	N	N	N	N
LIVER		N		N	
Focal necrosis	1	-	1	-	1
SPLEEN		N			
Extramedullary hematopoiesis	1	-	2	1	1
KIDNEY		N			
Nephrocalcinosis	1	-	1	1	1
HEART	N	N	N	N	N
OVARY	N	N	N	N	N

Tabulated Animal Data

PROJECT ID: TRL112 GROUP: Group 3 SEX: FEMALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID:	0986	0987	0988	0989	0990
BRAIN	N	N	N	N	N
LIVER	N	N	N	N	
Multinucleated hepatocyte	-	-	-	-	1
SPLEEN					
Extramedullary hematopoiesis	3	2	2	3	3
KIDNEY			N		N
Cortex, infarct	-	1	-	1	-
Nephrocalcinosis	1	1	-	1	-
HEART	N	N	N	N	N
OVARY	N	N	N	N	N

Tabulated Animal Data

PROJECT ID: TRL112 GROUP: Group 4 SEX: FEMALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID:	0996	0997	0998	0999	1000
BRAIN	N	N	N	N	N
LIVER	N	N		N	N
Focal necrosis	-	-	1	-	-
SPLEEN					
Extramedullary hematopoiesis	2	1	3	2	2
KIDNEY		N			N
Nephrocalcinosis	2	-	1	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 WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

Correlation of Gross & Micro Findings

PROJECT ID: TRL112 GROUP: Group 1 SEX: MALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID: 0961 PATHOLOGY ID. NO: TI112-0961 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 0962 PATHOLOGY ID. NO: TI112-0962 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 0963 PATHOLOGY ID. NO: TI112-0963 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 0964 PATHOLOGY ID. NO: TI112-0964 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 WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

Correlation of Gross & Micro Findings

PROJECT ID: TRL112 GROUP: Group 1 SEX: MALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID: 0965 PATHOLOGY ID. NO: TI112-0965 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice

DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>URINARY BLADDER, LUMEN - CALCULUS, SINGLE, IRREGULAR, WHITE, HARD, 6X3 MM	Not required by protocol

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PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

Correlation of Gross & Micro Findings

PROJECT ID: TRL112 GROUP: Group 2 SEX: MALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID: 0971 PATHOLOGY ID. NO: TI112-0971 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 0972 PATHOLOGY ID. NO: TI112-0972 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 0973 PATHOLOGY ID. NO: TI112-0973 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 0974 PATHOLOGY ID. NO: TI112-0974 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

>SKIN, NECK, VENTRAL - CRUST, SINGLE, IRREGULAR, RED, GRITTY, 20X8 MM — Not required by protocol

>SKIN, HEAD, DORSAL - CRUST, SINGLE, OVAL, RED, GRITTY, 20X10 MM — Not required by protocol

PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

Correlation of Gross & Micro Findings

PROJECT ID: TRL112 GROUP: Group 2 SEX: MALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID: 0975 PATHOLOGY ID. NO: TI112-0975 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>URINARY BLADDER, LUMEN - CALCULUS, SINGLE, IRREGULAR, WHITE, HARD, 5X3 MM	Not required by protocol

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Correlation of Gross & Micro Findings

ANIMAL ID: 0981 PATHOLOGY ID. NO: TI112-0981 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 0982 PATHOLOGY ID. NO: TI112-0982 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 0983 PATHOLOGY ID. NO: TI112-0983 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 0984 PATHOLOGY ID. NO: TI112-0984 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 WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

Correlation of Gross & Micro Findings

PROJECT ID: TRL112 GROUP: Group 3 SEX: MALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID: 0985 PATHOLOGY ID. NO: TI112-0985 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

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TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

Correlation of Gross & Micro Findings

PROJECT ID: TRL112 GROUP: Group 4 SEX: MALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID: 0991 PATHOLOGY ID. NO: TI112-0991 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 0992 PATHOLOGY ID. NO: TI112-0992 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 0993 PATHOLOGY ID. NO: TI112-0993 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 0994 PATHOLOGY ID. NO: TI112-0994 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 WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

Correlation of Gross & Micro Findings

PROJECT ID: TRL112 GROUP: Group 4 SEX: MALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID: 0995 PATHOLOGY ID. NO: TI112-0995 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 WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

Correlation of Gross & Micro Findings

PROJECT ID: TRL112 GROUP: Group 1 SEX: FEMALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID: 0966 PATHOLOGY ID. NO: TI112-0966 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 0967 PATHOLOGY ID. NO: TI112-0967 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 0968 PATHOLOGY ID. NO: TI112-0968 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 0969 PATHOLOGY ID. NO: TI112-0969 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

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TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

Correlation of Gross & Micro Findings

PROJECT ID: TRL112 GROUP: Group 1 SEX: FEMALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID: 0970 PATHOLOGY ID. NO: TI112-0970 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

ANIMAL ID: 0976 PATHOLOGY ID. NO: TI112-0976 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 0977 PATHOLOGY ID. NO: TI112-0977 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 0978 PATHOLOGY ID. NO: TI112-0978 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 0979 PATHOLOGY ID. NO: TI112-0979 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 WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

Correlation of Gross & Micro Findings

PROJECT ID: TRL112 GROUP: Group 2 SEX: FEMALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID: 0980 PATHOLOGY ID. NO: TI112-0980 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 WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

Correlation of Gross & Micro Findings

ANIMAL ID: 0986 PATHOLOGY ID. NO: TI112-0986 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>SPLEEN - ENLARGED, 50X15X11MM	SPLEEN- Extramedullary hematopoiesis

ANIMAL ID: 0987 PATHOLOGY ID. NO: TI112-0987 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>SPLEEN - ENLARGED, 45X15X10 MM	SPLEEN- Extramedullary hematopoiesis

ANIMAL ID: 0988 PATHOLOGY ID. NO: TI112-0988 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>SPLEEN - ENLARGED, 50X12X10 MM	SPLEEN- Extramedullary hematopoiesis

PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

Correlation of Gross & Micro Findings

PROJECT ID: TRL112 GROUP: Group 3 SEX: FEMALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID: 0989 PATHOLOGY ID. NO: TI112-0989 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>SPLEEN - ENLARGED	SPLEEN- Extramedullary hematopoiesis

ANIMAL ID: 0990 PATHOLOGY ID. NO: TI112-0990 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>SPLEEN - ENLARGED, 54X13X11 MM	SPLEEN- Extramedullary hematopoiesis

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PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

Correlation of Gross & Micro Findings

PROJECT ID: TRL112 GROUP: Group 4 SEX: FEMALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID: 0996 PATHOLOGY ID. NO: TI112-0996 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>SPLEEN - ENLARGED, 55X13X10 MM	SPLEEN- Extramedullary hematopoiesis

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ANIMAL ID: 0997 PATHOLOGY ID. NO: TI112-0997 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:

ANIMAL ID: 0998 PATHOLOGY ID. NO: TI112-0998 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:

ANIMAL ID: 0999 PATHOLOGY ID. NO: TI112-0999 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice
DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>SPLEEN - ENLARGED, 50X11X10 MM	SPLEEN- Extramedullary hematopoiesis

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PATHOLOGY ASSOCIATES, INC.
TWO WEEK ORAL DOSE RANGE-FINDING
TOXICITY STUDY OF WR269410 IN RATS
TOXICOLOGY RESEARCH LABORATORY, STUDY NUMBER 112

Correlation of Gross & Micro Findings

PROJECT ID: TRL112 GROUP: Group 4 SEX: FEMALE
DAYS: 14 FATES: Terminal Sacrifice

ANIMAL ID: 1000 PATHOLOGY ID. NO: TI112-1000 PATHOLOGIST: MJT
ANIMAL FATE: Terminal Sacrifice

DAYS ON TEST:14

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>SPLEEN - ENLARGED, 52X10X5 MM	SPLEEN- Extramedullary hematopoiesis

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SECTION VI

QUALITY ASSURANCE STATEMENT

QUALITY ASSURANCE STATEMENT

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
**	08/19/93	Individual Animal Data	08/20/93
**	08/19/93	Data Entry	08/20/93
**	08/19/93	Computer Validation	08/20/93
**	08/20/93	Draft Pathology Report	08/20/93
**	03/10/94	Final Pathology Report	03/10/94

* 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

03/10/94
Date

APPENDIX 10

Protocol and Amendments

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-7D
UIC/TRL Study No.: 112

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR269410 IN RATS

1.0 PURPOSE OF THE STUDY:

The purpose of this study is to determine the toxicity of WR269410 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 WR269410 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:	06/25/93
4.3	Proposed Necropsy Dates:	07/09/93
4.4	Proposed Study Completion Date (Draft Study Report):	09/09/93

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5.0 TEST ARTICLES

5.1 Name or Code No: WR269410 (p-Aminoheptanophenone; PAHP) Bottle number will be identified in the raw data.

5.2 TRL Chemical No: 1620614

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

6.0 PERSONNEL:

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
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/kg/day)[a]	Number of Males	Number of Females
1	Vehicle Control	0	5	5
2	WR269410	2.0	5	5
3	WR269410	6.0	5	5
4	WR269410	18.0	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. Samples of dosage formulations (including controls) used in 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). The overnight fasted animals will be anesthetized by carbon

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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	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 gland	Spinal cord (thoracic)
Femur with marrow	*Spleen
Gross lesions	Stomach
*Heart	*Testes/Epididymides
Ileum	Thymus
Jejunum	Thyroid glands/Parathyroids
*Kidneys	Tongue
*Liver	Trachea
Lungs/Bronchi	Urinary bladder
Lymph node (mesenteric)	Uterus
*Ovaries	Vagina
Pancreas	

*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/carrier mixture(s) be returned? No

11.0 PROTOCOL APPROVAL:

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

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

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

COMMENTS FROM THE COR:

PROTOCOL AMENDMENT

Study No.: 112

Title: Two Week Oral Dose Range-Finding Toxicity Study of WR269410 in Rats

1. Page 1 Section 4.0

Change the study dates as follows:

4.2 Proposed Initiation of Dosing: 06/25/93

4.3 Proposed Necropsy Date: 07/09/93

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

Reason: Study dates have been finalized.

2. 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 from "Ian Tebbett, Ph.D." to "Adam Negrusz, Ph.D."

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

3. Page 3 Section 7.9

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

Reason: Mistake in protocol.

4. Page 4 Section 8.1

A. Change the dose levels to read as follows:

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

"Mid" = "6.0" mg base/kg/day

"High" = "18.0" mg base/kg/day

B. Change the footnote [a] to indicated that dose levels were selected by the Sponsor.

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

PROTOCOL AMENDMENT

Study No.: 112

Title: Two Week Oral Dose Range-Finding Toxicity Study of WR269410 in Rats

5. Page 5 Section 8.5

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

Reason: Better suspendability was achieved with this vehicle.

6. Page 5 Section 8.7.3

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

Reason: Mistake in protocol.

7. 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.

8. 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

APPENDIX 11

Study Deviations

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-7D
UIC/TRL Study No.: 112

TWO WEEK ORAL DOSE RANGE-FINDING TOXICITY STUDY OF WR269410 IN RATS

Study Deviations*

Deviation Type	Specific Deviation	Effect on Study

No deviations occurred during the study.

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

3/21/94
Date