

Toxicology Research Laboratory

UIC The University of Illinois
at Chicago

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

20100915247

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Title Page

Draft Report for Task Order No. UIC-9

Volume 1 of 2

DRAFT ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

Sponsor: US Army Medical Materiel
Development Activity

Test Article: WR238605 Succinate

Contract No.: DAMD17-92-C-2001

Study Director

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

In-Life Phase Completed On

July 18, 1997

Performing Laboratory

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

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other documentation.

DRAFTForm Approved
OMB No. 0704-0188**REPORT DOCUMENTATION PAGE**

1a. REPORT SECURITY CLASSIFICATION			1b. RESTRICTIVE MARKINGS			
2a. SECURITY CLASSIFICATION AUTHORITY Unclassified			3. DISTRIBUTION/AVAILABILITY OF REPORT			
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE			Unlimited			
4. PERFORMING ORGANIZATION REPORT NUMBER(S) UIC-9 (UIC/TRL Study No. 219)			5. MONITORING ORGANIZATION REPORT NUMBER(S)			
6a. NAME OF PERFORMING ORGANIZATION Toxicology Research Laboratory University of Illinois at Chicago		6b. OFFICE SYMBOL (If applicable)		7a. NAME OF MONITORING ORGANIZATION U.S. Army Medical Materiel Development Activity		
6c. ADDRESS (City, State, and ZIP Code) Department of Pharmacology (M/C 868) 1940 W. Taylor Street Chicago, IL 60612-7353			7b. ADDRESS (City, State, and ZIP Code) ATTN: MCMR-RMA-RD Fort Detrick Frederick, MD 21702-5014			
8a. NAME OF FUNDING/SPONSORING ORGANIZATION U.S. Army Medical Materiel Development Activity		8b. OFFICE SYMBOL (If applicable) MCMR-UMP		9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER DAMD17-92-C-2001		
8c. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, MD 21702-5009			10. SOURCE OF FUNDING NUMBERS			
		PROGRAM ELEMENT NO. 63807A	PROJECT NO. 30463807	TASK NO. QC	WORK UNIT ACCESSION NO. 073	
11. TITLE (Include Security Classification) One Year Oral Toxicity Study of WR238605 Succinate in Dogs						
12. PERSONAL AUTHOR(S) Levine, B.S., Brown, A.P., and Morrissey, R.L. (PAI)						
13a. TYPE OF REPORT Study		13b. TIME COVERED FROM 5/09/96 TO _____		14. DATE OF REPORT (Year, Month, Day)		15. PAGE COUNT
16. SUPPLEMENTARY NOTATION						
17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)			
FIELD	GROUP	SUB-GROUP	WR238605		Pneumotoxicity	
			Antimalarial		Dogs	
			Methemoglobinemia			
19. ABSTRACT (Continue on reverse if necessary and identify by block number) <p>The purpose of this study was to determine specific target organ toxicity, dose-reponse relationships, and a no observed adverse effect level of WR238605 succinate in Beagle dogs following one year of daily oral administration. WR238605 succinate is being developed as an antimalarial agent. Dose levels studied were 0, 0.1, 1.0 and 4.0 mg base/kg/day. The dogs were \approx 7 - 8 months old and weighed 9.9 - 13.1 kg (males) and 8.0 - 11.4 kg (females) at dosing initiation. The primary toxicities of WR238605 succinate following one year of oral administration were to the lungs and red blood cells. No mortalities occurred in the study. Body weight gains were decreased in the males in a dose-dependent fashion, but were unaffected in females. Clinical signs were primarily seen in the mid and high dose groups and included diarrhea, emesis and blue tongue. Increased respiratory rate was observed in one high dose male. Methemoglobinemia was produced throughout the study in the mid and high dose groups. Chronic, low level intravascular hemolysis occurred in the mid and high dose groups, as evidenced by the presence of tissue pigmentation changes in Kupffer cells, renal cortex epithelium and in macrophages in spleen, gall bladder, tonsil and lymph nodes (mesenteric, mandibular, bronchial and mediastinal). Furthermore, increased reticulocyte counts, Heinz bodies and serum haptoglobin levels were seen. Thrombocytopenia was seen in the high dose group in week 4, but resolved thereafter. Pulmonary lesions were observed in all animals in the mid and high dose groups, and consisted of foamy macrophage accumulation and chronic interstitial inflammation. Bone marrow hyperplasia occurred in the mid and high dose groups. Lung, liver and splenic weights were increased at the high dose level. Although subtle ECG changes were seen and appear to be treatment-related, they may not represent significant toxicologic effects. A no-effect level was considered to be at or near the low dose of 0.1 mg base/kg/day.</p>						
20. DISTRIBUTION/AVAILABILITY OF ABSTRACT <input type="checkbox"/> UNCLASSIFIED/UNLIMITED <input checked="" type="checkbox"/> SAME AS RPT. <input type="checkbox"/> DTIC USERS			21. ABSTRACT SECURITY CLASSIFICATION Unclassified			
22a. NAME OF RESPONSIBLE INDIVIDUAL Barty S. Levine			22b. TELEPHONE (Include Area Code) (312) 996-5543		22c. OFFICE SYMBOL N/A	

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STATEMENT OF COMPLIANCE

Study No. 219 entitled "One Year Oral Toxicity Study of WR238605 Succinate in Dogs" 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.

Signatures

Study Director

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

Date

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QUALITY ASSURANCE STATEMENT

STUDY TITLE: ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE
IN DOGS

STUDY NUMBER: 219

STUDY DIRECTOR: BARRY S. LEVINE

INITIATION DATE: 5/9/96

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

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

INSPECT ON 5/9/96, TO STUDY DIR 5/9/96, TO MGMT 5/9/96
PHASES: PROTOCOL REVIEW

INSPECT ON 6/27/96, TO STUDY DIR 6/27/96, TO MGMT 7/1/96
PHASES: ANIMAL RECEIPT, ANIMAL IDENTIFICATION, BODY WEIGHT AND
PHYSICAL EXAMINATION

INSPECT ON 10/9/96, TO STUDY DIR 10/9/96, TO MGMT 10/9/96
PHASES: OPHTHALMIC EXAMINATION

INSPECT ON 3/4/97, TO STUDY DIR 3/4/97, TO MGMT 3/24/97
PHASES: BODY WEIGHT, DOSING AND CLINICAL SIGNS

INSPECT ON 7/18/97, TO STUDY DIR 7/21/97, TO MGMT 7/24/97
PHASES: NECROPSY AND BLOOD GASES

INSPECT ON 9/25-29/97, TO STUDY DIR 9/30/97, TO MGMT 10/9/97
PHASES: RAW DATA

INSPECT ON 10/15-16/97, TO STUDY DIR 10/16/97, TO MGMT 10/29/97
PHASES: RAW DATA AND DRAFT REPORT FROM THE ANALYTICAL LAB

INSPECT ON 12/2-4/97, TO STUDY DIR 12/4/97, TO MGMT 12/11/97
PHASES: DRAFT REPORT



QUALITY ASSURANCE

12/12/97

DATE

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Signature Page

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

TRL Chemical No.: 0720614

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

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

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

Alan P. Brown, Ph.D.
Toxicologist

Date

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

Date

Study Initiation: May 9, 1996
Dosing Initiation: July 18, 1996
In-Life Completion: July 18, 1997

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1. SUMMARY

The purpose of this study was to determine specific target organ toxicity, dose-reponse relationships, and a no observed adverse effect level of WR238605 succinate in Beagle dogs following one year of daily oral administration. WR238605 succinate is being developed as an antimalarial agent. Dose levels studied were 0, 0.1, 1.0 and 4.0 mg base/kg/day. The primary toxicities of WR238605 succinate following one year of oral administration were to the lungs and red blood cells. No mortalities occurred in the study. Body weight gains were decreased in the males in a dose-dependent fashion, but were unaffected in females. Clinical signs were primarily seen in the mid and high dose groups and included diarrhea, emesis and blue tongue. Increased respiratory rate was observed in one high dose male. Methemoglobinemia was produced throughout the study in the mid and high dose groups. Chronic, low level intravascular hemolysis occurred in the mid and high dose groups, as evidenced by the presence of tissue pigmentation changes in Kupffer cells, renal cortex epithelium and in macrophages in spleen, gall bladder, tonsil and lymph nodes (mesenteric, mandibular, bronchial and mediastinal). Furthermore, increased reticuloctye counts, Heinz bodies and serum haptoglobin levels were seen. Thrombocytopenia was seen in the high dose group in week 4, but resolved thereafter. Pulmonary lesions were observed in all animals in the mid and high dose groups, and consisted of foamy macrophage accumulation and chronic interstitial inflammation. Bone marrow hyperplasia occurred in the mid and high dose groups. Lung, liver and splenic weights were increased at the high dose level. Although subtle ECG changes were seen and appear to be treatment-related, they may not represent significant toxicologic effects. A no-effect level was considered to be at or near the low dose of 0.1 mg base/kg/day.

2. INTRODUCTION

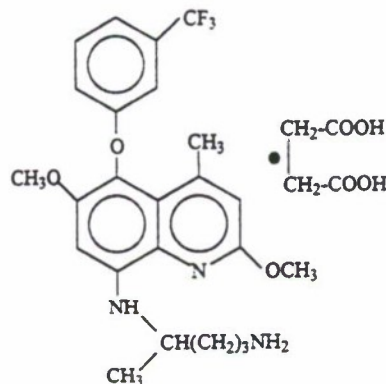
This study was conducted to determine the specific target organ toxicity, dose-response relationships and a potential no-adverse effect level of WR238605 succinate in dogs following one year of daily oral administration. WR238605 is a synthetic 8-aminoquinoline derivative of primaquine and is intended for use as a prophylactic antimalarial compound, as well as for the treatment of relapsing malaria. The study was conducted in accordance with the specifications of the Sponsor, as indicated in Task Order UIC-9. The FDA requires the use of two animal species, one which is a non-rodent, in preclinical toxicology studies. The dog is a standard and accepted non-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. No unforeseen circumstances affected the integrity of the study. Dosing was initiated on July 18, 1996 and the in-life portion was terminated on July 18, 1997.

3. MATERIALS AND METHODS

3.1 Test Article

WR238605 succinate (Bottle No. BN65479), a pale yellow powder, was provided by the Sponsor and was received on June 25, 1996 from Herner & Co., Rockville, MD. The chemical name of the test article is 8-[(4-amino-1-methylbutyl)amino]-2,6-dimethoxy-

4-methyl-5-(3-trifluoromethyl-phenoxy)quinoline succinate and the base mole fraction is 0.8. It was stored at 0 - 4° C, ambient humidity and protected from light in an amber bottle. The chemical structure is as follows..



WR238605 Succinate

The Analytical Chemistry Report is contained in Appendix A. The test article was previously identified by GC-MS (Bottle No. BN12562). The initial purity was determined by HPLC to be $99.99 \pm 0.004\%$. The purity was re-determined after approximately 6 months of dosing and following the completion of the in-life portion of the study. At the six month timepoint the purity was $100.00 \pm 0.000\%$ and at the completion of the in-life portion the purity was $100.00 \pm 0.000\%$. Thus, the test article was stable under storage conditions.

3.2 Animals

Twenty male and twenty female Beagle dogs were obtained from Marshall Farms, North Rose, NY on June 27, 1996. The animals were approximately 7 months old (dates of birth between 11/22/95 and 12/17/95) upon arrival at the UIC AAALAC Intl.-accredited animal facility. Each animal was given a facility-unique animal number upon arrival. This number was coded on a subcutaneously implanted microchip and also appeared on a cage card visible on the front of each cage. Animals were singly housed in runs, except as subsequently noted, in a temperature (65 - 84°F) and humidity ($50 \pm 20\%$) controlled room with a 12 hour light/12 hour dark cycle. Eight dogs were housed two/run (within sex) during the quarantine/pretest period, but were singly housed prior to initiation of the dosing phase. The run size, at least 15 square feet, was adequate to house dogs at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23. All runs were cleaned and bedding was replaced daily. The runs were sanitized once every two weeks.

The animals were quarantined for three weeks. During that time, the animals were observed daily for signs of illness and all unusual observations were reported to the Study Director or Clinical Veterinarian. Body weights and preliminary physical examinations were done upon arrival at the animal facility. Each dog was lightly sprayed with Para Pyrethrin Mist upon arrival for fleas, lice, and ticks. All dogs were previously vaccinated by the animal supplier against canine distemper, infectious canine hepatitis, oral

papilloma, leptospirosis, parainfluenza, parvo and rabies. Blood samples were collected within three days of arrival for quarantine clinical chemistry and hematology tests, and fecal samples were collected for internal parasite examinations. Animals were examined during quarantine and approved for use by the Clinical Veterinarian prior to being placed on test. Quarantine release was documented on the Clinical Veterinarian Log by the veterinarian prior to study initiation.

Certified Canine Diet No. 5007 (PMI Feeds Inc., St. Louis, MO), approximately 400 g on a daily basis (exactly 400 g on days when food consumption was measured), and tap water *ad libitum* from an automatic watering system in which the room distribution lines were flushed daily were provided from arrival until termination. The water was untreated with additional chlorine or HCl. The food was removed for an overnight fast (\approx 16 - 20 hours) prior to blood collection for clinical pathology, overnight urine collection, and/or scheduled sacrifice. There were no known contaminants in the feed or water which were expected to influence the study. The results of the most current comprehensive chemical analyses of Chicago water are documented in files maintained by Quality Assurance.

3.3 Experimental Design

Near the end of the quarantine/pretest period, 16 animals of each sex were selected for study on the basis of quarantine data including body weight, food consumption, clinical pathology, electrocardiograms, and ophthalmology examinations. These animals were randomized within sex into the groups shown in the following table using a restricted randomized procedure stratified by body weight. No litter mates were included in the same dose group.

<u>Treatment Group</u>	<u>Number of Males</u>	<u>Number of Females</u>	<u>Dose Level (mg base/kg/day)</u>	<u>Concentration (mg base/mL)</u>
1	4	4	0	0
2	4	4	0.1	0.625
3	4	4	1.0	6.25
4	4	4	4.0	25.0

Dose levels were selected by the Sponsor based upon the results of a previous thirteen week oral toxicity study of WR238605 succinate with a thirteen week recovery period in dogs (UIC/TRL Study No. 097). Dose levels refer to the base (WR238605).

Following assignment to a treatment group, the animal's number appeared on a card visible on the front of each run. The run card additionally contained the study number, test article identification, treatment group number, sex and dose level. Run cards were color-coded as a function of treatment group.

The test article was administered once daily as a suspension in 1% methylcellulose/0.2% Tween 80 (vehicle) in a gelatin capsule (size 13; capacity 3.2 mL) starting on day 1 for

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at least 52 weeks. The control animals received the vehicle alone within gelatin capsules. The dose volume was 0.16 mL/kg/day. The specific volume of the test article administered in the gelatin capsule was based on each animal's most recent body weight. All animals received vehicle alone in a gelatin capsule for at least 3 days during week -1 to acclimate them to the procedure. The animals were dosed up to and including the day prior to scheduled necropsy. The dogs weighed 9.9 - 13.1 kg (males) and 8.0 - 11.4 kg (females) on day -2 and were approximately 7 - 8 months old at initiation of treatment.

Concentrations of the dosing suspensions were adjusted for test article purity and the base mole fraction (0.80), while the control article comprising the vehicle was assumed to be 100% pure. The 1% methylcellulose/0.2% Tween 80 vehicle was prepared every two weeks by placing the required amount of deionized distilled water in a beaker and then adding the required amount of methylcellulose and volume of Tween 80, using its specific gravity of 1.08 (1.0 g of methylcellulose and 0.2 g Tween 80 per 100 mL of deionized distilled water). One lot no. each of methylcellulose and Tween 80 were used throughout the study. The mixture was stirred until homogeneous and then refrigerated.

The test article dosing suspensions were prepared every two weeks. Stability data from a previously conducted dog toxicity study by gastric intubation demonstrated that WR238605 succinate suspensions were stable for at least 28 days (UIC/TRL Study No. 047). Homogeneity data also obtained from UIC/TRL Study No. 047 demonstrated that the test article suspensions were homogeneous (coefficients of variation for sampling in the top, middle and bottom of several test suspensions were typically less than 4%). Each test article dosing suspension was prepared individually by adding the appropriate amount of WR238605 succinate with the required volume of 1.0% methylcellulose/0.2% Tween 80 vehicle in a pre-calibrated beaker. The contents were mixed with an Omni-Mixer homogenizer, for at least 5 minutes. All suspensions were stored at 2 - 8° C, and were allowed to warm to room temperature and stirred continuously before and during placement into gelatin capsules just prior to administration to each animal. Every other set of dosing suspensions (including controls), i.e., first, third, fifth etc., through the first six months of treatment were analyzed prior to use, and only suspensions within 10% of their target concentration were used. Analyzed samples were also analyzed for test article concentration after use. Following Sponsor review of dosage formulation analyses through the first six months, approval was given so that every third set of subsequent formulations were analyzed before and after use.

Non-fasted body weights were recorded weekly commencing in week -1, and at scheduled necropsy. Clinical signs were recorded once daily, approximately 1 - 2 hours after dosing. 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 during the quarantine/pretest period and weekly commencing in week -1. Food consumption was measured for all animals over an approximate 24 hour period twice during the quarantine/pretest period and once

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weekly during the treatment period. All dogs were examined by indirect ophthalmoscopy prior to study initiation (week -2) and in weeks 12, 25 and 51.

Hematology and clinical chemistry parameters were measured following an overnight fast in weeks -3, -1, 4, 13, 26, and 52. The overnight fasted animals were unanesthetized and sufficient blood was collected from the jugular vein 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 B.

Clinical Chemistry

Alanine aminotransferase (ALT)	Globulin (calculated)
Albumin	Glucose
Albumin/globulin ratio (calc.)	Haptoglobin
Alkaline phosphatase	Lactate dehydrogenase (LDH)
Aspartate aminotransferase (AST)	Inorganic phosphorus
Calcium	Potassium
Chloride	Sodium
Cholesterol	Total bilirubin
Creatinine	Total protein
Creatine kinase (CK)	Triglycerides
Gamma glutamyl transferase (GGT)	Urea nitrogen (BUN)

Hematology

Activated partial thromboplastin time (APTT)	Mean corpuscular hemoglobin (MCH)
^a Erythrocyte count and morphology	Mean corpuscular hemoglobin concentration (MCHC)
Heinz bodies	Mean corpuscular volume (MCV)
Hematocrit	^b Methemoglobin
Hemoglobin	Platelet count
Leukocyte count, total and differential	Prothrombin time
	Reticulocyte count

^aIncludes nucleated RBCs.

^bMeasured with a Co-oximeter (Instrumentation Laboratory, Model No. 482). The assay was performed within one hour of sample collection. The specimens were kept on wet ice prior to analysis.

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Urine specimens were collected in weeks -1, 13, 26 and 52. During the overnight fasting period, the animals were placed in a metabolism cage for urine collection. Water was available *ad libitum* during all fasting periods. The following parameters were measured.

Urinalysis Parameters

Qualitative

Bilirubin	Nitrite
Glucose	pH
Ketones	Protein
Occult Blood	Urobilinogen
Leukocytes	
Color	
Specific Gravity	
Microscopic examination of spun sediment	

Following anesthesia with sodium pentobarbital (I.V.; 20 - 30 mg/kg) and just prior to necropsy in week 53, a blood sample was collected from the abdominal aorta for measurement of the following blood gases.

Arterial Blood Gases

pCO ₂	O ₂ Saturation
pH	pO ₂
HCO ₃ ⁻¹	Total CO ₂

ECG tracings were collected from all dogs during the pretest period and in weeks 12, 25 and 51. Recordings from leads I, II, III, aV_R, aV_L, and aV_F were collected. Analysis included heart rate, the duration of the P wave, and PR, QRS and QT intervals.

Blood samples were collected from the jugular vein in week -1 (when clinical pathology samples were collected) and just prior to treatment at the beginning of weeks 4, 8, 13, 26, 40 and 52 from each dog for the determination of plasma drug levels. The plasma samples were stored frozen (-75 to -80°C) and sent to another facility as directed by the Sponsor. The plasma drug level data will not be included with this study report.

All animals were killed and necropsied in random order in week 53. This was accomplished by sodium pentobarbital anesthesia (i.v.; 20-30 mg/kg) and exsanguination. An extensive necropsy was performed under the direction and supervision of the pathologist. Terminal fasted 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 to include the external surface, all orifices, the cranial cavity,

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external surface of the brain, cross section of the spinal cord, the nasal cavity and nasal turbinates, thoracic, abdominal and pelvic cavities and their viscera, and cervical tissues and organs. The following tissues and organs were collected and fixed in 10% neutral buffered formalin (NBF). The exceptions were the eyes and optic nerve which were fixed in 3% glutaraldehyde and the testes with epididymides which were collected in Bouin's fixative.

*Adrenal glands	*Ovaries
Aorta (thoracic)	Pancreas
*Brain (fore-, mid-, and hind-)	*Pituitary
Cecum	Prostate
Colon	Rib with costochondral junction
Diaphragm	Rib with marrow
Duodenum	Salivary gland (mandibular)
Esophagus	Sciatic Nerve
Eyes and optic nerve	Skin
Gallbladder	Spinal cord (thoracic)
Gross lesions	*Spleen
*Heart	Stomach
Ileum	*Testes with epididymides
Jejunum	Thymus
*Kidneys	*Thyroid gland with parathyroids
*Liver (with gallbladder drained)	Tongue
*Lungs/Bronchi	Tonsil
Lymph node (mandibular and mesenteric)	Trachea
Mammary gland	Ureter
Muscle (skeletal)	Urinary bladder
	Uterus

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

The above tissues from all dogs sacrificed at scheduled necropsy were embedded in paraffin, sectioned, stained with hematoxylin and eosin, and examined microscopically. Bone marrow (rib) smears were prepared and myeloid:erythroid (M:E) ratios were determined for all animals.

3.4 Statistical Analyses

For each sex, Analysis of Variance tests were conducted on body weight, body weight gain, ECG measurements, hematology, clinical chemistry, urinary specific gravity and pH, arterial blood gas data and organ weight data. Organ weight analyses included weights relative to brain weights. If a significant F ratio was obtained ($p \leq 0.05$), Dunnett's test was used for

pair-wise comparisons with the concurrent control group. Food consumption data were analyzed by the Kruskal-Wallis test. Data were not corrected for baseline values, except that body weight analysis included absolute values, weekly changes and total weight changes.

4. RESULTS

4.1 Dosage Formulation Analyses

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

All predose dosage formulations were within 10% of the target concentration for the entire study. All test article dosage formulations analyzed after dosing were within 10% of their predose concentrations with minor exceptions for the 6.25 mg base/mL formulation prepared for study weeks 9 and 10 (71.8% of predose value and 69.5% of target concentration) and for study weeks 13 and 14 (77.1% of predose value and 78.4% of target value). Following the observation that the weeks 9 and 10 mid dose formulation (6.25 mg base/mL) was out of range, all dosage formulations used in weeks 11 and 12 were tested at the end of week 12. At that time, they were all within 10% of their target concentration.

4.2 Mortality/Clinical Signs

The summary of clinical signs is presented in Table 3. Individual clinical signs and daily incidence of clinical signs are contained in Appendix C. Individual weekly clinical observations and weekly clinical observation incidence are also contained in Appendix C.

No mortalities occurred in the study. Clinical signs were first noted during week 3 and continued throughout the study. Blue tongue (slight blue tinged color) was seen in all males in the mid and high dose groups at various times during the study, and on one occasion in a low dose male. Blue tongue was seen throughout the study in all high dose females, 3/4 mid dose females, and on one occasion in a low dose female. Diarrhea was periodically seen in all males in the mid and high dose groups, and on rare occasions in the low dose and control groups. Diarrhea occurred in a dose-dependent fashion in females with the incidence greatest at the high dose (4/4 females). One high dose female (animal no. 8933) had diarrhea (severity = 1 and 2) throughout the study. Emesis was produced periodically in the high dose animals and on one occasion in a mid dose female. One high dose male (animal no. 8921) had increased respiratory rate which was first observed on day 55 and last observed on day 174.

4.3 Body Weights

Summaries of body weights are presented in Tables 4.1 - 4.12 and graphically depicted in Figures 1 and 2. Summaries of weight gains are presented in Tables 5.1 - 5.12. Individual body weights and weight gains are contained in Appendix D.

Statistically significant decreases in body weights were seen in the mid and high dose males during the study. At the conclusion of the study (day 363), total weight gains were decreased in a dose-dependent fashion in the males resulting in body weights which were decreased 2%, 10% and 12% (compared to the control group) in the low, mid and high dose groups, respectively. This corresponds to reductions in body weight gains of 33%, 83%, and 94%, respectively. Because of significant variability, these reductions were only statistically significant in the high dose males. Administration of WR238605 to female dogs did not result in treatment-related changes in body weight. Total weight gain of the low dose group was incidentally increased significantly at the end of the study, resulting in a mean body weight which was increased 26% compared to the control group.

4.4 Food Consumption

Summaries of daily food consumption are in Tables 6.1 - 6.14. Individual food consumption data are shown in Appendix E.

Administration of WR238605 to male and female dogs did not affect food consumption.

4.5 Clinical Pathology

Summaries of clinical chemistry tests are presented in Tables 7.1 - 7.36. Individual clinical chemistry data are in Appendix F. Summaries of hematological tests are presented in Tables 8.1 - 8.36 and individual hematology data are in Appendix G. Individual urinalysis data are contained in Appendix H.

Clinical Chemistry

Serum total bilirubin values were slightly, but significantly increased in week 4 in high dose males (\uparrow 54%), and in mid and high dose females (\uparrow 46% and \uparrow 69%, respectively). Serum haptoglobin was generally elevated throughout the study in the high dose group, although the increases were not statistically significant except for high dose males in week 4. Although BUN values were slightly, but significantly elevated in the mid and high dose females in week 4 (\uparrow 21% and \uparrow 26%, respectively), the changes are considered to be biologically insignificant as BUN levels were unaffected at other time-points or in males. Increased serum globulin levels and decreased A/G ratios were present in weeks 4 and 13 in high dose females and males, respectively. Serum triglycerides were increased 92% in week 13 and 107% in week 52 in high dose males. No other changes in clinical chemistry parameters were considered to be biologically significant or treatment-related.

Hematology

Methemoglobinemia was produced throughout the study in the mid and high dose groups. Methemoglobin values (% hemoglobin) ranged from 3.5 - 4.0% in mid dose males, 8.9 - 11.9% in high dose males, 5.5 - 7.0% in mid dose females, and 12.1 - 12.5% in high dose females. The increases were typically statistically significant in high dose animals and mid dose females. Although statistically insignificant, RBC count, hemoglobin concentration, and hematocrit were slightly reduced, \approx 7% - 10%, in high dose animals throughout the study. Consequently, reticulocyte counts were slightly increased throughout the study in high dose females and in weeks 26 and 52 in high dose males. A non-statistically significant increase in Heinz bodies (1.3 - 1.9% RBCs) was observed in week 52 in the low, mid and high dose males. Slight alterations in erythrocyte morphology were periodically observed. Slight polychromasia was seen in week 13 in one mid dose male and in week 26 in two high dose males. Slight pyknotic RBCs were seen in one mid dose male and one high dose female in week 52. Slight Howell-Jolly bodies were seen periodically in females exposed to WR238605.

Thrombocytopenia was seen in week 4 as platelet counts were decreased 73% and 69% in high dose males and females, respectively. Recovery from thrombocytopenia occurred thereafter. White blood cell counts were increased in weeks 26 and 52, due to increased mature neutrophil counts, in high dose females. Mature neutrophil counts were also increased in high dose males in week 13.

No other changes in hematology parameters were considered to be biologically significant or treatment-related.

Urinalysis

There were no treatment-related changes in urinalysis parameters.

Arterial Blood Gases

Statistically significant changes in arterial blood gas parameters were not seen. However, one high dose male (animal no. 8921) had significantly reduced O₂ saturation (14.5%) and PO₂ (14 mmHg).

4.6 Electrocardiography

The Cardiology Report is contained in Appendix J.

In week 52, two males (nos. 8908 and 8921) and two females (nos. 8933 and 8936) receiving 4 mg base/kg/day and one female receiving 1 mg base/kg/day (no. 8929) had T-wave changes in which the T-waves became biphasic (+/-). These changes appear to represent a

a drug-effect. No other ECG alterations were considered drug-related. There were no drug-effects on heart rate, P-wave duration, or PR, QRS, or QT intervals. Increased P-wave duration for females receiving 4 mg base/kg/day in weeks 12, 25 and 51 was also seen in the baseline period (week -3).

4.7 Ophthalmology

The Ophthalmology Report is contained in Appendix K.

There were no treatment-related ophthalmic changes.

4.8 Organ Weights

Organ weight summaries are in Table 11. Individual organ weight data are contained in Appendix L.

Administration of WR238605 to dogs resulted in increased liver, lung and spleen weights (% brain weight) in the high dose group. Liver weights were increased 30% and 43% in males and females, respectively; lung weights were increased 142% and 105% in males and females, respectively; and spleen weights were increased 35% and 232% in males and females, respectively, compared to the control animal values.

4.9 Pathology

The Pathology Report is contained in Appendix L. A summary of microscopic lesions is shown in Table 12.

The lungs were the primary target organ for toxicity in the study. Gross lesions were observed at necropsy in the mid and high dose groups and included enlarged lung and multiple yellow foci. Chronic interstitial inflammation and accumulation of foamy macrophages were observed in all animals in the mid and high dose groups, and were considered to be primary treatment-related lesions. Chronic interstitial inflammation was characterized by the increased presence of alveolar macrophages in the alveolar lumens and thickened alveolar walls with increased basophilic staining. Foamy macrophage accumulation was diagnosed when luminal macrophages were very large with copious foamy cytoplasm. Foamy macrophage accumulation and chronic interstitial inflammation generally occurred in the same regions of the lung. These pulmonary lesions were not seen at the low dose.

Lesions were observed in the liver which included Kupffer cell pigmentation and subacute centrilobular inflammation. Kupffer cell pigmentation was characterized by the presence of enlarged Kupffer cells due to accumulation of brown granular material in their cytoplasm, and were seen in the mid and high dose groups and low dose females. Subacute centrilobular inflammation was only observed in the high dose group, and was characterized by the presence of lymphocytes and neutrophils surrounding the central veins.

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Pigmentation of renal cortex epithelium, characterized by the presence of brown granular pigment in the cytoplasm of some renal tubule epithelial cells, was seen in the high dose group, mid dose males and one low dose female. The pattern of pigmented cell distribution was most consistent with specific accumulation in the proximal convoluted tubules. Pigmentation of cortical epithelial cells was considered to be a morphologic indicator of chronic hemoglobin resorptive activity in the kidney.

Bone marrow hyperplasia, characterized by increased numbers of blood precursor cells and decreased lipid cells, was seen in the mid and high dose groups. The incidence and severity of bone marrow hyperplasia was greatest at the high dose.

Macrophage pigmentation, due to the presence of brown granular material in the cytoplasm, was seen in the spleen, gall bladder, tonsil, and mesenteric and mandibular lymph nodes in male and female dogs. Pigmentation in the spleen was present in all treatment groups, but the incidence and severity were greatest in the mid and high dose animals. Pigmentation of macrophages in gall bladder submucosa was seen only at the high dose. Pigmentation of macrophages in the tonsil and mesenteric lymph node were seen at the mid and high dose levels. Pigmentation of macrophages in the mandibular lymph node was seen in all dose groups, but the incidence and severity were greatest at the high dose level. Accumulation of pigmented macrophages and hemorrhage were seen in mediastinal lymph nodes collected as gross lesions (altered pigmentation) in two males and two females in the high dose group. Hemorrhage in the mediastinal was also seen in one low dose male. Accumulation of pigmented macrophages was seen in bronchial lymph nodes collected as gross lesions (enlarged) in all animals at the high dose, and two males and one female in the mid dose group. Hemorrhage was seen in one high dose male, and one mid and high dose female.

No other microscopic changes were considered to be related to WR238605 treatment.

5. DISCUSSION/CONCLUSION

This study was conducted to determine the specific target organ toxicity, dose-response relationships and a potential no-adverse effect level of WR238605 succinate in dogs following one year of daily oral administration in gelatin capsules. WR238605 is a synthetic 8-aminoquinoline derivative of primaquine and is intended for use as a prophylactic antimalarial compound, as well as for the treatment of relapsing malaria. Dose levels studied were 0, 0.1, 1.0 and 4.0 mg base/kg/day.

No mortalities occurred in the study. Clinical signs of toxicity were observed throughout the study, primarily at the high dose level, and included blue tongue, diarrhea, emesis and increased respiratory rate. Blue tongue was indicative of cyanosis, due most likely to methemoglobinemia produced by WR238605 administration. One high dose male had increased respiratory rate. Oral administration of WR238605 produced diarrhea and emesis in a dose-dependent fashion, with the incidence of diarrhea greatest in the high dose females. Although diarrhea occurred throughout the study in the high dose females, treatment-related changes in body weights or electrolytes were not seen in these

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animals. Body weight gains were, however, decreased in the males in a dose-dependent fashion. Food consumption was unaffected by treatment.

The lungs were the primary target organ for toxicity in the study. Chronic interstitial inflammation and accumulation of foamy macrophages were observed in all animals in the mid and high dose groups, and considered to be primary treatment-related lesions. Also, significantly increased lung weights were seen at the high dose level. Pulmonary lesions were not seen at 0.1 mg base/kg/day. Although statistically significant changes in arterial blood gases were not seen in week 53, PO₂ and O₂ saturation were greatly reduced in one high dose male. Increased respiratory rate was observed in this animal and the lung weight was increased to the greatest extent in comparison to the other high dose males.

In a previous thirteen week oral toxicity study of WR238605 with a thirteen week recovery period in dogs (UIC/TRL Study No. 097), pulmonary lesions were seen. At the end of the treatment period, alveolar proteinosis was seen in the 2 and 6 mg base/kg/day dose groups, and subacute inflammation was seen in the 0.1, 2 and 6 mg base/kg/day dose groups. At the end of the recovery period, the alveolar proteinosis had completely resolved in males and almost completely in females. However, by the end of the recovery period, chronic inflammation had developed secondary to resolution. In a previous six month oral toxicity study of WR238605 succinate in rats (UIC/TRL Study No. 152), foamy macrophage accumulation, chronic interstitial inflammation and hemorrhage were observed.

The mechanism(s) for the pulmonary lesions observed in the current study is unknown, but may be related to chronic, low grade hemorrhage due to damage of the capillary endothelium and/or type I pneumocytes. The presence of erythrocytes and blood protein in the alveolar lumen could attract macrophages. The macrophages may develop copious foamy cytoplasm in an attempt to digest the lipid membranes of the erythrocytes. The macrophages could then release inflammatory mediators resulting in an interstitial inflammatory response. Bronchial and mediastinal lymph nodes collected as gross lesions from mid and high dose animals had accumulation of pigmented macrophages and hemorrhage. This suggests that pulmonary hemorrhage had occurred during the study. The pulmonary lesions produced by WR238605 may be related to lesions characterized as pulmonary phospholipidosis. Cationic amphiphilic drugs, of which WR238605 is a structural member, can produce a lipid storage disorder due to excessive accumulation of intracellular phospholipids (Halliwell, 1997). Although phospholipidosis can occur in many tissues, the lung and alveolar macrophages are usually prominent in a pathologic response to administration of cationic amphiphilic drugs. The lesion is characterized by excessive accumulation of foamy alveolar macrophages, mononuclear cells, and amorphous material in the alveolar spaces (Halliwell, 1997). The pulmonary lesions in the current study may have resulted from a low grade hemorrhage with macrophage accumulation and alteration of macrophage phospholipid metabolism upon WR238605 administration.

WR238605 administration resulted in oxidative injury to erythrocytes in the mid and high dose groups. Methemoglobinemia was produced throughout the study in the mid and high dose groups. A slight increase in Heinz bodies was seen in week 52 in the low, mid and high dose females. Also, slight changes in erythrocyte morphology were observed periodically. Although statistically and

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biologically significant changes in red blood cell counts, hematocrit or hemoglobin were not seen, chronic low level hemolysis was evident due to the presence of tissue pigmentation changes in numerous tissues. Pigmentation was seen in Kupffer cells, renal cortex epithelium and in macrophages in spleen, gall bladder, tonsil and lymph nodes (mesenteric, mandibular, bronchial and mediastinal). This pigmentation is suggestive of uptake of free hemoglobin following intravascular hemolysis. Further evidence that hemolysis had occurred was the increased levels of serum haptoglobin in high dose animals. Haptoglobin is a glycoprotein that combines with hemoglobin as a mechanism to prevent loss of iron following intravascular hemolysis. Both hemolytic anemia and methemoglobinemia were treatment-related effects produced by WR238605 succinate administration in previous dog and rat studies (UIC/TRL Study No. 097 and UIC/TRL Study No. 152, respectively). 8-Aminoquinolines, including WR238605, have been shown to produce hemolytic anemia and methemoglobinemia (Levine *et al.*, 1997; Anders *et al.*, 1988).

Selected organ changes seen were most likely secondary to intravascular hemolysis and/or the pulmonary lesions. In the liver, subacute centrilobular inflammation was observed in high dose animals and may have been due to hypoxia produced by anemia and/or reduced pulmonary function. Liver weights were also increased in the high dose group. Bone marrow hyperplasia was seen in the mid and high dose group and may have been a response to hemolysis and/or pulmonary inflammation. However, myeloid:erythroid ratios were not affected by treatment. Weights of the spleen were increased in the high dose group, and this change may have been in response to the uptake of free hemoglobin.

Thrombocytopenia was seen in high dose animals in week 4, with recovery occurring thereafter. Increases in white blood cells and mature neutrophil counts were seen in the high dose animals and may have been a response to the changes occurring in the lungs.

At the end of the study (week 51), changes in the electrocardiograms were observed that appear to be treatment-related. Two males and two females in the high dose group, and one female in the mid dose group had diphasic T-waves (-/+). Changes in T-waves indicate alterations in repolarization due, most likely, to alterations in conductance over specific ionic channels, most likely potassium channels. However, the changes noted were rather subtle and may not represent significant toxicologic effects.

In summary, the primary toxicities of WR238605 succinate following one year of oral administration were to the lungs and red blood cells. No mortalities occurred in the study. Body weight gains were decreased in the males in a dose-dependent fashion, but were unaffected in females. Clinical signs were primarily seen in the mid and high dose groups and included diarrhea, emesis and blue tongue. Increased respiratory rate was observed in one high dose male. Methemoglobinemia was produced throughout the study in the mid and high dose groups. Chronic, low level intravascular hemolysis occurred in the mid and high dose groups, as evidenced by the presence of tissue pigmentation changes in Kupffer cells, renal cortex epithelium and in macrophages in spleen, gall bladder, tonsil and lymph nodes (mesenteric, mandibular, bronchial and mediastinal). Furthermore, increased reticuloctye counts, Heinz bodies and serum haptoglobin levels were seen. Thrombocytopenia was

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seen in the high dose group in week 4, but resolved thereafter. Pulmonary lesions were observed in all animals in the mid and high dose groups, and consisted of foamy macrophage accumulation and chronic interstitial inflammation. Bone marrow hyperplasia occurred in the mid and high dose groups. Lung, liver and splenic weights were increased at the high dose level. Although subtle ECG changes were seen and appear to be treatment-related, they may not represent significant toxicologic effects. A no-effect level was considered to be at or near the low dose of 0.1 mg base/kg/day.

6. PERSONNEL

Study Director	Barry S. Levine, D.Sc., D.A.B.T.
Toxicologist	Alan P. Brown, Ph.D.
Pathologist	Robert L. Morrissey, D.V.M., Ph.D., D.A.C.V.P.
Analytical Chemist	Thomas Tolhurst, B.S.
Clinical Veterinarian	Terry Hewett, D.V.M., D.A.C.L.A.M.
Ophthalmologist	Samuel J. Vainisi, D.V.M., D.A.C.V.O.
Cardiologist	Robert L. Hamlin, D.V.M., Ph.D., D.A.C.V.I.M.
Clinical Laboratory	Maria Lang, A.H.T., C.V.T.
Tox. Lab Supervisor	Soudabeh Soura, B.S.
Lead Technician	Teresa O'Neill, B.S.
Quality Assurance	Ronald Schoenbeck

Report preparation was assisted by Mukesh Pitroda, B.A.

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.

8. REFERENCES

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Table 1
 ONE YEAR ORAL TOXICITY STUDY OF
 WR238605 SUCCINATE IN DOGS
 Summary of Toxic Responses

Dose (mg base/kg/day)	0	0.1	1.0	4.0
Dogs/Sex	4	4	4	4
Deaths	0	0	0	0
Body Weight Gain	-	↑ F	↓ M	↓ M
Food Consumption	-	NE	NE	NE
Daily Clinical Signs	-	NE	Diarrhea (4M/3F) Blue Tongue (1F)	Diarrhea (4M/4F) Blue Tongue (4M/3F) Emesis (3M/2F)
Weekly Clinical Observations	-	Blue Tongue (1M/1F)	Blue Tongue (4M/3F)	Blue Tongue (4M/4F) Respiratory Rate Increased (1M)
Clinical Chemistry ^a	-	NE	↑ TBILI (F)	↑ TBILI ↑ HAPT ↑ GLOB ↓ A/G ↑ TRIG (M)
Hematology ^b	-	↑ Heinz (M?)	↑ METHGB ↑ Heinz (M?)	↑ METHGB ↑ Retic ↓ PLT ↑ WBC (F) ↑ MNEUT ↑ Heinz (M?)
Arterial Blood Gases	-	NE	NE	↓ O ₂ Sat. (M?) ↓ PO ₂ (M?)
Urinalysis	-	NE	NE	NE
Electrocardiography	-	NE	T-wave changes (1F)	T-wave changes (2M/2F)
Ophthalmology	-	NE	NE	NE
Organ Weights	-	NE	NE	↑ Liver ↑ Lung ↑ Spleen
Histopathology	-	<u>Liver</u> - Kupffer cell pigmentation (2F) <u>Mediastinal Lymph Node</u> - Hemorrhage (1M)	<u>Lung</u> - chronic interstitial inflammation (4M/4F) - accumulation, foamy macrophages (4M/4F) <u>Liver</u> - Kupffer cell pigmentation (3M/4F) <u>Kidney</u> - Renal cortex pigmentation (2M) <u>Spleen</u> - pigmentation (3M/4F) Bone marrow hyperplasia (1M/1F) <u>Tonsil</u> - pigmentation of macrophages (3M/1F) <u>Mesenteric Lymph Node</u> - pigmentation of macrophages (3M/4F) <u>Bronchial Lymph Node</u> - Accumulation, pigmented macrophages (2M/1F) - Hemorrhage (1F)	<u>Lung</u> - chronic interstitial inflammation (4M/4F) - accumulation, foamy macrophages (4M/4F) <u>Liver</u> - Kupffer cell pigmentation (4M/4F) - Subacute centrilobular inflammation (3M/2F) <u>Kidney</u> - Renal cortex pigmentation (4M/2F) <u>Spleen</u> - pigmentation (4M/4F) Bone marrow hyperplasia (3M/4F) <u>Gall Bladder</u> - pigmentation of macrophages (2M/1F) <u>Tonsil</u> - pigmentation of macrophages (4M/4F) <u>Mandibular Lymph Node</u> - pigmentation of macrophages (4M/4F) <u>Mesenteric Lymph Node</u> - pigmentation of macrophages (4M/4F) <u>Bronchial Lymph Node</u> - Accumulation, pigmented macrophages (4M/4F) - Hemorrhage (1M/1F) <u>Mediastinal Lymph Node</u> - Accumulation, pigmented macrophages (2M/2F) - Hemorrhage (2M/2F)
<p>CONCLUSIONS: The purpose of this study was to determine specific target organ toxicity, dose-reponse relationships, and a no observed adverse effect level of WR238605 succinate in Beagle dogs following one year of daily oral administration. WR238605 succinate is being developed as an antimalarial agent. Dose levels studied were 0, 0.1, 1.0 and 4.0 mg base/kg/day. The dogs were ≈ 7 - 8 months old and weighed 9.9 - 13.1 kg (males) and 8.0 - 11.4 kg (females) at dosing initiation. The primary toxicities of WR238605 succinate following one year of oral administration were to the lungs and red blood cells. No mortalities occurred in the study. Body weight gains were decreased in the males in a dose-dependent fashion, but were unaffected in females. Clinical signs were primarily seen in the mid and high dose groups and included diarrhea, emesis and blue tongue. Increased respiratory rate was observed in one high dose male. Methemoglobinemia was produced throughout the study in the mid and high dose groups. Chronic, low level intravascular hemolysis occurred in the mid and high dose groups, as evidenced by the presence of tissue pigmentation changes in Kupffer cells, renal cortex epithelium and in macrophages in spleen, gall bladder, tonsil and lymph nodes (mesenteric, mandibular, bronchial and mediastinal). Furthermore, increased reticulocyte counts, Heinz bodies and serum haptoglobin levels were seen. Thrombocytopenia was seen in the high dose group in week 4, but resolved thereafter. Pulmonary lesions were observed in all animals in the mid and high dose groups, and consisted of foamy macrophage accumulation and chronic interstitial inflammation. Bone marrow hyperplasia occurred in the mid and high dose groups. Lung, liver and splenic weights were increased at the high dose level. Although subtle ECG changes were seen and appear to be treatment-related, they may not represent significant toxicologic effects. A no-effect level was considered to be at or near the low dose of 0.1 mg base/kg/day.</p>				

M - Male, F = Female

^aA/G = albumin/globulin ratio, HAPT = haptoglobin, TRIG = triglycerides, TBILI = total bilirubin, GLOB = globulin

^bMETHGB = methemoglobin, Retic = reticulocytes, PLT = platelets, WBC = leukocytes, MNEUT = mature neutrophils, Heinz = Heinz bodies

NE = No effect, ? = Possible effect

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Table 2
 ONE YEAR ORAL TOXICITY STUDY OF
 WR238605 SUCCINATE IN DOGS

Dosage Formulation Analyses^a

Study Weeks	Target Concentration (mg base/ml)	Predose Analysis ^a			Postdose Analysis ^b		
		Date	(mg base/ml)	% Target	Date	(mg base/ml)	% Predose
1 & 2	0.000	07/16/96	0	-	08/01/96	0	-
	0.625		0.650 ± 0.005	104.0		0.593 ± 0.010	91.2
	6.250		6.468 ± 0.278	103.5		6.409 ± 0.027	99.1
	25.000		25.406 ± 0.278	101.6		27.330 ± 0.179	107.6
5 & 6	0.000	08/13/96	0	-	08/29/96	0	-
	0.625		0.593 ± 0.006	94.9		0.598 ± 0.019	100.8
	6.250		6.267 ± 0.031	100.3		6.192 ± 0.020	98.8
	25.000		25.000 ± 0.080	100.0		24.286 ± 0.524	97.1
9 & 10	0.000	09/10/96	0	-	09/26/96	0	-
	0.625		0.592 ± 0.012	94.7		0.579 ± 0.001	97.8
	6.250		6.047 ± 0.058	96.8		4.341 ± 0.022 ^b	71.8
	25.000		24.928 ± 0.111	99.7		24.963 ± 0.804	99.9
11 & 12*	0.000	-	-	-	10/08/96	0	-
	0.625		-	-		0.594 ± 0.004	95.0 ^c
	6.250		-	-		6.326 ± 0.249	101.2 ^c
	25.000		-	-		25.775 ± 0.061	103.1 ^c
13 & 14	0.000	10/08/96	0	-	10/24/96	0	-
	0.625		0.564 ± 0.017	90.2		0.593 ± 0.004	105.1
	6.250		6.352 ± 0.049	101.6		4.897 ± 0.063	77.1
	25.000		24.521 ± 1.577	98.1		25.923 ± 0.186	105.7
17 & 18	0.000	11/05/96	0	-	11/21/96	0	-
	0.625		0.625 ± 0.019	100.0		0.580 ± 0.013	92.8
	6.250		6.120 ± 0.254	97.9		6.415 ± 0.069	104.8
	25.000		25.318 ± 0.550	101.3		25.227 ± 0.252	99.6
21 & 22	0.000	12/03/96	0	-	12/19/96	0	-
	0.625		0.623 ± 0.007	99.7		0.603 ± 0.033	96.8
	6.250		6.395 ± 0.109	102.3		5.974 ± 0.305	93.4
	25.000		26.038 ± 0.215 ^d	104.2		25.876 ± 1.238	99.4
25 & 26	0.000	12/30/96	0	-	01/16/97	0	-
	0.625		0.611 ± 0.002	97.8		0.595 ± 0.001	97.4
	6.250		6.302 ± 0.155	100.8		6.024 ± 0.026	95.6
	25.000		24.773 ± 0.072	99.1		25.489 ± 0.112	102.9
31&32	0.000	02/11/97	0	-	02/27/97	0	-
	0.625		0.609 ± 0.003	97.4		0.622 ± 0.013	102.1
	6.250		6.336 ± 0.033	101.4		6.548 ± 0.091	103.3
	25.000		23.906 ± 1.070	95.6		25.534 ± 0.193	106.8
37 & 38	0.000	03/25/97	0	-	04/10/97	0	-
	0.625		0.602 ± 0.002	96.3		0.602 ± 0.003	100.0
	6.250		6.021 ± 0.093	96.3		6.206 ± 0.041	103.1
	25.000		24.987 ± 0.192	99.9		24.993 ± 0.175	100.0
43 & 44	0.000	05/06/97	0	-	05/22/97	0	-
	0.625		0.636 ± 0.003	101.8		0.600 ± 0.001	94.3
	6.250		6.159 ± 0.284	98.5		5.975 ± 0.040	97.0
	25.000		26.471 ± 0.427	105.9		25.958 ± 0.003	98.1
49 & 50	0.000	06/17/97	0	-	07/03/97	0	-
	0.625		0.602 ± 0.021	96.3		0.593 ± 0.003	98.5
	6.250		6.300 ± 0.078 ^d	100.8		6.299 ± 0.085	100.0
	25.000		25.256 ± 1.138	101.0		25.162 ± 1.278	99.6

^an=3

^bn=6

^c% Target

^dn=2

*Predose samples not submitted for analysis

Table 3

ONE YEAR ORAL TOXICITY STUDY OF
 WR238605 SUCCINATE IN DOGS

Summary of Clinical Signs*

Males

DOSE GROUP:	1-M	2-M	3-M	4-M
DOSE (mg base/kg/day)	0	0.1	1.0	4.0
Blue tongue (severity = 1)	0	0	0	4 (20,41,51,71,120,124,126,147,152,170,197,260,293)
Diarrhea (severity = 1)	1 (202,281)	1 (217)	4 (27,37,68,84,90,103,153,230,271,287,334)	4 (27,28,32,34,49,132,181,362)
Diarrhea (severity = 2)	0	0	0	2 (181,209,350)
Diarrhea with red material	0	0	1 (348)	0
Vomit seen in run	0	0	0	3 (154,169,189,320)

Females

DOSE GROUP:	1-F	2-F	3-F	4-F
DOSE (mg base/kg/day)	0	0.1	1.0	4.0
Blue tongue (severity = 1)	0	0	1 (20)	3 (18,20,28,61,65,73-75,91,92,110,111,115,118,120,122-126,128,129,131,132,134,136,139,171,143,146,147,149,152,161,167,169,170,172-175,180,183,188,191-193,198,208,211,215,225,243,252,278)
Diarrhea (severity = 1)	1 (188)	1 (21,55)	3 (62,83,211)	4 (27-30,34,49,55,75,88,90,95,96,105,106,108,127,134,143,148,149,146,147,200,202,205,207,212,221,230,240,241,251,281)
Diarrhea (severity = 2)	0	1 (223)	0	1 (21,89,168,174)
Vomit seen in run	0	0	1 (38)	2 (157,195)

*Number(s) in parentheses represent the day(s) the sign was observed.

Blue tongue, severity 1 = slight blue tinged color

Diarrhea, severity 1 = semi-solid feces

Diarrhea, severity 2 = semi-solid to liquid feces

Table 4.1

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS**DRAFT**

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 219

SEX: MALE

PERIOD	DOSE: GROUP:	(mg base/kg/day)			
		0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
DAY -2	MEAN	11.6	11.9	11.7	11.7
	S.D.	1.36	0.62	0.56	0.65
	N	4	4	4	4
DAY 6	MEAN	11.5	11.5	11.6	11.5
	S.D.	1.36	0.64	0.46	0.54
	N	4	4	4	4
DAY 13	MEAN	11.6	11.5	11.5	11.5
	S.D.	1.23	0.46	0.36	0.55
	N	4	4	4	4
DAY 20	MEAN	11.7	11.5	11.4	11.4
	S.D.	1.17	0.65	0.40	0.55
	N	4	4	4	4
DAY 27	MEAN	11.6	11.3	11.3	11.2
	S.D.	1.15	0.55	0.54	0.60
	N	4	4	4	4
DAY 34	MEAN	11.8	11.4	11.3	11.3
	S.D.	1.20	0.48	0.51	0.40
	N	4	4	4	4
DAY 41	MEAN	11.7	11.2	11.2	11.3
	S.D.	1.23	0.51	0.52	0.33
	N	4	4	4	4
DAY 48	MEAN	11.8	11.2	11.1	11.3
	S.D.	1.17	0.39	0.48	0.38
	N	4	4	4	4
DAY 55	MEAN	12.0	11.4	11.4	11.4
	S.D.	0.99	0.41	0.52	0.37
	N	4	4	4	4
DAY 62	MEAN	12.0	11.4	11.4	11.4
	S.D.	0.88	0.37	0.45	0.42
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

Table 4.2

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS**DRAFT**

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 219

SEX: MALE

PERIOD	DOSE: GROUP:	(mg base/kg/day)			
		0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
DAY 69	MEAN	12.2	11.4	11.4	11.5
	S.D.	0.72	0.33	0.40	0.43
	N	4	4	4	4
DAY 76	MEAN	12.1	11.5	11.6	11.6
	S.D.	0.56	0.41	0.37	0.31
	N	4	4	4	4
DAY 83	MEAN	12.3	11.7	11.6	11.6
	S.D.	0.58	0.22	0.41	0.31
	N	4	4	4	4
DAY 90	MEAN	12.1	11.5	11.5	11.5
	S.D.	0.62	0.29	0.42	0.30
	N	4	4	4	4
DAY 97	MEAN	12.1	11.4	11.6	11.3
	S.D.	0.67	0.37	0.47	0.26
	N	4	4	4	4
DAY 104	MEAN	12.2	11.6	11.6	11.5
	S.D.	0.67	0.37	0.55	0.21
	N	4	4	4	4
DAY 111	MEAN	12.2	11.6	11.5	11.4
	S.D.	0.65	0.36	0.59	0.15
	N	4	4	4	4
DAY 118	MEAN	12.4	11.6	11.3*	11.2*
	S.D.	0.73	0.42	0.63	0.22
	N	4	4	4	4
DAY 125	MEAN	12.2	11.5	11.3	11.1
	S.D.	0.82	0.61	0.62	0.13
	N	4	4	4	4
DAY 132	MEAN	12.2	11.6	11.1*	11.1*
	S.D.	0.64	0.54	0.66	0.15
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

Table 4.3

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS**DRAFT**

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 219

SEX: MALE

PERIOD	DOSE: GROUP:	(mg base/kg/day)			
		0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
DAY 139	MEAN	12.4	11.7	11.4*	11.2*
	S.D.	0.59	0.50	0.48	0.14
	N	4	4	4	4
DAY 146	MEAN	12.5	11.8	11.4*	11.2*
	S.D.	0.66	0.51	0.66	0.17
	N	4	4	4	4
DAY 153	MEAN	12.6	11.9	11.4*	11.2*
	S.D.	0.68	0.39	0.73	0.18
	N	4	4	4	4
DAY 160	MEAN	12.5	12.0	11.3*	11.2*
	S.D.	0.74	0.33	0.76	0.17
	N	4	4	4	4
DAY 167	MEAN	13.0	12.4	12.0*	11.6*
	S.D.	0.64	0.35	0.69	0.38
	N	4	4	4	4
DAY 174	MEAN	12.5	12.1	11.7	11.1
	S.D.	0.66	0.39	0.82	0.60
	N	4	4	4	4
DAY 181	MEAN	12.5	12.0	11.5	11.1*
	S.D.	0.61	0.34	0.83	0.47
	N	4	4	4	4
DAY 188	MEAN	12.5	12.2	11.5	11.2*
	S.D.	0.47	0.32	0.81	0.56
	N	4	4	4	4
DAY 195	MEAN	12.4	12.1	10.9	11.1
	S.D.	0.70	0.58	1.82	0.60
	N	4	4	4	4
DAY 202	MEAN	12.4	12.3	11.6	11.1
	S.D.	0.58	0.47	1.02	0.62
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

Table 4.4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 219		SEX: MALE			
PERIOD	DOSE: GROUP:	0 1-M	0.1 2-M	1.0 3-M	4.0 4-M (mg base/kg/day)
DAY 209	MEAN	12.4	12.2	11.6	11.1
	S.D.	0.67	0.57	1.06	0.68
	N	4	4	4	4
DAY 216	MEAN	12.5	12.3	11.7	11.2
	S.D.	0.52	0.59	1.09	0.65
	N	4	4	4	4
DAY 223	MEAN	12.5	12.2	11.7	11.3
	S.D.	0.38	0.75	1.11	0.62
	N	4	4	4	4
DAY 230	MEAN	12.4	12.1	11.4	11.2
	S.D.	0.54	0.89	1.36	0.71
	N	4	4	4	4
DAY 237	MEAN	12.5	12.3	11.7	11.2
	S.D.	0.61	0.90	1.23	0.96
	N	4	4	4	4
DAY 244	MEAN	13.0	12.6	11.9	11.4
	S.D.	0.57	0.81	1.22	0.82
	N	4	4	4	4
DAY 251	MEAN	12.9	12.7	11.8	11.4*
	S.D.	0.43	0.71	1.04	0.74
	N	4	4	4	4
DAY 258	MEAN	12.9	12.7	12.0	11.5
	S.D.	0.41	0.63	1.05	0.77
	N	4	4	4	4
DAY 265	MEAN	13.0	12.9	12.1	11.7
	S.D.	0.49	0.84	1.17	0.72
	N	4	4	4	4
DAY 272	MEAN	13.6	13.3	12.6	12.2
	S.D.	0.79	0.79	0.93	0.66
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

Table 4.5

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS**DRAFT**

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 219

SEX: MALE

PERIOD	DOSE: GROUP:	(mg base/kg/day)			
		0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
DAY 279	MEAN	13.3	13.1	12.2	11.8
	S.D.	0.83	0.93	1.03	0.66
	N	4	4	4	4
DAY 286	MEAN	13.1	12.9	12.1	11.8
	S.D.	0.67	0.91	0.97	0.67
	N	4	4	4	4
DAY 293	MEAN	13.1	12.7	11.9	11.8
	S.D.	0.61	0.88	0.99	0.59
	N	4	4	4	4
DAY 300	MEAN	13.0	12.8	11.9	11.8
	S.D.	0.56	1.05	1.14	0.70
	N	4	4	4	4
DAY 307	MEAN	13.2	13.0	12.0	11.9
	S.D.	0.72	1.10	1.12	0.75
	N	4	4	4	4
DAY 314	MEAN	13.2	13.0	11.8	11.9
	S.D.	0.74	0.97	0.97	0.62
	N	4	4	4	4
DAY 321	MEAN	13.6	13.1	12.2	12.1
	S.D.	0.85	0.78	0.96	0.54
	N	4	4	4	4
DAY 328	MEAN	13.5	13.2	12.2	12.2
	S.D.	0.78	0.77	1.01	0.60
	N	4	4	4	4
DAY 335	MEAN	13.5	13.2	12.2	12.1
	S.D.	0.80	0.68	0.90	0.56
	N	4	4	4	4
DAY 342	MEAN	13.5	13.1	12.1	12.0
	S.D.	0.75	0.94	1.00	0.61
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

Table 4.6

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 219		SEX: MALE				
PERIOD	DOSE: GROUP:	0 1-M	0.1 2-M	1.0 3-M	4.0 4-M	(mg base/kg/day)
DAY 349	MEAN	13.6	13.2	12.1	12.0	
	S.D.	0.79	0.94	1.03	0.71	
	N	4	4	4	4	
DAY 356	MEAN	13.9	13.3	12.3	12.1	
	S.D.	0.83	1.02	0.97	0.74	
	N	4	4	4	4	
DAY 363	MEAN	13.4	13.1	12.0	11.8	
	S.D.	0.85	1.10	0.91	0.79	
	N	4	4	4	4	

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

Table 4.7

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 219

SEX: FEMALE

PERIOD	DOSE: GROUP:	(mg base/kg/day)			
		0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
DAY -2	MEAN	9.7	9.7	9.6	9.5
	S.D.	1.45	1.31	0.93	1.17
	N	4	4	4	4
DAY 6	MEAN	9.6	10.0	9.5	9.4
	S.D.	1.43	1.15	0.88	1.20
	N	4	4	4	4
DAY 13	MEAN	9.5	10.0	9.5	9.7
	S.D.	1.53	1.06	0.78	1.15
	N	4	4	4	4
DAY 20	MEAN	9.8	10.0	9.4	9.6
	S.D.	1.58	1.12	0.90	1.10
	N	4	4	4	4
DAY 27	MEAN	9.7	9.9	9.1	9.5
	S.D.	1.57	1.04	0.82	1.14
	N	4	4	4	4
DAY 34	MEAN	10.0	10.1	9.3	9.5
	S.D.	1.65	1.07	0.93	1.11
	N	4	4	4	4
DAY 41	MEAN	9.8	10.1	9.2	9.4
	S.D.	1.81	1.00	0.83	1.04
	N	4	4	4	4
DAY 48	MEAN	9.9	10.3	9.1	9.6
	S.D.	1.77	1.04	0.78	1.15
	N	4	4	4	4
DAY 55	MEAN	10.2	10.5	9.3	9.8
	S.D.	1.70	1.06	0.91	1.27
	N	4	4	4	4
DAY 62	MEAN	10.1	10.5	9.3	9.8
	S.D.	1.68	1.07	0.78	1.23
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

Table 4.8

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS**DRAFT**

SUMMARY OF BODY WEIGHTS (kilograms)

STUDY: 219		SEX: FEMALE			
PERIOD	DOSE: GROUP:	0 1-F	0.1 2-F	1.0 3-F	4.0 4-F (mg base/kg/day)
DAY 69	MEAN	10.1	10.7	9.4	10.0
	S.D.	1.65	1.16	0.79	1.31
	N	4	4	4	4
DAY 76	MEAN	10.1	10.8	9.5	9.9
	S.D.	1.57	1.26	0.86	1.29
	N	4	4	4	4
DAY 83	MEAN	10.1	11.1	9.3	10.0
	S.D.	1.67	1.32	0.86	1.27
	N	4	4	4	4
DAY 90	MEAN	9.9	11.0	9.0	9.9
	S.D.	1.68	1.27	1.00	1.17
	N	4	4	4	4
DAY 97	MEAN	9.8	11.0	8.9	9.8
	S.D.	1.90	1.24	1.12	1.13
	N	4	4	4	4
DAY 104	MEAN	9.7	11.2	9.1	9.8
	S.D.	1.81	1.27	1.10	1.25
	N	4	4	4	4
DAY 111	MEAN	9.6	11.2	9.2	9.6
	S.D.	1.84	1.18	1.15	1.25
	N	4	4	4	4
DAY 118	MEAN	9.8	11.2	9.2	9.6
	S.D.	1.78	1.32	1.27	1.28
	N	4	4	4	4
DAY 125	MEAN	9.8	11.1	9.2	9.6
	S.D.	1.76	1.37	1.30	1.21
	N	4	4	4	4
DAY 132	MEAN	9.7	11.2	9.3	9.5
	S.D.	1.80	1.21	1.06	1.19
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

Table 4.9

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS**DRAFT**

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 219

SEX: FEMALE

PERIOD	DOSE: GROUP:	(mg base/kg/day)			
		0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
DAY 139	MEAN	9.8	11.4	9.5	9.6
	S.D.	1.94	1.31	1.13	1.26
	N	4	4	4	4
DAY 146	MEAN	9.8	11.5	9.6	9.6
	S.D.	1.96	1.44	1.11	1.20
	N	4	4	4	4
DAY 153	MEAN	9.8	11.6	9.4	9.7
	S.D.	1.97	1.57	1.21	1.19
	N	4	4	4	4
DAY 160	MEAN	9.9	11.2	9.4	9.6
	S.D.	2.04	1.35	1.23	1.31
	N	4	4	4	4
DAY 167	MEAN	10.1	11.6	9.8	9.8
	S.D.	1.88	1.61	1.45	1.33
	N	4	4	4	4
DAY 174	MEAN	9.9	11.4	9.6	9.8
	S.D.	1.87	1.47	1.17	1.27
	N	4	4	4	4
DAY 181	MEAN	9.9	11.5	9.4	9.6
	S.D.	1.86	1.70	1.37	1.28
	N	4	4	4	4
DAY 188	MEAN	9.8	11.4	9.5	9.6
	S.D.	1.81	1.70	1.45	1.28
	N	4	4	4	4
DAY 195	MEAN	9.9	11.5	9.8	9.6
	S.D.	1.87	1.71	1.68	1.23
	N	4	4	4	4
DAY 202	MEAN	10.0	11.5	9.5	9.9
	S.D.	1.87	1.67	1.56	1.27
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

Table 4.10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS**DRAFT**

SUMMARY OF BODY WEIGHTS (kilograms)

STUDY: 219

SEX: FEMALE

PERIOD	DOSE: GROUP:	(mg base/kg/day)			
		0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
DAY 209	MEAN	10.1	11.5	9.4	9.8
	S.D.	1.92	1.71	1.46	1.31
	N	4	4	4	4
DAY 216	MEAN	10.1	11.6	9.5	9.9
	S.D.	1.79	1.73	1.48	1.19
	N	4	4	4	4
DAY 223	MEAN	10.2	11.6	9.6	10.0
	S.D.	1.85	1.88	1.39	1.28
	N	4	4	4	4
DAY 230	MEAN	10.2	11.6	9.7	10.0
	S.D.	1.86	1.85	1.39	1.13
	N	4	4	4	4
DAY 237	MEAN	9.9	11.8	9.7	10.0
	S.D.	1.83	1.96	1.73	1.15
	N	4	4	4	4
DAY 244	MEAN	10.2	11.9	10.0	10.4
	S.D.	1.76	2.07	1.62	1.23
	N	4	4	4	4
DAY 251	MEAN	10.0	12.1	9.9	10.3
	S.D.	1.53	2.10	1.67	1.10
	N	4	4	4	4
DAY 258	MEAN	10.2	12.2	9.9	10.4
	S.D.	1.41	2.16	1.60	1.08
	N	4	4	4	4
DAY 265	MEAN	10.4	12.3	10.1	10.3
	S.D.	1.47	2.19	1.92	1.15
	N	4	4	4	4
DAY 272	MEAN	10.8	12.7	10.6	10.7
	S.D.	1.67	2.57	2.08	1.18
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

Table 4.11

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS**DRAFT**

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 219		SEX: FEMALE			
PERIOD	DOSE: GROUP:	0 1-F	0.1 2-F	1.0 3-F	4.0 4-F (mg base/kg/day)
DAY 279	MEAN	10.6	12.5	10.4	10.4
	S.D.	1.61	2.36	1.97	1.04
	N	4	4	4	4
DAY 286	MEAN	10.5	12.6	10.2	10.5
	S.D.	1.60	2.35	1.74	0.95
	N	4	4	4	4
DAY 293	MEAN	10.5	12.6	10.3	10.4
	S.D.	1.71	2.43	1.92	0.87
	N	4	4	4	4
DAY 300	MEAN	10.4	12.7	10.4	10.4
	S.D.	1.78	2.47	1.81	0.99
	N	4	4	4	4
DAY 307	MEAN	10.6	12.7	10.6	10.4
	S.O.	1.84	2.37	2.25	1.15
	N	4	4	4	4
DAY 314	MEAN	10.3	12.8	10.5	10.5
	S.D.	2.06	2.42	2.13	1.03
	N	4	4	4	4
DAY 321	MEAN	10.5	13.0	10.8	10.6
	S.D.	2.16	2.70	2.52	1.01
	N	4	4	4	4
DAY 328	MEAN	10.6	13.1	11.0	10.6
	S.D.	2.27	2.67	2.52	1.07
	N	4	4	4	4
DAY 335	MEAN	10.6	13.2	10.8	10.6
	S.O.	2.31	2.48	2.45	1.08
	N	4	4	4	4
DAY 342	MEAN	10.3	13.1	10.8	10.5
	S.D.	2.25	2.15	2.17	0.97
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

Table 4.12

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 219

SEX: FEMALE

PERIOD	DOSE: GROUP:	0	0.1	1.0	4.0	(mg base/kg/day)
		1-F	2-F	3-F	4-F	
DAY 349	MEAN	10.4	13.0	10.7	10.5	
	S.D.	2.45	2.22	2.35	1.04	
	N	4	4	4	4	
DAY 356	MEAN	10.4	13.2	10.7	10.6	
	S.D.	2.17	2.22	2.54	0.87	
	N	4	4	4	4	
DAY 363	MEAN	10.4	13.1	10.6	10.5	
	S.D.	2.19	2.16	2.31	0.77	
	N	4	4	4	4	

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

Table 5.1

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS**DRAFT**

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 219

SEX: MALE

PERIOD ^a	DOSE: GROUP:	(mg base/kg/day)			
		0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
DAY 6 ^b	MEAN	-0.1	-0.3	-0.2	-0.2
	S.D.	0.12	0.13	0.21	0.22
	N	4	4	4	4
DAY 13	MEAN	0.1	-0.1	-0.1	-0.1
	S.D.	0.13	0.21	0.19	0.10
	N	4	4	4	4
DAY 20	MEAN	0.1	0.0	-0.1	-0.1
	S.D.	0.13	0.33	0.17	0.13
	N	4	4	4	4
DAY 27	MEAN	-0.1	-0.3	-0.2	-0.2
	S.D.	0.10	0.33	0.15	0.05
	N	4	4	4	4
DAY 34	MEAN	0.2	0.1	0.0	0.1
	S.D.	0.08	0.22	0.12	0.20
	N	4	4	4	4
DAY 41	MEAN	-0.1	-0.2	-0.1	0.0
	S.D.	0.08	0.13	0.06	0.10
	N	4	4	4	4
DAY 48	MEAN	0.1	0.0	-0.1	0.1
	S.D.	0.10	0.17	0.13	0.06
	N	4	4	4	4
DAY 55	MEAN	0.2	0.2	0.3	0.1
	S.D.	0.25	0.14	0.10	0.06
	N	4	4	4	4
DAY 62	MEAN	0.0	0.0	0.0	0.1
	S.D.	0.13	0.08	0.10	0.13
	N	4	4	4	4
DAY 69	MEAN	0.2	0.0	0.1	0.1
	S.D.	0.21	0.13	0.05	0.05
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aWeight gains compared to the previous period
^bBaseline is Day -2

Table 5.2

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 219		SEX: MALE			
PERIOD ^a	DOSE: GROUP:	0 1-M	0.1 2-M	1.0 3-M	4.0 4-M (mg base/kg/day)
DAY 76	MEAN	-0.1	0.1	0.2	0.1
	S.D.	0.22	0.12	0.17	0.14
	N	4	4	4	4
DAY 83	MEAN	0.1	0.3	0.0	0.0
	S.D.	0.10	0.21	0.08	0.00
	N	4	4	4	4
DAY 90	MEAN	-0.1	-0.2	-0.2	-0.2
	S.D.	0.17	0.27	0.13	0.10
	N	4	4	4	4
DAY 97	MEAN	-0.1	-0.1	0.1	-0.2
	S.D.	0.10	0.26	0.08	0.19
	N	4	4	4	4
DAY 104	MEAN	0.1	0.2	0.0	0.2
	S.D.	0.00	0.00	0.10	0.10
	N	4	4	4	4
DAY 111	MEAN	0.0	0.0	-0.1	-0.1
	S.D.	0.05	0.14	0.10	0.08
	N	4	4	4	4
DAY 118	MEAN	0.2	0.0	-0.1	-0.2
	S.D.	0.17	0.18	0.21	0.24
	N	4	4	4	4
DAY 125	MEAN	-0.2	-0.1	-0.1	-0.1
	S.D.	0.19	0.25	0.13	0.12
	N	4	4	4	4
DAY 132	MEAN	0.1	0.1	-0.2	-0.1
	S.D.	0.21	0.12	0.13	0.10
	N	4	4	4	4
DAY 139	MEAN	0.2	0.1	0.2	0.1
	S.D.	0.10	0.13	0.21	0.19
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aWeight gains compared to the previous period

Table 5.3

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 219

SEX: MALE

PERIOD ^a	DOSE: GROUP:	(mg base/kg/day)			
		0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
DAY 146	MEAN	0.1	0.1	0.1	-0.1
	S.D.	0.08	0.21	0.19	0.10
	N	4	4	4	4
DAY 153	MEAN	0.1	0.1	0.0	0.1
	S.D.	0.12	0.13	0.18	0.06
	N	4	4	4	4
DAY 160	MEAN	0.0	0.1	-0.1	0.0
	S.D.	0.17	0.10	0.05	0.15
	N	4	4	4	4
DAY 167	MEAN	0.5	0.4	0.6	0.3
	S.D.	0.24	0.10	0.10	0.25
	N	4	4	4	4
DAY 174	MEAN	-0.5	-0.3	-0.3	-0.5
	S.D.	0.19	0.05	0.15	0.25
	N	4	4	4	4
DAY 181	MEAN	0.1	-0.1	-0.2	-0.1
	S.D.	0.19	0.30	0.08	0.24
	N	4	4	4	4
DAY 188	MEAN	-0.1	0.2	0.1	0.1
	S.D.	0.17	0.05	0.13	0.17
	N	4	4	4	4
DAY 195	MEAN	-0.1	-0.2	-0.6	-0.1
	S.D.	0.26	0.33	1.27	0.32
	N	4	4	4	4
DAY 202	MEAN	0.0	0.2	0.7	0.1
	S.D.	0.16	0.18	1.16	0.15
	N	4	4	4	4
DAY 209	MEAN	0.0	0.0	-0.1	0.0
	S.D.	0.10	0.13	0.10	0.13
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aWeight gains compared to the previous period

Table 5.4

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 219		SEX: MALE			
PERIOD ^a	DOSE: GROUP:	0 1-M	0.1 2-M	1.0 3-M	4.0 4-M (mg base/kg/day)
DAY 216	MEAN	0.1	0.1	0.1	0.1
	S.D.	0.21	0.13	0.05	0.05
	N	4	4	4	4
DAY 223	MEAN	0.0	-0.1	0.0	0.0
	S.D.	0.27	0.22	0.05	0.05
	N	4	4	4	4
DAY 230	MEAN	-0.1	-0.1	-0.3	0.0
	S.D.	0.18	0.22	0.37	0.19
	N	4	4	4	4
DAY 237	MEAN	0.1	0.2	0.3	0.0
	S.D.	0.35	0.36	0.39	0.35
	N	4	4	4	4
DAY 244	MEAN	0.5	0.3	0.2	0.2
	S.D.	0.31	0.10	0.22	0.19
	N	4	4	4	4
DAY 251	MEAN	-0.1	0.1	-0.1	-0.1
	S.D.	0.22	0.22	0.34	0.15
	N	4	4	4	4
DAY 258	MEAN	0.0	0.0	0.2	0.2
	S.D.	0.05	0.10	0.31	0.13
	N	4	4	4	4
DAY 265	MEAN	0.1	0.2	0.1	0.2
	S.D.	0.13	0.24	0.17	0.21
	N	4	4	4	4
DAY 272	MEAN	0.6	0.4	0.5	0.4
	S.D.	0.34	0.21	0.42	0.28
	N	4	4	4	4
DAY 279	MEAN	-0.2	-0.2	-0.4	-0.3
	S.D.	0.21	0.40	0.21	0.24
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aWeight gains compared to the previous period

Table 5.5

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 219

SEX: MALE

PERIOD ^a	DOSE: GROUP:	(mg base/kg/day)			
		0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
DAY 286	MEAN	-0.2	-0.2	-0.1	0.0
	S.D.	0.24	0.29	0.21	0.13
	N	4	4	4	4
DAY 293	MEAN	-0.1	-0.2	-0.2	-0.1
	S.D.	0.06	0.16	0.24	0.13
	N	4	4	4	4
DAY 300	MEAN	-0.1	D.1	-0.1	0.0
	S.D.	D.06	D.21	D.17	D.15
	N	4	4	4	4
DAY 307	MEAN	0.2	D.2	0.2	0.1
	S.D.	0.24	0.13	0.13	0.05
	N	4	4	4	4
DAY 314	MEAN	0.1	0.0	-0.2	0.0
	S.D.	0.17	0.17	0.31	D.14
	N	4	4	4	4
DAY 321	MEAN	0.4	0.1	0.3	0.2
	S.D.	0.22	0.20	0.05	0.17
	N	4	4	4	4
DAY 328	MEAN	-0.1	0.1	0.0	0.2
	S.D.	0.21	0.14	0.17	0.19
	N	4	4	4	4
DAY 335	MEAN	0.0	0.0	0.1	-0.1
	S.D.	D.17	0.20	0.24	0.15
	N	4	4	4	4
DAY 342	MEAN	0.0	-0.1	-0.2	-0.1
	S.D.	0.17	0.32	0.13	0.12
	N	4	4	4	4
DAY 349	MEAN	0.1	0.1	0.0	0.0
	S.D.	0.16	0.10	0.15	0.18
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aWeight gains compared to the previous period

Table 5.6

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 219		SEX: MALE			
PERIOD ^a	DOSE:	0	0.1	1.0	4.0 (mg base/kg/day)
	GROUP:	1-M	2-M	3-M	4-M
DAY 356	MEAN	0.3	0.1	0.2	0.1
	S.D.	0.19	0.15	0.22	0.14
	N	4	4	4	4
DAY 363	MEAN	-0.5	-0.3	-0.3	-0.3
	S.D.	0.13	0.25	0.26	0.17
	N	4	4	4	4
TOTAL GAIN	MEAN	1.8	1.2	0.3	0.1*
	S.D.	0.57	0.85	1.07	0.61
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aWeight gains compared to the previous period

Table 5.7

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 219

SEX: FEMALE

PERIOD ^a	DOSE: GROUP:	(mg base/kg/day)			
		0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
DAY 6 ^b	MEAN	-0.1	0.3	-0.1	-0.1
	S.D.	0.06	0.24	0.25	0.14
	N	4	4	4	4
DAY 13	MEAN	-0.1	0.0	0.0	0.3*
	S.D.	0.13	0.16	0.13	0.15
	N	4	4	4	4
DAY 20	MEAN	0.3	0.0	-0.1	-0.1
	S.D.	0.26	0.17	0.19	0.21
	N	4	4	4	4
DAY 27	MEAN	-0.1	-0.1	-0.3	-0.2
	S.D.	0.12	0.08	0.14	0.06
	N	4	4	4	4
DAY 34	MEAN	0.4	0.2	0.2	0.1*
	S.D.	0.10	0.10	0.16	0.15
	N	4	4	4	4
DAY 41	MEAN	-0.2	-0.1	-0.2	-0.1
	S.D.	0.19	0.17	0.17	0.17
	N	4	4	4	4
DAY 48	MEAN	0.1	0.2	0.0	0.2
	S.D.	0.13	0.10	0.13	0.18
	N	4	4	4	4
DAY 55	MEAN	0.3	0.3	0.2	0.2
	S.D.	0.19	0.13	0.13	0.13
	N	4	4	4	4
DAY 62	MEAN	-0.1	0.0	0.1	0.0
	S.D.	0.10	0.08	0.17	0.05
	N	4	4	4	4
DAY 69	MEAN	0.1	0.2	0.0	0.2
	S.D.	0.24	0.21	0.05	0.10
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aWeight gains compared to the previous period^bBaseline is Day -2

Table 5.8

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF WEIGHT GAINS (kilograms)

STUDY: 219		SEX: FEMALE			
PERIOD ^a	DOSE: GROUP:	0 1-F	0.1 2-F	1.0 3-F	4.0 4-F (mg base/kg/day)
DAY 76	MEAN	-0.1	0.1	0.1	-0.1
	S.O.	0.10	0.16	0.08	0.17
	N	4	4	4	4
DAY 83	MEAN	0.0	0.4	-0.2	0.1
	S.O.	0.13	0.17	0.34	0.10
	N	4	4	4	4
DAY 90	MEAN	-0.2	-0.1	-0.2	-0.1
	S.D.	0.22	0.05	0.17	0.13
	N	4	4	4	4
DAY 97	MEAN	-0.1	0.0	-0.1	-0.1
	S.O.	0.22	0.16	0.14	0.22
	N	4	4	4	4
DAY 104	MEAN	-0.1	0.2	0.2	0.0
	S.O.	0.13	0.06	0.10	0.14
	N	4	4	4	4
DAY 111	MEAN	-0.1	0.0	0.1	-0.1
	S.O.	0.22	0.12	0.10	0.05
	N	4	4	4	4
DAY 118	MEAN	0.2	0.0	0.0	0.0
	S.O.	0.13	0.14	0.17	0.05
	N	4	4	4	4
DAY 125	MEAN	0.0	-0.1	-0.1	0.0
	S.O.	0.05	0.13	0.13	0.12
	N	4	4	4	4
DAY 132	MEAN	-0.1	0.1	0.2	-0.1
	S.D.	0.05	0.22	0.29	0.15
	N	4	4	4	4
DAY 139	MEAN	0.1	0.2	0.2	0.2
	S.O.	0.14	0.15	0.17	0.17
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aWeight gains compared to the previous period

Table 5.9

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS**DRAFT**

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 219

SEX: FEMALE

PERIOD ^a	DOSE: GROUP:	(mg base/kg/day)			
		0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
DAY 146	MEAN	0.1	0.1	0.1	0.0
	S.D.	0.10	0.17	0.17	0.14
	N	4	4	4	4
DAY 153	MEAN	0.0	0.1	-0.1	0.1
	S.D.	0.05	0.24	0.13	0.17
	N	4	4	4	4
DAY 160	MEAN	0.1	-0.4	-0.1	-0.1
	S.D.	0.17	0.37	0.06	0.21
	N	4	4	4	4
DAY 167	MEAN	0.3	0.4	0.4	0.2
	S.D.	0.17	0.28	0.36	0.32
	N	4	4	4	4
DAY 174	MEAN	-0.2	-0.2	-0.2	0.0
	S.D.	0.05	0.16	0.33	0.32
	N	4	4	4	4
DAY 181	MEAN	-0.1	0.1	-0.2	-0.2
	S.D.	0.10	0.25	0.33	0.22
	N	4	4	4	4
DAY 188	MEAN	-0.1	-0.1	0.1	0.1
	S.D.	0.06	0.17	0.15	0.06
	N	4	4	4	4
DAY 195	MEAN	0.1	0.1	0.3	-0.1
	S.D.	0.10	0.05	1.00	0.06
	N	4	4	4	4
DAY 202	MEAN	0.1	0.1	-0.3	0.3
	S.D.	0.00	0.06	1.14	0.22
	N	4	4	4	4
DAY 209	MEAN	0.1	-0.1	-0.1	-0.1
	S.D.	0.08	0.13	0.10	0.22
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aWeight gains compared to the previous period

Table 5.10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS**DRAFT**

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 219

SEX: FEMALE

PERIOD ^a	DOSE: GROUP:	(mg base/kg/day)			
		0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
DAY 216	MEAN	0.1	0.2	0.1	0.2
	S.D.	0.13	0.05	0.10	0.26
	N	4	4	4	4
DAY 223	MEAN	0.1	-0.1	0.1	0.1
	S.D.	0.06	0.21	0.10	0.13
	N	4	4	4	4
DAY 230	MEAN	0.0	0.1	0.1	0.0
	S.D.	0.13	0.06	0.17	0.21
	N	4	4	4	4
DAY 237	MEAN	-0.3	0.2	0.1	-0.1
	S.D.	0.26	0.17	0.40	0.17
	N	4	4	4	4
DAY 244	MEAN	0.3	0.2	0.3	0.4
	S.D.	0.37	0.24	0.24	0.10
	N	4	4	4	4
DAY 251	MEAN	-0.2	0.2*	-0.1	-0.2
	S.D.	0.23	0.10	0.10	0.17
	N	4	4	4	4
DAY 258	MEAN	0.3	0.1	0.0	0.1
	S.D.	0.21	0.22	0.15	0.19
	N	4	4	4	4
DAY 265	MEAN	0.1	0.2	0.2	-0.1
	S.D.	0.17	0.06	0.36	0.13
	N	4	4	4	4
DAY 272	MEAN	0.4	0.4	0.5	0.4
	S.D.	0.22	0.39	0.21	0.13
	N	4	4	4	4
DAY 279	MEAN	-0.2	-0.2	-0.2	-0.3
	S.D.	0.13	0.26	0.35	0.15
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aWeight gains compared to the previous period

Table 5.11

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF WEIGHT GAINS (kilograms)

STUDY: 219

SEX: FEMALE

PERIOD ^a	DOSE: GROUP:	(mg base/kg/day)			
		0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
DAY 286	MEAN	-0.1	0.1	-0.2	0.1
	S.D.	0.10	0.08	0.44	0.12
	N	4	4	4	4
DAY 293	MEAN	0.0	0.0	0.1	-0.1
	S.D.	0.13	0.14	0.21	0.10
	N	4	4	4	4
DAY 300	MEAN	-0.1	0.1	0.2	0.0
	S.D.	0.13	0.10	0.13	0.14
	N	4	4	4	4
DAY 307	MEAN	0.2	0.0	0.2	0.0
	S.D.	0.30	0.17	0.46	0.22
	N	4	4	4	4
DAY 314	MEAN	-0.2	0.1	-0.1	0.2
	S.D.	0.26	0.24	0.24	0.25
	N	4	4	4	4
DAY 321	MEAN	0.2	0.2	0.3	0.1
	S.D.	0.12	0.43	0.45	0.10
	N	4	4	4	4
DAY 328	MEAN	0.1	0.1	0.2	0.0
	S.D.	0.15	0.13	0.14	0.14
	N	4	4	4	4
DAY 335	MEAN	-0.1	0.1	-0.2	0.0
	S.D.	0.19	0.32	0.12	0.10
	N	4	4	4	4
DAY 342	MEAN	-0.3	-0.1	-0.1	-0.2
	S.D.	0.10	0.34	0.30	0.13
	N	4	4	4	4
DAY 349	MEAN	0.1	-0.1	-0.1	0.1
	S.D.	0.22	0.15	0.24	0.13
	N	4	4	4	4

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aWeight gains compared to the previous period

Table 5.11

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 219

SEX: FEMALE

PERIOD ^a	DOSE: GROUP:	0	0.1	1.0	4.0	(mg base/kg/day)
		1-F	2-F	3-F	4-F	
DAY 356	MEAN	0.0	0.2	0.0	0.1	
	S.D.	0.29	0.17	0.19	0.17	
	N	4	4	4	4	
DAY 363	MEAN	0.0	-0.1	-0.2	-0.1	
	S.D.	0.13	0.08	0.24	0.17	
	N	4	4	4	4	
TOTAL GAIN	MEAN	0.8	3.4*	1.0	1.0	
	S.D.	0.79	1.46	1.73	0.46	
	N	4	4	4	4	

* P less than .05

Analysis of Variance using DUNNETT'S Procedure

^aWeight gains compared to the previous period

Table 6.1

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 219

SEX: MALE

PERIOD	DOSE: GROUP:	(mg base/kg/day)			
		0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
DAY -15	INTAKE (g)	388	284	365	318
	S.D.	18.9	131.1	25.3	75.4
	N	4	4	4	4
DAY -9	INTAKE (g)	400	392	348	400
	S.D.	0.0	16.5	104.5	0.0
	N	4	4	4	4
DAY 7	INTAKE (g)	373	385	370	400
	S.D.	54.5	30.5	59.5	0.0
	N	4	4	4	4
DAY 14	INTAKE (g)	400	400	400	400
	S.D.	0.0	0.0	0.0	0.0
	N	4	4	4	4
DAY 21	INTAKE (g)	400	400	396	400
	S.D.	0.0	0.0	8.0	0.0
	N	4	4	4	4
DAY 28	INTAKE (g)	400	400	394	400
	S.D.	0.0	0.0	12.5	0.0
	N	4	4	4	4
DAY 35	INTAKE (g)	400	400	400	400
	S.D.	0.0	0.0	0.0	0.0
	N	4	4	4	4
DAY 42	INTAKE (g)	400	400	400	400
	S.D.	0.0	0.0	0.0	0.0
	N	4	4	4	4

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

Table 6.2

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 219

SEX: MALE

PERIOD	DOSE: GROUP:	DOSE:				(mg base/kg/day)
		0 1-M	0.1 2-M	1.0 3-M	4.0 4-M	
DAY 49	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 56	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 63	INTAKE (g)	400	400	382	400	
	S.D.	0.0	0.0	35.5	0.0	
	N	4	4	4	4	
DAY 70	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 77	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 84	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 91	INTAKE (g)	400	400	384	400	
	S.D.	0.0	0.0	31.5	0.0	
	N	4	4	4	4	
DAY 98	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	

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

Table 6.3

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 219

SEX: MALE

PERIOD	DOSE: GROUP:	0	0.1	1.0	4.0	(mg base/kg/day)
		1-M	2-M	3-M	4-M	
DAY 105	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 112	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 119	INTAKE (g)	400	400	396	400	
	S.D.	0.0	0.0	7.5	0.0	
	N	4	4	4	4	
DAY 126	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 133	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 140	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 147	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 154	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	

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

Table 6.4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 219

SEX: MALE

PERIOD	DOSE: GROUP:	0	0.1	1.0	4.0	(mg base/kg/day)
		1-M	2-M	3-M	4-M	
DAY 161	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 169	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 175	INTAKE (g)	400	400	379	400	
	S.D.	0.0	0.0	43.0	0.0	
	N	4	4	4	4	
DAY 182	INTAKE (g)	400	400	383	400	
	S.D.	0.0	0.0	33.5	0.0	
	N	4	4	4	4	
DAY 189	INTAKE (g)	400	400	375	400	
	S.D.	0.0	0.0	49.5	0.0	
	N	4	4	4	4	
DAY 196	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 203	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 210	INTAKE (g)	400	391	400	400	
	S.D.	0.0	19.0	0.0	0.0	
	N	4	4	4	4	

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

Table 6.5

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 219

SEX: MALE

PERIOD	DOSE: GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
		(mg base/kg/day)			
DAY 217	INTAKE (g)	338	400	400	400
	S.D.	125.0	0.0	0.0	0.0
	N	4	4	4	4
DAY 224	INTAKE (g)	400	400	400	400
	S.D.	0.0	0.0	0.0	0.0
	N	4	4	4	4
DAY 231	INTAKE (g)	400	400	400	400
	S.D.	0.0	0.0	0.0	0.0
	N	4	4	4	4
DAY 238	INTAKE (g)	400	400	400	400
	S.D.	0.0	0.0	0.0	0.0
	N	4	4	4	4
DAY 245	INTAKE (g)	400	400	400	400
	S.D.	0.0	0.0	0.0	0.0
	N	4	4	4	4
DAY 252	INTAKE (g)	400	400	400	400
	S.D.	0.0	0.0	0.0	0.0
	N	4	4	4	4
DAY 259	INTAKE (g)	400	400	400	400
	S.D.	0.0	0.0	0.0	0.0
	N	4	4	4	4
DAY 266	INTAKE (g)	400	400	400	400
	S.D.	0.0	0.0	0.0	0.0
	N	4	4	4	4

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

Table 6.6

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 219

SEX: MALE

PERIOD	DOSE: GROUP:	0 1-M	0.1 2-M	1.0 3-M	4.0 4-M	(mg base/kg/day)
DAY 273	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 280	INTAKE (g)	400	400	359	400	
	S.D.	0.0	0.0	83.0	0.0	
	N	4	4	4	4	
DAY 287	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 294	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 301	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 308	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 315	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 322	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	

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

Table 6.7

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 219

SEX: MALE

PERIOD	DOSE: GROUP:	0	0.1	1.0	4.0	(mg base/kg/day)
		1-M	2-M	3-M	4-M	
DAY 329	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 336	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 343	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 350	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 357	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	
DAY 364	INTAKE (g)	400	400	400	400	
	S.D.	0.0	0.0	0.0	0.0	
	N	4	4	4	4	

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

Table 6.8

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 219

SEX: FEMALE

PERIOD	DOSE: GROUP:	(mg base/kg/day)			
		0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
DAY -15	INTAKE (g)	259	197	339	321
	S.D.	88.0	126.7	78.8	59.0
	N	4	4	4	4
DAY -9	INTAKE (g)	282	311	298	316
	S.D.	96.2	39.1	142.8	80.6
	N	4	4	4	4
DAY 7	INTAKE (g)	394	400	397	339
	S.D.	12.5	0.0	5.5	74.4
	N	4	4	4	4
DAY 14	INTAKE (g)	396	256	337	342
	S.D.	8.0	96.8	102.3	80.6
	N	4	4	4	4
DAY 21	INTAKE (g)	399	346	367	344
	S.D.	2.5	64.8	66.0	94.4
	N	4	4	4	4
DAY 28	INTAKE (g)	400	356	374	362
	S.D.	0.0	60.8	45.5	46.4
	N	4	4	4	4
DAY 35	INTAKE (g)	400	370	370	366
	S.D.	0.0	61.0	59.5	69.0
	N	4	4	4	4
DAY 42	INTAKE (g)	400	382	369	400
	S.D.	0.0	36.0	35.8	0.0
	N	4	4	4	4

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

Table 6.9

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 219

SEX: FEMALE

PERIOD	DOSE: GROUP:	0	0.1	1.0	4.0	(mg base/kg/day)
		1-F	2-F	3-F	4-F	
DAY 49	INTAKE (g)	400	384	396	400	
	S.D.	0.0	32.0	8.0	0.0	
	N	4	4	4	4	
DAY 56	INTAKE (g)	400	364	400	367	
	S.D.	0.0	73.0	0.0	40.1	
	N	4	4	4	4	
DAY 63	INTAKE (g)	400	327	400	400	
	S.D.	0.0	84.9	0.0	0.0	
	N	4	4	4	4	
DAY 70	INTAKE (g)	400	294	400	346	
	S.D.	0.0	123.0	0.0	86.8	
	N	4	4	4	4	
DAY 77	INTAKE (g)	400	326	392	358	
	S.D.	0.0	90.5	16.0	84.5	
	N	4	4	4	4	
DAY 84	INTAKE (g)	400	393	400	372	
	S.D.	0.0	15.0	0.0	57.0	
	N	4	4	4	4	
DAY 91	INTAKE (g)	400	400	400	362	
	S.D.	0.0	0.0	0.0	75.5	
	N	4	4	4	4	
DAY 98	INTAKE (g)	400	387	400	353	
	S.D.	0.0	26.5	0.0	94.5	
	N	4	4	4	4	

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

Table 6.10

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 219

SEX: FEMALE

PERIOD	DOSE: GROUP:	(mg base/kg/day)			
		0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
DAY 105	INTAKE (g)	400	400	400	339
	S.D.	0.0	0.0	0.0	121.5
	N	4	4	4	4
DAY 112	INTAKE (g)	400	389	400	353
	S.D.	0.0	22.0	0.0	94.0
	N	4	4	4	4
DAY 119	INTAKE (g)	400	386	400	386
	S.D.	0.0	29.0	0.0	28.5
	N	4	4	4	4
DAY 126	INTAKE (g)	400	400	400	400
	S.D.	0.0	0.0	0.0	0.0
	N	4	4	4	4
DAY 133	INTAKE (g)	400	400	400	380
	S.D.	0.0	0.0	0.0	40.5
	N	4	4	4	4
DAY 140	INTAKE (g)	400	369	400	400
	S.D.	0.0	62.5	0.0	0.0
	N	4	4	4	4
DAY 147	INTAKE (g)	400	365	400	400
	S.D.	0.0	71.0	0.0	0.0
	N	4	4	4	4
DAY 154	INTAKE (g)	400	304	400	400
	S.D.	0.0	114.1	0.0	0.0
	N	4	4	4	4

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

Table 6.11

DRAFTONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 219

SEX: FEMALE

PERIOD	DOSE: GROUP:	(mg base/kg/day)			
		0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
DAY 161	INTAKE (g)	400	360	400	400
	S.D.	0.0	46.8	0.0	0.0
	N	4	4	4	4
DAY 169	INTAKE (g)	400	369	400	400
	S.D.	0.0	61.5	0.0	0.0
	N	4	4	4	4
DAY 175	INTAKE (g)	400	275	400	354
	S.D.	0.0	162.4	0.0	92.5
	N	4	4	4	4
DAY 182	INTAKE (g)	400	353	400	400
	S.D.	0.0	94.5	0.0	0.0
	N	4	4	4	4
DAY 189	INTAKE (g)	400	400	400	400
	S.D.	0.0	0.0	0.0	0.0
	N	4	4	4	4
DAY 196	INTAKE (g)	400	366	370	400
	S.D.	0.0	68.0	59.5	0.0
	N	4	4	4	4
DAY 203	INTAKE (g)	400	357	347	400
	S.D.	0.0	85.5	105.5	0.0
	N	4	4	4	4
DAY 210	INTAKE (g)	400	400	400	400
	S.D.	0.0	0.0	0.0	0.0
	N	4	4	4	4

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

Table 6.12

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 219

SEX: FEMALE

PERIOD	DOSE: GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F (mg base/kg/day)
DAY 217	INTAKE (g)	400	394	365	382
	S.D.	0.0	12.5	71.0	37.0
	N	4	4	4	4
DAY 224	INTAKE (g)	400	366	383	365
	S.D.	0.0	69.0	34.5	70.0
	N	4	4	4	4
DAY 231	INTAKE (g)	400	361	375	382
	S.D.	0.0	79.0	50.5	36.5
	N	4	4	4	4
DAY 238	INTAKE (g)	400	400	400	400
	S.D.	0.0	0.0	0.0	0.0
	N	4	4	4	4
DAY 245	INTAKE (g)	400	380	336	393
	S.D.	0.0	39.5	128.0	13.5
	N	4	4	4	4
DAY 252	INTAKE (g)	400	382	400	388
	S.D.	0.0	35.5	0.0	25.0
	N	4	4	4	4
DAY 259	INTAKE (g)	400	379	400	319
	S.D.	0.0	42.5	0.0	162.0
	N	4	4	4	4
DAY 266	INTAKE (g)	400	330	400	354
	S.D.	0.0	140.5	0.0	92.0
	N	4	4	4	4

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

Table 6.13

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 219

SEX: FEMALE

PERIOD	DOSE: GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F (mg base/kg/day)
DAY 273	INTAKE (g)	400	313	400	400
	S.D.	0.0	174.0	0.0	0.0
	N	4	4	4	4
DAY 280	INTAKE (g)	400	347	345	357
	S.D.	0.0	106.0	111.0	86.5
	N	4	4	4	4
DAY 287	INTAKE (g)	367	330	400	360
	S.D.	66.0	141.0	0.0	79.5
	N	4	4	4	4
DAY 294	INTAKE (g)	400	370	400	335
	S.D.	0.0	60.5	0.0	129.5
	N	4	4	4	4
DAY 301	INTAKE (g)	400	400	400	347
	S.D.	0.0	0.0	0.0	107.0
	N	4	4	4	4
DAY 308	INTAKE (g)	400	356	400	400
	S.D.	0.0	88.5	0.0	0.0
	N	4	4	4	4
DAY 315	INTAKE (g)	346	400	400	400
	S.D.	108.5	0.0	0.0	0.0
	N	4	4	4	4
DAY 322	INTAKE (g)	344	372	400	400
	S.D.	112.5	57.0	0.0	0.0
	N	4	4	4	4

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

Table 6.14

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 219

SEX: FEMALE

PERIOD	DOSE: GROUP:	4.0 (mg base/kg/day)			
		0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
DAY 329	INTAKE (g)	362	342	400	367
	S.D.	76.0	117.0	0.0	66.5
	N	4	4	4	4
DAY 336	INTAKE (g)	400	374	400	400
	S.D.	0.0	51.5	0.0	0.0
	N	4	4	4	4
DAY 343	INTAKE (g)	400	400	400	400
	S.D.	0.0	0.0	0.0	0.0
	N	4	4	4	4
DAY 350	INTAKE (g)	400	400	400	400
	S.D.	0.0	0.0	0.0	0.0
	N	4	4	4	4
DAY 357	INTAKE (g)	400	400	400	363
	S.D.	0.0	0.0	0.0	74.0
	N	4	4	4	4
DAY 364	INTAKE (g)	400	323	367	383
	S.D.	0.0	155.0	66.0	35.0
	N	4	4	4	4

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

Table 7.1

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	ALT	AST	TP	ALB	GLOB	A/G	TBILI	ALKP	GGT
UNITS:	IU/L	IU/L	g/dL	g/dL	g/dL	-	mg/dL	IU/L	IU/L
Group: 1-M : 0 mg base/kg/day									
MEAN	45	33	6.6	3.5	3.1	1.15	0.13	116	5.0
SD	14.5	8.1	0.29	0.29	0.06	0.103	0.005	15.0	1.43
N	4	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day									
MEAN	31	27	6.7	3.5	3.2	1.10	0.13	98	6.0
SD	5.1	6.1	0.54	0.32	0.33	0.118	0.021	21.9	0.91
N	4	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day									
MEAN	33	28	6.7	3.5	3.2	1.12	0.11	107	4.4
SD	3.5	3.2	0.39	0.29	0.30	0.150	0.010	13.0	1.34
N	4	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day									
MEAN	44	29	6.5	3.3	3.1	1.07	0.13	158*	5.8
SD	12.2	2.8	0.13	0.17	0.10	0.082	0.013	22.6	1.38
N	4	4	4	4	4	4	4	4	4

*-Significant Difference from Control P < .05

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L	K mEq/L	CL mEq/L
Group: 1-M : 0 mg base/kg/day									
MEAN	231	52	69	276	12.0	0.70	146	4.64	113.5
SD	49.0	7.8	66.9	90.9	2.73	0.133	1.3	0.176	2.43
N	4	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day									
MEAN	241	45	37	246	11.4	0.71	145	4.55	113.0
SD	58.0	16.5	14.3	113.4	3.69	0.065	1.9	0.151	2.00
N	4	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day									
MEAN	259	56	51	212	15.1	0.72	145	4.52	114.3
SD	33.7	19.6	12.3	38.8	2.50	0.024	2.5	0.095	1.52
N	4	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day									
MEAN	247	50	43	295	14.8	0.69	146	4.51	113.5
SD	64.4	15.6	7.1	64.4	2.18	0.036	1.7	0.133	3.13
N	4	4	4	4	4	4	4	4	4

Table 7.3

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(S):	CA	IP	GLU	HAPT
UNITS:	mg/dL	mg/dL	mg/dL	mg/dL
Group: 1-M : 0 mg base/kg/day				
MEAN	11.0	6.5	121	46.3
SD	0.34	1.12	3.1	5.37
N	4	4	4	2
Group: 2-M : 0.1 mg base/kg/day				
MEAN	11.2	6.5	118	63.7
SD	0.33	0.39	4.6	28.12
N	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day				
MEAN	11.1	7.0	111*	49.4
SD	0.32	0.67	4.6	26.65
N	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day				
MEAN	10.9	6.6	113	62.3
SD	0.29	1.08	5.4	13.51
N	4	4	4	3

*-Significant Difference from Control P < .05

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	ALT	AST	TP	ALB	GLOB	A/G	TBILI	ALKP	GGT
UNITS:	IU/L	IU/L	g/dL	g/dL	g/dL	-	mg/dL	IU/L	IU/L
Group: 1-M : 0 mg base/kg/day									
MEAN	41	45	6.1	3.2	2.9	1.13	0.14	115	4.5
SD	12.1	13.3	0.17	0.13	0.06	0.032	0.031	15.6	1.29
N	4	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day									
MEAN	30	31	6.3	3.5*	2.8	1.28	0.14	97	4.6
SD	2.6	1.7	0.18	0.10	0.19	0.111	0.019	25.7	1.07
N	4	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day									
MEAN	36	36	6.3	3.5*	2.8	1.28	0.13	112	4.9
SD	7.8	6.8	0.36	0.13	0.29	0.122	0.021	13.0	0.66
N	4	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day									
MEAN	28	37	6.2	3.3	2.9	1.12	0.14	159*	5.8
SD	5.6	6.1	0.26	0.15	0.13	0.034	0.024	30.7	1.30
N	4	4	4	4	4	4	4	4	4

*-Significant Difference from Control P < .05

Table 7.5

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L	K mEq/L	CL mEq/L
Group: 1-M : 0 mg base/kg/day									
MEAN	184	54	90	429	12.0	0.69	145	4.64	111.0
SD	21.3	3.2	42.5	211.3	3.92	0.130	1.5	0.687	4.07
N	4	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day									
MEAN	177	50	45	245	10.4	0.68	145	4.38	110.5
SD	24.3	14.0	7.8	38.2	2.33	0.037	1.3	0.128	5.03
N	4	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day									
MEAN	202	61	66	298	10.7	0.69	145	4.40	113.4
SD	26.2	11.6	16.1	87.6	1.79	0.029	0.5	0.241	4.36
N	4	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day									
MEAN	170	52	61	265	13.1	0.66	145	4.45	113.6
SD	22.5	12.5	17.5	23.0	1.49	0.037	0.8	0.168	4.07
N	4	4	4	4	4	4	4	4	4

Table 7.6

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	CA	IP	GLU	HAPT
UNITS:	mg/dL	mg/dL	mg/dL	mg/dL
Group: 1-M : 0 mg base/kg/day				
MEAN	10.6	5.3	125	28.5
SD	0.18	0.87	12.1	13.36
N	4	4	4	2
Group: 2-M : 0.1 mg base/kg/day				
MEAN	10.6	6.2	120	48.6
SD	0.19	0.53	5.9	21.33
N	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day				
MEAN	10.7	6.2	117	38.4
SD	0.31	0.70	10.7	16.93
N	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day				
MEAN	10.5	6.5	118	50.2
SD	0.21	0.38	8.5	20.21
N	4	4	4	4

Table 7.7

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	ALT	AST	TP	ALB	GLOB	A/G	TBILI	ALKP	GGT
UNITS:	IU/L	IU/L	g/dL	g/dL	g/dL	-	mg/dL	IU/L	IU/L
Group: 1-M : 0 mg base/kg/day									
MEAN	36	32	6.2	3.2	3.0	1.10	0.13	104	2.9
SD	10.9	4.5	0.42	0.25	0.26	0.107	0.013	18.9	0.99
N	4	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day									
MEAN	32	31	6.3	3.3	3.0	1.09	0.11	87	4.5
SD	5.3	7.1	0.24	0.06	0.29	0.126	0.024	16.5	1.12
N	4	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day									
MEAN	28	33	6.2	3.3	2.9	1.15	0.12	91	3.8
SD	3.0	5.4	0.26	0.14	0.15	0.049	0.015	9.6	0.73
N	4	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day									
MEAN	26	32	6.2	3.2	3.1	1.05	0.20*	103	3.4
SD	5.0	3.0	0.05	0.17	0.17	0.116	0.054	20.3	2.74
N	4	4	4	4	4	4	4	4	4

*-Significant Difference from Control P < .05

Table 7.8

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	CHOL	TRIG	LDH	CK	BUN	CREAT	NA	K	CL
UNITS:	mg/dL	mg/dL	IU/L	IU/L	mg/dL	mg/dL	mEq/L	mEq/L	mEq/L
Group: 1-M : 0 mg base/kg/day									
MEAN	185	46	64	170	13.1	0.68	145	4.67	111.9
SD	22.0	17.5	54.9	53.9	1.80	0.025	0.8	0.327	2.50
N	4	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day									
MEAN	178	58	42	185	15.3	0.73	146	4.48	112.4
SD	25.5	19.8	22.7	59.7	2.24	0.033	1.5	0.433	1.04
N	4	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day									
MEAN	185	60	53	227	16.9	0.74	145	4.39	113.0
SD	22.0	15.4	11.7	76.5	2.67	0.047	1.0	0.258	2.30
N	4	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day									
MEAN	181	56	75	175	16.4	0.75	145	4.30	113.6
SD	17.2	5.9	20.8	26.4	1.65	0.099	1.4	0.089	3.13
N	4	4	4	4	4	4	4	4	4

Table 7.9

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	CA	IP	GLU	HAPT
UNITS:	mg/dL	mg/dL	mg/dL	mg/dL
Group: 1-M : 0 mg base/kg/day				
MEAN	10.9	6.3	115	59.0
SD	0.26	0.42	4.0	8.89
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	10.8	5.9	112	72.6
SD	0.37	0.46	3.0	31.84
N	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day				
MEAN	10.8	6.1	111	62.1
SD	0.32	0.63	6.9	14.23
N	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day				
MEAN	10.9	5.8	107	118.7*
SD	0.17	0.92	5.1	19.92
N	4	4	4	4

*-Significant Difference from Control P < .05

Table 7.10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	ALT IU/L	AST IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBILI mg/dL	ALKP IU/L	GGT IU/L
Group: 1-M : 0 mg base/kg/day									
MEAN	36	44	6.1	3.3	2.8	1.19	0.17	74	3.7
SD	4.3	12.0	0.28	0.22	0.13	0.083	0.026	11.6	1.39
N	4	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day									
MEAN	38	36	6.2	3.5	2.7	1.27	0.18	71	2.9
SD	8.8	5.0	0.10	0.10	0.17	0.119	0.021	20.8	1.94
N	4	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day									
MEAN	30	40	6.1	3.2	2.8	1.15	0.18	77	0.7
SD	1.7	1.7	0.25	0.10	0.22	0.093	0.014	14.7	0.47
N	4	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day									
MEAN	34	52	6.3	3.1	3.1*	1.00*	0.19	98	2.2
SD	6.0	9.4	0.19	0.05	0.17	0.053	0.021	30.5	1.40
N	4	4	4	4	4	4	4	4	4

*-Significant Difference from Control P < .05

Table 7.11

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 13

STUDY 10: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	CHOL mg/dL	TRIG mg/dL	LOH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L	K mEq/L	CL mEq/L
Group: 1-M : 0 mg base/kg/day									
MEAN	158	36	82	321	17.2	0.78	147	4.10	109.8
SD	16.1	9.5	43.4	218.9	3.91	0.095	1.9	0.141	3.76
N	4	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day									
MEAN	152	42	71	192	16.9	0.77	145	4.28	107.5
SD	20.3	9.7	6.6	53.1	3.26	0.034	1.8	0.308	3.01
N	4	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day									
MEAN	187	52	114	186	19.2	0.86	143	3.97	110.3
SD	42.3	13.0	33.5	24.9	1.86	0.041	0.5	0.250	3.59
N	4	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day									
MEAN	175	69*	121	264	19.9	0.87	145	4.09	110.1
SD	27.2	6.6	44.3	17.4	1.91	0.039	2.4	0.353	2.68
N	4	4	4	4	4	4	4	4	4

*-Significant Difference from Control P < .05

Table 7.12

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	CA	IP	GLU	HAPT
UNITS:	mg/dL	mg/dL	mg/dL	mg/dL
Group: 1-M : 0 mg base/kg/day				
MEAN	10.3	4.7	109	67.3
SD	0.14	0.42	4.0	39.07
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	10.2	4.7	110	56.1
SD	0.18	0.26	4.2	26.78
N	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day				
MEAN	10.0	4.3	106	40.8
SD	0.10	0.74	7.4	13.93
N	4	4	4	2
Group: 4-M : 4.0 mg base/kg/day				
MEAN	9.9	4.5	97*	109.2
SD	0.36	0.80	6.1	49.90
N	4	4	4	4

*-Significant Difference from Control P < .05

Table 7.13

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	ALT IU/L	AST IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBILI mg/dL	ALKP IU/L	GGT IU/L
Group: 1-M : 0 mg base/kg/day									
MEAN	33	41	5.9	3.2	2.7	1.26	0.15	84	4.0
SD	3.9	9.9	0.17	0.53	0.38	0.432	0.026	17.7	1.69
N	4	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day									
MEAN	39	40	6.5	3.9	2.6	1.50	0.15	69	3.8
SD	15.3	7.2	0.31	0.36	0.22	0.231	0.015	21.2	1.74
N	4	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day									
MEAN	26	37	5.7	3.2	2.6	1.27	0.13	69	3.5
SD	2.4	3.0	0.56	0.60	0.44	0.427	0.015	11.1	1.12
N	4	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day									
MEAN	34	46	5.9	3.0	2.9	1.04	0.17	87	4.5
SD	12.9	8.0	0.47	0.15	0.33	0.076	0.042	24.7	0.93
N	4	4	4	4	4	4	4	4	4

Table 7.14

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L	K mEq/L	CL mEq/L
Group: 1-M : 0 mg base/kg/day									
MEAN	155	34	91	239	14.5	0.78	147	4.24	118.2
SD	26.2	7.1	27.7	126.8	6.46	0.111	1.3	0.187	5.13
N	4	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day									
MEAN	158	31	115	121	15.3	0.72	148	4.34	118.2
SD	29.2	10.4	64.7	33.7	2.03	0.057	3.1	0.307	8.14
N	4	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day									
MEAN	141	39	80	114	15.6	0.74	146	4.34	118.7
SD	43.0	7.5	51.6	24.2	1.27	0.048	1.3	0.173	2.44
N	4	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day									
MEAN	145	45	125	144	18.3	0.80	146	4.28	116.0
SD	6.7	6.9	92.8	48.0	2.90	0.039	1.5	0.238	2.89
N	4	4	4	4	4	4	4	4	4

Table 7.15

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	CA	IP	GLU	HAPT
UNITS:	mg/dL	mg/dL	mg/dL	mg/dL
Group: 1-M : 0 mg base/kg/day				
MEAN	10.1	4.3	102	91.7
SD	0.10	0.49	9.1	30.36
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	10.6	4.4	103	114.2
SD	0.41	0.39	14.7	91.59
N	4	4	4	3
Group: 3-M : 1.0 mg base/kg/day				
MEAN	9.8	4.5	96	109.9
SD	0.54	0.45	13.5	27.89
N	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day				
MEAN	9.8	4.4	92	138.3
SD	0.42	0.34	14.8	36.20
N	4	4	4	4

Table 7.16

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	ALT	AST	TP	ALB	GLOB	A/G	TBILI	ALKP	GGT
UNITS:	IU/L	IU/L	g/dL	g/dL	g/dL	-	mg/dL	IU/L	IU/L
Group: 1-M : 0 mg base/kg/day									
MEAN	38	43	6.2	3.2	3.0	1.09	0.18	60	5.3
SD	2.5	13.2	0.31	0.14	0.17	0.024	0.028	9.1	0.96
N	4	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day									
MEAN	41	37	6.2	3.3	2.9	1.15	0.17	59	4.5
SD	15.2	6.6	0.26	0.14	0.21	0.090	0.031	23.8	2.41
N	4	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day									
MEAN	31	39	6.0	3.2	2.8	1.14	0.16	66	6.1
SD	1.3	9.6	0.59	0.13	0.48	0.161	0.005	26.8	1.05
N	4	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day									
MEAN	43	49	6.2	3.1	3.1	0.99	0.17	78	5.4
SD	16.2	13.1	0.13	0.06	0.12	0.039	0.062	26.3	0.67
N	4	4	4	4	4	4	4	4	4

Table 7.17

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L	K mEq/L	CL mEq/L
Group: 1-M : 0 mg base/kg/day									
MEAN	151	30	74	366	14.4	0.88	149	4.30	109.3
SD	16.4	9.4	47.5	349.9	4.34	0.097	2.5	0.134	3.08
N	4	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day									
MEAN	148	40	69	141	13.2	0.86	149	4.45	108.8
SD	20.6	19.6	29.6	21.0	3.27	0.031	1.3	0.216	1.93
N	4	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day									
MEAN	177	46	107	146	17.9	0.85	148	4.46	109.6
SD	60.8	11.6	83.6	80.1	3.32	0.084	1.5	0.350	1.86
N	4	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day									
MEAN	163	62*	76	127	19.1	0.89	148	4.79	109.1
SD	36.1	14.2	33.7	61.5	1.71	0.050	1.3	0.435	2.17
N	4	4	4	4	4	4	4	4	4

*-Significant Difference from Control P < .05

Table 7.18

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	CA	IP	GLU	HAPT
UNITS:	mg/dL	mg/dL	mg/dL	mg/dL
Group: 1-M : 0 mg base/kg/day				
MEAN	10.1	3.6	110	108.7
SD	0.24	0.55	5.1	8.27
N	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day				
MEAN	9.8	3.2	106	149.4
SD	0.17	0.33	7.2	113.01
N	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day				
MEAN	9.7	3.4	96	62.4
SD	0.38	0.45	10.0	31.96
N	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day				
MEAN	9.7	4.2	96	175.9
SD	0.55	1.18	9.4	43.81
N	4	4	4	4

Table 7.19

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	ALT	AST	TP	ALB	GLOB	A/G	TBILI	ALKP	GGT
UNITS:	IU/L	IU/L	g/dL	g/dL	g/dL	-	mg/dL	IU/L	IU/L
Group: 1-F : 0 mg base/kg/day									
MEAN	39	27	5.9	3.6	2.3	1.57	0.13	109	5.2
SD	6.7	2.9	0.14	0.14	0.14	0.135	0.013	19.5	0.34
N	4	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day									
MEAN	33	33	5.8	3.9	2.0	2.38	0.12	128	3.1*
SD	8.1	6.2	0.14	0.64	0.68	1.623	0.022	41.9	0.67
N	4	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day									
MEAN	37	34	6.0	3.6	2.4	1.55	0.12	134	3.6*
SD	9.9	10.9	0.24	0.19	0.13	0.112	0.015	64.5	0.98
N	4	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day									
MEAN	33	30	6.2	3.5	2.7	1.32	0.13	130	3.6*
SD	10.9	1.0	0.39	0.31	0.50	0.303	0.019	42.0	0.68
N	4	4	4	4	4	4	4	4	4

*Significant Difference from Control P < .05

Table 7.20

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L	K mEq/L	CL mEq/L
Group: 1-F : 0 mg base/kg/day									
MEAN	207	53	46	179	11.9	0.69	146	4.39	119.6
SD	6.1	12.8	10.7	31.2	1.01	0.067	2.1	0.056	1.65
N	4	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day									
MEAN	191	49	75	335	12.2	0.68	146	4.34	119.6
SD	26.2	14.7	27.8	161.6	2.84	0.085	2.5	0.243	1.43
N	4	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day									
MEAN	221	52	72	285	14.4	0.74	146	4.43	118.9
SD	41.5	6.8	45.8	141.7	5.19	0.031	1.4	0.228	4.73
N	4	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day									
MEAN	236	49	39	219	11.6	0.73	145	4.50	116.9
SD	74.6	10.8	14.9	36.9	1.85	0.060	1.5	0.261	1.83
N	4	4	4	4	4	4	4	4	4

Table 7.21

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	CA	IP	GLU	HAPT
UNITS:	mg/dL	mg/dL	mg/dL	mg/dL
Group: 1-F : 0 mg base/kg/day				
MEAN	11.1	6.8	119	43.4
SD	0.22	0.52	5.0	37.62
N	4	4	4	2
Group: 2-F : 0.1 mg base/kg/day				
MEAN	10.9	5.8	123	43.8
SD	0.17	0.67	1.5	28.10
N	4	4	4	3
Group: 3-F : 1.0 mg base/kg/day				
MEAN	11.2	6.0	122	25.6
SD	0.16	1.08	5.7	6.67
N	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day				
MEAN	11.3	6.3	119	44.8
SD	0.34	0.76	9.0	7.57
N	4	4	4	2

Table 7.22

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	ALT IU/L	AST IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBILI mg/dL	ALKP IU/L	GGT IU/L
Group: 1-F : 0 mg base/kg/day									
MEAN	29	32	6.2	3.4	2.8	1.25	0.14	100	5.0
SD	4.8	5.3	0.35	0.32	0.26	0.205	0.019	21.3	0.47
N	4	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day									
MEAN	32	32	6.1	3.4	2.7	1.24	0.14	125	4.2
SD	11.6	5.2	0.15	0.19	0.13	0.111	0.013	42.4	1.00
N	4	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day									
MEAN	35	35	6.3	3.5	2.8	1.25	0.14	123	3.6
SD	9.2	11.0	0.10	0.10	0.05	0.049	0.006	43.1	0.74
N	4	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day									
MEAN	26	31	6.6	3.4	3.2*	1.07	0.15	129	4.7
SD	6.9	4.2	0.44	0.24	0.29	0.096	0.022	44.0	1.92
N	4	4	4	4	4	4	4	4	4

*-Significant Difference from Control P < .05

Table 7.23

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L	K mEq/L	CL mEq/L
Group: 1-F : 0 mg base/kg/day									
MEAN	170	51	71	209	12.8	0.67	145	4.24	113.1
SD	12.7	9.5	36.1	39.4	1.22	0.047	0.6	0.142	3.65
N	4	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day									
MEAN	160	43	58	238	12.3	0.66	145	4.30	111.6
SD	28.8	9.3	23.1	68.4	2.09	0.057	0.5	0.384	4.84
N	4	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day									
MEAN	176	50	70	271	13.9	0.68	145	4.32	112.8
SD	14.2	5.8	48.7	141.5	3.37	0.036	1.7	0.366	3.81
N	4	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day									
MEAN	205	60	50	248	14.0	0.70	144	4.40	111.7
SD	46.1	8.2	22.2	78.9	1.44	0.081	1.3	0.266	2.80
N	4	4	4	4	4	4	4	4	4

Table 7.24

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	CA	IP	GLU	HAPT
UNITS:	mg/dL	mg/dL	mg/dL	mg/dL
Group: 1-F : 0 mg base/kg/day				
MEAN	10.8	6.2	113	44.1
SD	0.28	0.39	4.2	28.09
N	4	4	4	3
Group: 2-F : 0.1 mg base/kg/day				
MEAN	10.6	6.0	113	70.0
SD	0.35	0.61	5.9	NA
N	4	4	4	1
Group: 3-F : 1.0 mg base/kg/day				
MEAN	10.5	5.7	124	31.7
SD	0.14	1.11	5.4	10.66
N	4	4	4	3
Group: 4-F : 4.0 mg base/kg/day				
MEAN	10.9	6.1	121	38.9
SD	0.22	0.44	16.1	6.31
N	4	4	4	3

NA-Not Applicable

Table 7.25

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	ALT IU/L	AST IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBILI mg/dL	ALKP IU/L	GGT IU/L
Group: 1-F : 0 mg base/kg/day									
MEAN	35	34	6.2	3.4	2.8	1.22	0.13	92	3.4
SD	15.7	6.7	0.12	0.12	0.00	0.040	0.016	18.9	2.33
N	4	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day									
MEAN	31	30	6.2	3.3	2.9	1.12	0.14	120	3.4
SD	13.2	6.7	0.14	0.10	0.10	0.047	0.032	57.9	0.63
N	4	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day									
MEAN	35	38	6.3	3.4	2.9	1.18	0.19*	101	3.7
SD	5.9	8.1	0.13	0.19	0.10	0.098	0.033	49.7	1.89
N	4	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day									
MEAN	26	33	6.5	3.1	3.3*	0.94*	0.22*	98	4.1
SD	8.7	6.9	0.19	0.19	0.19	0.094	0.025	22.9	1.24
N	4	4	4	4	4	4	4	4	4

*-Significant Difference from Control P < .05

Table 7.26

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L	K mEq/L	CL mEq/L
Group: 1-F : 0 mg base/kg/day									
MEAN	177	51	87	217	14.1	0.70	146	4.58	115.4
SD	11.8	8.6	29.4	79.0	1.09	0.114	0.0	0.122	4.68
N	4	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day									
MEAN	167	44	61	197	13.9	0.68	145	4.39	110.5
SD	26.7	5.9	32.6	98.7	1.72	0.071	1.4	0.040	0.97
N	4	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day									
MEAN	173	50	66	217	17.0*	0.73	145	4.46	114.3
SD	24.5	15.6	31.9	101.9	1.41	0.074	0.8	0.400	3.42
N	4	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day									
MEAN	190	49	82	166	17.7*	0.76	146	4.29	115.0
SD	32.2	11.2	37.3	59.3	1.60	0.047	1.3	0.307	3.53
N	4	4	4	4	4	4	4	4	4

*-Significant Difference from Control P < .05

Table 7.27

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	CA	IP	GLU	HAPT
UNITS:	mg/dL	mg/dL	mg/dL	mg/dL
Group: 1-F : 0 mg base/kg/day				
MEAN	11.2	5.4	105	37.1
SD	0.15	0.58	6.0	NA
N	4	4	4	1
Group: 2-F : 0.1 mg base/kg/day				
MEAN	11.1	5.7	106	95.6
SD	0.36	0.81	5.0	59.40
N	4	4	4	2
Group: 3-F : 1.0 mg base/kg/day				
MEAN	10.9	5.2	112	39.8
SD	0.31	0.68	2.6	32.92
N	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day				
MEAN	11.1	5.9	113	139.4
SD	0.42	0.32	13.3	52.68
N	4	4	4	3

NA-Not Applicable

Table 7.28

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	ALT IU/L	AST IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBILI mg/dL	ALKP IU/L	GGT IU/L
Group: 1-F : 0 mg base/kg/day									
MEAN	34	34	6.5	3.5	3.0	1.14	0.15	66	3.0
SD	20.0	9.6	0.25	0.13	0.19	0.074	0.019	11.6	2.16
N	4	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day									
MEAN	34	38	6.4	3.4	3.0	1.15	0.21	85	3.3
SD	17.4	16.2	0.17	0.12	0.22	0.110	0.057	30.0	2.18
N	4	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day									
MEAN	34	37	6.2	3.3	2.9	1.16	0.16	81	1.6
SD	7.8	10.6	0.17	0.08	0.21	0.110	0.027	37.5	2.31
N	4	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day									
MEAN	27	37	6.5	3.2	3.3	0.97	0.19	74	2.8
SD	5.7	8.9	0.29	0.14	0.25	0.082	0.070	12.9	1.88
N	4	4	4	4	4	4	4	4	4

Table 7.29

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	CHOL	TRIG	LDH	CK	BUN	CREAT	NA	K	CL
UNITS:	mg/dL	mg/dL	IU/L	IU/L	mg/dL	mg/dL	mEq/L	mEq/L	mEq/L
Group: 1-F : 0 mg base/kg/day									
MEAN	219	70	98	189	20.8	0.73	145	4.53	111.5
SD	34.5	49.4	72.4	65.5	3.09	0.037	3.1	0.350	3.86
N	4	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day									
MEAN	210	45	90	382	17.1	0.72	145	4.04	110.2
SD	69.6	6.2	14.4	433.4	1.35	0.062	0.8	0.243	2.25
N	4	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day									
MEAN	183	56	82	167	17.4	0.77	144	4.24	109.6
SD	35.2	27.7	32.2	82.6	3.10	0.075	1.7	0.384	2.75
N	4	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day									
MEAN	214	71	91	177	18.7	0.85	144	4.29	109.2
SD	55.5	20.9	55.5	76.7	3.03	0.133	0.5	0.269	4.51
N	4	4	4	4	4	4	4	4	4

Table 7.30

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	CA	IP	GLU	HAPT
UNITS:	mg/dL	mg/dL	mg/dL	mg/dL
Group: 1-F : 0 mg base/kg/day				
MEAN	10.3	4.7	107	41.1
SD	0.31	0.17	9.9	NA
N	4	4	4	1
Group: 2-F : 0.1 mg base/kg/day				
MEAN	10.2	4.3	113	58.5
SD	0.21	0.77	6.3	26.99
N	4	4	4	3
Group: 3-F : 1.0 mg base/kg/day				
MEAN	10.1	3.7	109	52.4
SD	0.45	0.59	5.0	3.25
N	4	4	4	2
Group: 4-F : 4.0 mg base/kg/day				
MEAN	10.3	4.4	103	109.3
SD	0.15	0.59	6.6	41.72
N	4	4	4	4

NA-Not Applicable

Table 7.31

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	ALT	AST	TP	ALB	GLOB	A/G	TBILI	ALKP	GGT
UNITS:	IU/L	IU/L	g/dL	g/dL	g/dL	-	mg/dL	IU/L	IU/L
Group: 1-F : 0 mg base/kg/day									
MEAN	33	37	6.0	3.6	2.4	1.64	0.16	63	4.7
SD	7.4	5.3	0.19	0.70	0.61	0.682	0.034	16.0	2.01
N	4	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day									
MEAN	27	32	5.8	3.1	2.7	1.16	0.16	64	3.2
SD	9.3	9.3	0.17	0.15	0.14	0.092	0.030	22.6	2.12
N	4	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day									
MEAN	35	39	6.2	3.9	2.3	1.76	0.17	71	5.2
SD	9.5	13.2	0.29	0.43	0.33	0.393	0.017	25.4	0.68
N	4	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day									
MEAN	26	41	6.2	3.3	2.9	1.22	0.17	73	3.9
SD	5.8	9.2	0.34	0.39	0.60	0.350	0.041	15.5	0.55
N	4	4	4	4	4	4	4	4	4

Table 7.32

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L	K mEq/L	CL mEq/L
Group: 1-F : 0 mg base/kg/day									
MEAN	149	44	87	164	14.2	0.79	146	4.31	116.5
SD	19.9	6.3	21.8	77.7	1.99	0.053	1.7	0.390	4.41
N	4	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day									
MEAN	128	42	93	122	13.8	0.75	146	4.34	114.6
SD	18.0	10.8	65.3	48.8	2.14	0.114	1.3	0.208	1.82
N	4	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day									
MEAN	183	55	119	156	18.2	0.79	145	4.30	121.1
SD	32.1	7.4	68.8	45.2	3.97	0.087	1.9	0.142	5.42
N	4	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day									
MEAN	146	55	103	137	16.1	0.86	146	4.31	117.0
SD	35.3	16.0	88.5	47.6	1.86	0.093	0.0	0.279	3.75
N	4	4	4	4	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	CA	IP	GLU	HAPT
UNITS:	mg/dL	mg/dL	mg/dL	mg/dL
Group: 1-F : 0 mg base/kg/day				
MEAN	10.2	4.1	99	61.0
SD	0.22	0.29	9.5	46.53
N	4	4	4	2
Group: 2-F : 0.1 mg base/kg/day				
MEAN	10.1	3.4	96	42.9
SD	0.25	1.25	7.5	35.99
N	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day				
MEAN	10.3	4.3	100	60.0
SD	0.30	1.09	4.9	38.19
N	4	4	4	3
Group: 4-F : 4.0 mg base/kg/day				
MEAN	10.2	3.6	95	99.1
SD	0.35	0.58	8.2	60.66
N	4	4	4	4

Table 7.34

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	ALT IU/L	AST IU/L	TP g/dL	ALB g/dL	GLOB g/dL	A/G -	TBILI mg/dL	ALKP IU/L	GGT IU/L
Group: 1-F : 0 mg base/kg/day									
MEAN	32	30	5.8	3.2	2.7	1.20	0.16	65	7.1
SD	6.9	7.2	0.38	0.13	0.31	0.134	0.050	36.2	1.12
N	4	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day									
MEAN	32	33	6.4	3.3	3.1	1.05	0.18	72	6.4
SD	15.6	8.0	0.14	0.10	0.22	0.102	0.026	33.1	0.28
N	4	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day									
MEAN	33	41	6.1	3.2	2.9	1.12	0.16	59	4.0*
SD	4.7	16.8	0.48	0.25	0.32	0.113	0.034	26.8	1.64
N	4	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day									
MEAN	33	38	6.2	3.0	3.2	0.94*	0.15	69	5.4
SD	10.2	8.8	0.32	0.14	0.27	0.084	0.029	4.3	0.68
N	4	4	4	4	4	4	4	4	4

*-Significant Difference from Control P < .05

Table 7.35

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	CHOL mg/dL	TRIG mg/dL	LDH IU/L	CK IU/L	BUN mg/dL	CREAT mg/dL	NA mEq/L	K mEq/L	CL mEq/L
Group: 1-F : 0 mg base/kg/day									
MEAN	164	34	61	114	13.0	0.78	148	4.33	111.3
SD	18.2	14.4	33.4	41.3	1.68	0.079	1.3	0.073	1.17
N	4	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day									
MEAN	224	50	136	221	14.3	0.70	148	4.66	106.1*
SD	18.3	17.2	62.8	177.2	0.95	0.058	1.3	0.404	0.92
N	4	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day									
MEAN	207	51	70	205	15.7	0.85	147	4.42	107.8
SD	77.2	24.9	35.4	189.7	2.85	0.088	1.3	0.253	3.09
N	4	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day									
MEAN	225	60	83	153	16.5	0.80	148	4.51	108.8
SD	108.0	23.0	39.8	60.7	2.08	0.108	1.5	0.246	3.05
N	4	4	4	4	4	4	4	4	4

*-Significant Difference from Control P < .05

Table 7.36

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF CLINICAL CHEMISTRY TESTS
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	CA	IP	GLU	HAPT
UNITS:	mg/dL	mg/dL	mg/dL	mg/dL
Group: 1-F : 0 mg base/kg/day				
MEAN	9.8	3.6	103	29.9
SD	0.17	0.57	9.0	15.57
N	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day				
MEAN	10.2	3.8	103	71.9
SD	0.33	0.90	6.2	47.99
N	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day				
MEAN	9.6	3.2	112	66.5
SD	0.45	0.59	11.0	63.37
N	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day				
MEAN	10.0	4.1	96	110.8
SD	0.22	0.47	6.7	83.97
N	4	4	4	4

Table 8.1

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	RBC	HGB	HCT	MCV	MCH	MCHC	RETICS	NRBC
UNITS:	10 ⁶ /mm ³	g/dL	%	fL	pg	g/dL	% RBCs	COUNT
Group: 1-M : 0 mg base/kg/day								
MEAN	6.27	15.1	43.4	69.3	24.1	34.7	0.2	0
SD	0.133	0.26	1.22	2.46	0.66	0.51	0.17	0.0
N	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day								
MEAN	6.63	15.5	44.8	67.7	23.3	34.5	0.1	0
SD	0.597	1.12	3.51	1.35	0.49	0.24	0.10	0.0
N	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day								
MEAN	6.58	15.6	45.7	69.3	23.6	34.1	0.3	0
SD	0.417	1.07	3.11	1.36	0.56	0.48	0.29	0.0
N	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day								
MEAN	6.05	14.4	41.8	69.1	23.9	34.5	0.3	0
SD	0.411	0.85	2.50	1.27	0.56	0.15	0.30	0.5
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

Table 8.2

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	HB % RBCs	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
Group: 1-M : 0 mg base/kg/day					
MEAN	0.0	0.7	290	8.8	10.0
SD	0.00	0.22	42.4	0.64	0.25
N	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day					
MEAN	0.0	0.5	337	8.4	11.1*
SD	0.00	0.22	67.7	0.24	0.70
N	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day					
MEAN	0.0	0.5	288	8.5	10.5
SD	0.00	0.05	61.9	0.37	0.21
N	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day					
MEAN	0.1	0.5	315	8.5	10.6
SD	0.10	0.13	60.9	0.10	0.08
N	4	4	4	4	4

*-Significant Difference from Control P < .05

Table 8.3

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	WBC	M. Neutrop	I. Neutrop	Lymphocyte	Monocytes	Eosinophil	Basophils	Atypical L
UNITS:	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³
Group: 1-M : 0 mg base/kg/day								
MEAN	7.9	4.6	0.1	2.4	0.3	0.5	0.0	0.1
SD	0.65	0.69	0.05	0.17	0.25	0.32	0.00	0.10
N	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day								
MEAN	7.4	4.7	0.1	2.3	0.1	0.3	0.0	0.0
SD	0.98	0.76	0.05	1.20	0.05	0.15	0.00	0.05
N	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day								
MEAN	7.5	4.3	0.0	2.6	0.1	0.3	0.0	0.1
SD	0.91	0.72	0.05	0.72	0.05	0.13	0.00	0.13
N	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day								
MEAN	7.6	4.1	0.1	2.7	0.3	0.4	0.0	0.0
SD	2.61	1.56	0.10	0.57	0.19	0.53	0.00	0.00
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

Table 8.4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY OUNNETT'S PROCEDURE

TEST(s):	RBC	HGB	HCT	MCV	MCH	MCHC	RETICS	NRBC
UNITS:	10 ⁶ /mm ³	g/dL	%	fL	pg	g/dL	% RBCs	COUNT
Group: 1-M : 0 mg base/kg/day								
MEAN	6.06	14.4	41.9	69.3	23.8	34.4	0.4	0
SD	0.240	0.22	0.92	2.32	0.83	0.22	0.38	0.0
N	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day								
MEAN	6.44	14.9	43.5	67.6	23.1	34.2	0.3	0
SD	0.653	1.15	3.67	1.68	0.59	0.43	0.28	0.5
N	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day								
MEAN	6.07	14.4	42.0	69.1	23.8	34.4	0.4	0
SD	0.320	1.12	2.64	1.54	0.76	0.57	0.29	0.5
N	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day								
MEAN	5.76	13.7	39.7	68.9	23.8	34.5	0.2	0
SD	0.246	0.39	1.12	1.56	0.79	0.46	0.27	0.5
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

Table 8.5

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	HB % RBCs	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
Group: 1-M : 0 mg base/kg/day					
MEAN	0.1	0.6	272	8.8	9.7
SD	0.10	0.15	45.1	0.81	0.17
N	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day					
MEAN	0.0	0.7	303	8.5	10.4
SD	0.00	0.36	16.0	0.35	0.86
N	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day					
MEAN	0.0	0.6	274	8.4	10.7
SD	0.00	0.14	43.0	0.10	0.73
N	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day					
MEAN	0.0	0.6	272	8.5	10.1
SD	0.00	0.22	58.0	0.17	0.17
N	4	4	4	4	4

Table 8.6

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	WBC	M. Neutrop	I. Neutrop	Lymphocyte	Monocytes	Eosinophil	Basophils	Atypical L
UNITS:	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³
Group: 1-M : 0 mg base/kg/day								
MEAN	9.6	6.1	0.1	2.5	0.2	0.5	0.0	0.3
SD	0.39	0.82	0.15	0.94	0.17	0.06	0.00	0.10
N	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day								
MEAN	8.4	5.9	0.1	2.0	0.2	0.2*	0.0	0.1
SD	1.68	1.54	0.05	0.30	0.13	0.20	0.00	0.10
N	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day								
MEAN	8.4	5.4	0.1	2.5	0.2	0.2*	0.0	0.1
SD	0.50	0.62	0.10	0.80	0.10	0.05	0.00	0.10
N	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day								
MEAN	8.5	5.8	0.1	2.1	0.3	0.2*	0.0	0.1*
SD	1.27	1.29	0.08	0.44	0.13	0.06	0.00	0.06
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

Table 8.7

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	RBC	HGB	HCT	MCV	MCH	MCHC	RETICS	NRBC
UNITS:	10 ⁶ /mm ³	g/dL	%	fL	pg	g/dL	% RBCs	COUNT
Group: 1-M : 0 mg base/kg/day								
MEAN	6.22	14.8	42.8	68.8	23.7	34.5	0.0	0
SD	0.305	0.78	2.25	2.13	0.92	0.35	0.05	0.5
N	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day								
MEAN	6.41	14.9	43.2	67.5	23.3	34.5	0.0	0
SD	0.513	1.06	3.09	1.17	0.34	0.15	0.05	0.5
N	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day								
MEAN	6.48	15.3	44.7	68.8	23.6	34.3	0.4*	0
SD	0.461	1.40	4.08	1.56	0.59	0.39	0.06	0.0
N	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day								
MEAN	5.57	13.2	38.7	69.4	23.6	34.0	0.2	1
SD	0.282	0.70	1.83	1.72	0.67	0.22	0.17	1.4
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

Table 8.8

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	HB % RBCs	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
Group: 1-M : 0 mg base/kg/day					
MEAN	0.0	0.6	223	9.3	10.5
SD	0.00	0.17	57.8	0.71	0.21
N	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day					
MEAN	0.0	0.9	262	8.7	11.5
SD	0.05	0.31	25.9	0.29	1.13
N	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day					
MEAN	0.1	4.0	155	8.7	10.8
SD	0.10	2.29	33.6	0.18	0.38
N	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day					
MEAN	0.0	11.9*	60*	8.4	10.9
SD	0.00	3.67	20.5	0.13	0.17
N	4	4	4	4	4

*-Significant Difference from Control P < .05

Table 8.9

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	WBC	M. Neutrop	I. Neutrop	Lymphocyte	Monocytes	Eosinophil	Basophils	Atypical L
UNITS:	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$
Group: 1-M : 0 mg base/kg/day								
MEAN	8.3	5.6	0.1	2.1	0.3	0.3	0.0	0.1
SD	0.86	0.76	0.05	0.26	0.17	0.00	0.00	0.06
N	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day								
MEAN	8.8	5.8	0.0	2.4	0.4	0.2	0.0	0.0
SD	1.59	0.94	0.05	1.26	0.21	0.10	0.00	0.05
N	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day								
MEAN	8.6	5.4	0.1	2.4	0.4	0.3	0.0	0.1
SD	1.25	0.78	0.08	0.71	0.28	0.27	0.00	0.10
N	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day								
MEAN	9.4	6.3	0.1	2.3	0.5	0.3	0.0	0.1
SD	2.40	1.79	0.10	0.37	0.37	0.16	0.00	0.05
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

Table 8.10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	RBC	HGB	HCT	MCV	MCH	MCHC	RETICS	NRBC
UNITS:	10 ⁶ /mm ³	g/dL	%	fL	pg	g/dL	% RBCs	COUNT
Group: 1-M : 0 mg base/kg/day								
MEAN	6.36	15.7	44.1	69.4	24.8	35.7	0.7	0
SD	0.350	0.59	1.81	2.55	1.04	0.50	0.49	0.0
N	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day								
MEAN	6.84	16.5	46.4	67.7	24.1	35.6	0.4	0
SD	0.397	0.98	2.97	1.48	0.34	0.73	0.10	0.0
N	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day								
MEAN	6.60	16.3	45.9	69.5	24.7	35.5	1.0	0
SD	0.236	0.94	1.87	0.99	0.64	0.65	0.70	0.0
N	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day								
MEAN	6.30	15.1	43.2	68.5	24.0	35.0	1.1	1
SD	0.495	0.83	2.88	0.85	0.59	0.45	0.24	2.0
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

Table 8.11

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	HB	% METHGB	PLT	PT	APTT
UNITS:	% RBCs	% HGBs	10 ³ /mm ³	sec	sec
Group: 1-M : 0 mg base/kg/day					
MEAN	0.1	0.8	210	9.5	10.0
SD	0.12	0.22	33.2	1.02	0.29
N	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day					
MEAN	0.2	0.9	250	9.2	10.1
SD	0.17	0.25	35.2	0.26	0.76
N	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day					
MEAN	0.1	3.9	168	9.1	10.1
SD	0.13	1.81	51.0	0.22	0.41
N	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day					
MEAN	0.1	9.8*	150	8.9	10.1
SD	0.19	3.14	60.3	0.26	0.24
N	4	4	4	4	4

*-Significant Difference from Control P < .05

DRAFTONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGSSUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 13STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	WBC M.	Neutrop I.	Neutrop	Lymphocyte	Monocytes	Eosinophil	Basophils	Atypical L
UNITS:	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³
Group: 1-M : 0 mg base/kg/day								
MEAN	10.7	8.0	0.1	2.1	0.2	0.2	0.0	0.1
SD	1.38	1.42	0.10	0.38	0.19	0.15	0.00	0.10
N	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day								
MEAN	9.2	6.5	0.0	2.2	0.3	0.1	0.0	0.1
SD	1.68	1.01	0.00	0.76	0.14	0.08	0.00	0.08
N	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day								
MEAN	9.8	6.7	0.0	2.5	0.2	0.4	0.0	0.2
SD	1.35	0.45	0.00	0.70	0.17	0.17	0.00	0.05
N	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day								
MEAN	13.3	10.7*	0.0	1.9	0.5	0.2	0.0	0.1
SD	1.71	1.47	0.00	0.37	0.29	0.22	0.00	0.06
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

Table 8.13

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	RBC	HGB	HCT	MCV	MCH	MCHC	RETICS	NRBC
UNITS:	10 ⁶ /mm ³	g/dL	%	fL	pg	g/dL	% RBCs	COUNT
Group: 1-M : 0 mg base/kg/day								
MEAN	6.29	15.9	43.5	69.2	25.4	36.7	0.3	0
SD	0.569	1.04	3.16	2.96	1.09	0.36	0.10	0.5
N	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day								
MEAN	6.69	16.4	45.0	67.3	24.6	36.6	0.3	1
SD	0.525	1.07	2.95	1.16	0.32	0.50	0.15	0.6
N	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day								
MEAN	6.20	15.6	42.6	68.7	25.2	36.6	0.7	0
SD	0.378	1.16	3.01	1.55	0.52	0.28	0.30	0.0
N	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day								
MEAN	5.80	14.3	39.9	68.7	24.7	35.9	0.9*	0
SD	0.446	1.02	3.19	1.20	0.67	0.51	0.45	0.5
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	HB % RBCs	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
Group: 1-M : 0 mg base/kg/day					
MEAN	0.1	0.9	239	8.8	10.0
SD	0.14	0.13	25.2	0.68	0.35
N	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day					
MEAN	0.3	1.0	254	8.6	10.8
SD	0.42	0.17	40.4	0.35	0.87
N	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day					
MEAN	0.2	4.0	165	8.5	10.3
SD	0.13	1.58	33.4	0.25	0.33
N	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day					
MEAN	0.1	10.8*	186	8.4	10.0
SD	0.19	4.36	69.6	0.12	0.37
N	4	4	4	4	4

*-Significant Difference from Control P < .05

Table 8.15

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	WBC	M. Neutrop	I. Neutrop	Lymphocyte	Monocytes	Eosinophil	Basophils	Atypical L
UNITS:	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$
Group: 1-M : 0 mg base/kg/day								
MEAN	11.0	8.0	0.1	2.2	0.1	0.5	0.0	0.1
SD	1.81	2.01	0.14	0.59	0.08	0.06	0.00	0.13
N	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day								
MEAN	13.9	12.1	0.0	1.4	0.1	0.2	0.0	0.1
SD	10.56	10.32	0.05	0.17	0.13	0.15	0.00	0.06
N	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day								
MEAN	9.4	5.9	0.0	2.8	0.2	0.4	0.0	0.3
SD	2.10	1.59	0.05	1.01	0.17	0.10	0.00	0.31
N	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day								
MEAN	12.3	10.4	0.1	1.4	0.3	0.2	0.0	0.0
SD	2.30	1.64	0.20	0.73	0.26	0.23	0.00	0.00
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	RBC	HGB	HCT	MCV	MCH	MCHC	RETICS	NRBC
UNITS:	10 ⁶ /mm ³	g/dL	%	fL	pg	g/dL	% RBCs	COUNT
Group: 1-M : 0 mg base/kg/day								
MEAN	7.22	17.5	49.3	68.4	24.4	35.6	0.5	0
SD	0.642	1.11	3.20	2.31	0.90	0.13	0.29	0.0
N	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day								
MEAN	7.53	17.9	50.0	66.5	23.7	35.7	0.5	1
SD	0.456	0.86	2.45	1.11	0.29	0.33	0.38	0.6
N	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day								
MEAN	7.06	17.3	48.3	68.4	24.5	35.9	0.9	0
SD	0.452	1.31	3.27	0.83	0.48	0.33	0.50	0.0
N	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day								
MEAN	6.95	16.6	47.1	67.8	23.9	35.2	1.1	0
SD	0.741	1.49	4.15	1.45	0.46	0.10	0.28	0.0
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

Table 8.17

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	HB	% METHGB	PLT	PT	APTT
UNITS:	% RBCs	% HGBs	10 ³ /mm ³	sec	sec
Group: 1-M : 0 mg base/kg/day					
MEAN	0.6	0.7	188	8.9	9.3
SD	0.77	0.06	31.8	0.61	0.19
N	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day					
MEAN	1.3	1.0	217	8.6	10.4
SD	0.83	0.36	68.0	0.29	0.80
N	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day					
MEAN	1.7	3.5	161	8.5	10.1
SD	1.45	1.07	69.9	0.34	0.66
N	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day					
MEAN	1.9	8.9*	182	8.4	9.9
SD	1.99	3.27	54.3	0.08	0.17
N	4	4	4	4	4

*-Significant Difference from Control P < .05

Table 8.18

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	WBC	M. Neutrop	I. Neutrop	Lymphocyte	Monocytes	Eosinophil	Basophils	Atypical L
UNITS:	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$
Group: 1-M : 0 mg base/kg/day								
MEAN	9.8	7.1	0.0	2.2	0.2	0.4	0.0	0.0
SD	1.17	1.59	0.00	0.78	0.10	0.24	0.00	0.00
N	4	4	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day								
MEAN	9.2	6.6	0.0	2.3	0.2	0.2	0.0	0.0
SD	4.02	3.75	0.05	0.48	0.20	0.13	0.00	0.00
N	4	4	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day								
MEAN	10.1	6.2	0.1	3.0	0.5	0.4	0.0	0.0
SD	1.12	0.81	0.10	1.18	0.29	0.17	0.00	0.00
N	4	4	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day								
MEAN	13.2	10.1	0.0	2.2	0.7	0.3	0.0	0.0
SD	3.22	2.57	0.05	0.31	0.61	0.29	0.00	0.00
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

Table 8.19

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	RBC	HGB	HCT	MCV	MCH	MCHC	RETICS	NRBC
UNITS:	10 ⁶ /mm ³	g/dL	%	fL	pg	g/dL	% RBCs	COUNT
Group: 1-F : 0 mg base/kg/day								
MEAN	6.39	15.3	44.8	70.2	24.0	34.2	0.2	0
SD	0.596	1.40	4.26	2.55	0.56	0.50	0.17	0.0
N	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day								
MEAN	6.35	15.3	44.9	70.9	24.1	34.0	0.4	0
SD	0.335	0.62	1.56	2.08	0.45	0.41	0.16	0.0
N	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day								
MEAN	6.59	15.8	45.9	69.7	24.0	34.4	0.2	0
SD	0.418	0.75	2.34	1.03	0.39	0.33	0.13	0.0
N	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day								
MEAN	6.37	15.5	45.4	71.4	24.4	34.2	0.2	0
SD	0.453	1.00	3.63	1.01	0.30	0.56	0.17	0.0
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	HB % RBCs	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
Group: 1-F : 0 mg base/kg/day					
MEAN	0.0	0.6	252	8.7	10.7
SD	0.00	0.10	69.1	0.28	0.53
N	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day					
MEAN	0.0	0.7	282	8.5	11.1
SD	0.00	0.39	50.2	0.10	1.09
N	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day					
MEAN	0.0	0.6	348	8.5	10.6
SD	0.00	0.14	75.2	0.24	0.42
N	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day					
MEAN	0.0	0.7	283	8.8	10.9
SD	0.00	0.10	53.9	0.13	0.50
N	4	4	4	4	4

Table 8.21

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK -3

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	WBC	M. Neutrop	I. Neutrop	Lymphocyte	Monocytes	Eosinophil	Basophils	Atypical L
UNITS:	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$
Group: 1-F : 0 mg base/kg/day								
MEAN	7.7	4.7	0.2	2.5	0.2	0.2	0.0	0.2
SD	1.36	1.53	0.10	0.69	0.22	0.10	0.00	0.10
N	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day								
MEAN	7.5	4.8	0.1	2.3	0.1	0.2	0.0	0.1
SD	3.19	2.26	0.10	0.86	0.10	0.10	0.00	0.10
N	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day								
MEAN	8.9	6.1	0.2	2.1	0.3	0.2	0.0	0.1
SD	2.12	2.66	0.13	0.64	0.14	0.17	0.00	0.06
N	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day								
MEAN	6.3	3.8	0.1	2.2	0.1	0.1	0.0	0.1
SD	1.02	0.51	0.05	0.61	0.10	0.10	0.00	0.05
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

Table 8.22

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	RBC	HGB	HCT	MCV	MCH	MCHC	RETICS	NRBC
UNITS:	10 ⁶ /mm ³	g/dL	%	fL	pg	g/dL	% RBCs	COUNT
Group: 1-F : 0 mg base/kg/day								
MEAN	6.26	15.1	44.0	70.3	24.1	34.3	0.3	0
SD	0.349	0.63	2.13	2.60	0.53	0.62	0.21	0.0
N	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day								
MEAN	6.10	14.8	43.2	71.0	24.3	34.3	0.2	1
SD	0.462	0.84	2.33	1.59	0.54	0.35	0.13	1.0
N	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day								
MEAN	6.36	15.4	44.3	69.7	24.2	34.7	0.1	0
SD	0.487	0.90	2.97	1.03	0.45	0.33	0.10	0.0
N	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day								
MEAN	6.21	15.3	44.2	71.3	24.7	34.6	0.3	0
SD	0.294	0.64	1.80	1.05	0.29	0.37	0.42	0.5
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	HB % RBCs	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
Group: 1-F : 0 mg base/kg/day					
MEAN	0.0	0.6	266	8.6	10.5
SD	0.00	0.21	41.7	0.26	0.15
N	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day					
MEAN	0.1	0.7	277	8.7	10.7
SD	0.10	0.10	55.3	0.13	0.92
N	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day					
MEAN	0.1	0.6	355	8.7	10.4
SD	0.10	0.08	101.1	0.31	0.39
N	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day					
MEAN	0.0	0.6	282	8.9	10.9
SD	0.00	0.10	88.6	0.13	0.46
N	4	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK -1

STUDY 10: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	WBC	M. Neutrop	I. Neutrop	Lymphocyte	Monocytes	Eosinophil	Basophils	Atypical L
UNITS:	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$
Group: 1-F : 0 mg base/kg/day								
MEAN	9.0	5.2	0.1	2.9	0.5	0.1	0.0	0.2
SD	1.52	0.99	0.08	1.09	0.13	0.13	0.00	0.08
N	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day								
MEAN	8.6	5.4	0.1	2.5	0.4	0.3	0.0	0.1
SD	2.82	2.25	0.06	0.52	0.19	0.17	0.00	0.15
N	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day								
MEAN	10.0	6.9	0.1	2.4	0.4	0.2	0.0	0.1
SD	2.66	2.49	0.05	1.03	0.26	0.14	0.00	0.06
N	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day								
MEAN	8.1	5.1	0.1	2.3	0.2	0.3	0.0	0.1
SD	2.28	1.48	0.10	0.80	0.14	0.24	0.00	0.15
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

Table 8.25

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY OUNNETT'S PROCEDURE

TEST(s):	RBC	HGB	HCT	MCV	MCH	MCHC	RETICS	NRBC
UNITS:	10 ⁶ /mm ³	g/dL	%	fL	pg	g/dL	% RBCs	COUNT
Group: 1-F : 0 mg base/kg/day								
MEAN	6.38	15.3	44.6	69.9	24.0	34.4	0.1	0
SD	0.294	0.82	3.00	2.38	0.45	0.59	0.08	0.0
N	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day								
MEAN	6.57	15.7	46.1	70.3	24.0	34.1	0.2	0
SD	0.300	0.40	1.33	1.71	0.56	0.20	0.17	0.0
N	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day								
MEAN	6.16	14.9	43.1	70.0	24.2	34.6	0.5	0
SD	0.381	0.85	2.20	1.38	0.26	0.39	0.57	0.0
N	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day								
MEAN	5.92	14.5	42.7	72.1	24.6	34.0	1.0	0
SD	0.292	0.57	1.28	1.40	0.52	0.57	0.83	0.0
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	HB % RBCs	% METHGB % HGBs	PLT 10 ³ /mm ³	PT sec	APTT sec
Group: 1-F : 0 mg base/kg/day					
MEAN	0.0	0.7	240	9.2	10.7
SD	0.00	0.19	69.0	0.37	0.24
N	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day					
MEAN	0.1	0.8	224	8.9	11.2
SD	0.10	0.05	32.1	0.15	1.28
N	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day					
MEAN	0.1	6.0*	159	8.9	10.6
SD	0.10	2.07	44.5	0.31	0.24
N	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day					
MEAN	0.2	12.4*	74*	8.9	11.1
SD	0.35	3.89	12.3	0.10	0.85
N	4	4	4	4	4

*-Significant Difference from Control P < .05

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 4

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	WBC	M. Neutrop	I. Neutrop	Lymphocyte	Monocytes	Eosinophil	Basophils	Atypical L
UNITS:	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$
Group: 1-F : 0 mg base/kg/day								
MEAN	10.2	6.7	0.1	2.8	0.3	0.2	0.0	0.2
SD	2.27	2.85	0.10	1.07	0.18	0.10	0.00	0.10
N	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day								
MEAN	9.2	6.1	0.1	2.3	0.4	0.2	0.0	0.1
SD	4.75	3.44	0.15	0.54	0.51	0.22	0.05	0.13
N	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day								
MEAN	9.7	6.8	0.0	2.0	0.6	0.3	0.0	0.1
SD	2.85	2.74	0.05	0.59	0.10	0.22	0.00	0.10
N	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day								
MEAN	9.5	7.1	0.0	2.0	0.2	0.2	0.0	0.1
SD	0.81	0.86	0.05	0.17	0.19	0.08	0.00	0.10
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

Table 8.28

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	RBC	HGB	HCT	MCV	MCH	MCHC	RETICS	NRBC
UNITS:	10 ⁶ /mm ³	g/dL	%	fL	pg	g/dL	% RBCs	COUNT
Group: 1-F : 0 mg base/kg/day								
MEAN	6.75	16.8	47.7	70.5	24.9	35.3	0.5	0
SD	0.645	1.91	6.18	2.70	0.63	0.56	0.30	0.0
N	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day								
MEAN	6.56	16.6	46.1	70.3	25.3	36.0	0.5	0
SD	0.696	1.56	4.67	1.42	0.42	0.42	0.29	0.0
N	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day								
MEAN	6.39	16.0	45.1	70.5	25.0	35.5	0.7	0
SD	0.332	0.84	2.85	1.97	0.24	0.67	0.31	0.0
N	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day								
MEAN	6.27	15.9	44.8	71.5	25.3	35.4	1.1	0
SD	0.469	1.16	3.16	1.53	0.33	0.55	0.45	0.0
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	HB	% METHGB	PLT	PT	APTT
UNITS:	% RBCs	% HGBs	10 ³ /mm ³	sec	sec
Group: 1-F : 0 mg base/kg/day					
MEAN	0.1	1.2	238	9.5	10.2
SD	0.10	0.70	36.7	0.24	0.51
N	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day					
MEAN	0.1	0.9	260	9.8	10.1
SD	0.05	0.21	26.9	0.45	1.35
N	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day					
MEAN	0.2	5.5	209	9.1	10.5
SD	0.24	0.81	81.3	0.13	0.39
N	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day					
MEAN	0.2	12.5*	178	9.4	10.5
SD	0.29	4.45	85.9	0.10	0.85
N	4	4	4	4	4

*-Significant Difference from Control P < .05

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	WBC	M. Neutrop	I. Neutrop	Lymphocyte	Monocytes	Eosinophil	Basophils	Atypical L
UNITS:	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$
Group: 1-F : 0 mg base/kg/day								
MEAN	9.8	6.6	0.0	2.6	0.2	0.3	0.0	0.2
SD	0.65	0.82	0.05	0.54	0.13	0.26	0.00	0.17
N	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day								
MEAN	9.5	6.9	0.0	2.2	0.2	0.2	0.0	0.1
SD	3.05	2.59	0.05	0.67	0.08	0.14	0.00	0.10
N	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day								
MEAN	10.4	7.7	0.1	1.9	0.4	0.4	0.0	0.1
SD	4.17	4.19	0.10	0.39	0.29	0.17	0.00	0.14
N	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day								
MEAN	10.5	8.1	0.0	1.9	0.2	0.3	0.0	0.1
SD	1.02	1.08	0.00	0.38	0.10	0.13	0.00	0.10
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

Table 8.31

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY ND: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	RBC	HGB	HCT	MCV	MCH	MCHC	RETICS	NRBC
UNITS:	10 ⁶ /mm ³	g/dL	%	fL	pg	g/dL	% RBCs	COUNT
Group: 1-F : 0 mg base/kg/day								
MEAN	7.04	18.0	49.3	70.1	25.6	36.6	0.3	0
SD	0.212	0.48	2.04	2.93	0.75	0.54	0.17	0.0
N	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day								
MEAN	6.74	17.4	47.4	70.4	25.8	36.7	0.5	0
SD	0.615	1.26	3.55	1.81	0.75	0.10	0.28	0.0
N	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day								
MEAN	6.23	16.0	43.7	70.2	25.7	36.6	0.7	0
SD	0.295	0.60	1.69	1.23	0.37	0.24	0.43	0.0
N	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day								
MEAN	6.55	16.8	46.7	71.3	25.7	36.0	1.3*	0
SD	0.428	1.26	3.59	1.28	0.28	0.71	0.56	0.0
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	HB	% METHGB	PLT	PT	APTT
UNITS:	% RBCs	% HGBs	10 ³ /mm ³	sec	sec
Group: 1-F : 0 mg base/kg/day					
MEAN	0.0	0.9	238	8.9	10.4
SD	0.05	0.17	50.0	0.39	0.13
N	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day					
MEAN	0.1	1.0	271	8.7	10.5
SD	0.20	0.19	36.2	0.19	0.97
N	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day					
MEAN	0.1	5.6	284	8.6	10.4
SD	0.20	2.06	102.4	0.21	0.17
N	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day					
MEAN	0.2	12.4*	196	8.8	10.9
SD	0.45	5.28	110.4	0.15	0.87
N	4	4	4	4	4

*-Significant Difference from Control P < .05

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	WBC	H. Neutrop	I. Neutrop	Lymphocyte	Monocytes	Eosinophil	Basophils	Atypical L
UNITS:	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$	$10^3/\text{mm}^3$
Group: 1-F : 0 mg base/kg/day								
MEAN	7.6	4.7	0.0	2.5	0.1	0.2	0.0	0.2
SD	1.46	0.81	0.05	0.95	0.08	0.15	0.00	0.06
N	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day								
MEAN	8.7	5.2	0.1	2.7	0.1	0.3	0.0	0.3
SD	3.08	2.49	0.08	0.70	0.05	0.24	0.00	0.36
N	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day								
MEAN	10.4	7.9	0.1	2.0	0.2	0.2	0.0	0.1
SD	1.98	2.02	0.06	0.26	0.17	0.21	0.00	0.06
N	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day								
MEAN	13.0*	10.3*	0.0	2.2	0.0	0.5	0.0	0.0
SD	2.68	2.66	0.05	0.63	0.05	0.47	0.00	0.00
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

Table 8.34

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	RBC 10 ⁶ /mm ³	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RETICS % RBCs	NRBC COUNT
Group: 1-F : 0 mg base/kg/day								
MEAN	7.14	17.7	49.9	69.9	24.8	35.5	0.5	0
SD	0.343	0.95	3.64	2.51	0.38	0.79	0.44	0.0
N	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day								
MEAN	6.68	16.6	46.3	69.5	24.9	35.9	0.2	0
SD	0.739	1.60	4.28	2.27	0.59	0.37	0.14	0.0
N	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day								
MEAN	6.54	16.2	45.6	69.8	24.8	35.5	0.6	0
SD	0.594	1.47	4.31	0.84	0.33	0.25	0.26	0.0
N	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day								
MEAN	5.99	16.0	43.3	72.3	27.1	37.4	1.4*	1
SD	0.916	0.70	6.40	0.64	3.97	5.33	0.62	1.4
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

*-Significant Difference from Control P < .05

Table 8.35

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	HB	% METHGB	PLT	PT	APTT
UNITS:	% RBCs	% HGBs	10 ³ /mm ³	sec	sec
Group: 1-F : 0 mg base/kg/day					
MEAN	0.6	0.8	217	9.1	10.0
SD	0.45	0.44	44.2	0.50	0.33
N	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day					
MEAN	1.3	1.0	306	8.7	10.3
SD	0.91	0.18	52.9	0.22	1.09
N	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day					
MEAN	1.3	7.0*	272	8.5	10.0
SD	0.91	1.70	87.7	0.15	0.45
N	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day					
MEAN	0.5	12.1*	186	8.8	10.5
SD	0.26	5.28	63.8	0.19	0.48
N	4	4	4	4	4

*-Significant Difference from Control P < .05

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF HEMATOLOGY TESTS
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	WBC	M. Neutrop	I. Neutrop	Lymphocyte	Monocytes	Eosinophil	Basophils	Atypical L
UNITS:	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³	10 ³ /mm ³
Group: 1-F : 0 mg base/kg/day								
MEAN	8.4	5.5	0.1	2.3	0.3	0.3	0.0	0.0
SD	2.54	2.37	0.06	0.49	0.31	0.19	0.00	0.00
N	4	4	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day								
MEAN	8.4	4.9	0.1	3.1	0.2	0.2	0.0	0.0
SD	1.91	1.46	0.10	0.34	0.05	0.08	0.00	0.00
N	4	4	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day								
MEAN	11.7	8.2	0.0	2.8	0.5	0.2	0.0	0.0
SD	4.08	3.95	0.05	0.62	0.16	0.15	0.00	0.00
N	4	4	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day								
MEAN	13.0	9.8	0.2	2.1	0.4	0.6	0.0	0.0
SD	3.84	3.87	0.16	0.32	0.12	0.17	0.00	0.00
N	4	4	4	4	4	4	4	4

WBC corrected for NRBC = or > 10

Table 9.1

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF URINALYSIS TESTS
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): PH SG
UNITS: - g/ml

Group: 1-M : 0 mg base/kg/day
MEAN 7 1.048
SD 0.6 0.0075
N 4 4

Group: 2-M : 0.1 mg base/kg/day
MEAN 6 1.049
SD 0.5 0.0113
N 4 4

Group: 3-M : 1.0 mg base/kg/day
MEAN 7 1.040
SD 1.5 0.0208
N 4 4

Group: 4-M : 4.0 mg base/kg/day
MEAN 7 1.032
SD 0.8 0.0209
N 4 4

Table 9.2

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF URINALYSIS TESTS
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	PH	SG
UNITS:	-	g/ml

Group: 1-M : 0 mg base/kg/day		
MEAN	7	1.050
SD	1.5	0.0261
N	4	4

Group: 2-M : 0.1 mg base/kg/day		
MEAN	6	1.054
SD	0.5	0.0034
N	4	4

Group: 3-M : 1.0 mg base/kg/day		
MEAN	5	1.071
SD	0.0	0.0329
N	4	4

Group: 4-M : 4.0 mg base/kg/day		
MEAN	6	1.060
SD	0.5	0.0082
N	4	4

Table 9.3

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF URINALYSIS TESTS
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): PH SG
UNITS: - g/ml

Group: 1-M : 0 mg base/kg/day
MEAN 7 1.073
SD 1.5 0.0252
N 4 4

Group: 2-M : 0.1 mg base/kg/day
MEAN 7 1.041
SD 0.6 0.0186
N 4 4

Group: 3-M : 1.0 mg base/kg/day
MEAN 6 1.050
SD 0.5 0.0362
N 4 4

Group: 4-M : 4.0 mg base/kg/day
MEAN 7 1.069
SD 0.6 0.0244
N 4 4

Table 9.4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF URINALYSIS TESTS
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	PH	SG
UNITS:	-	g/ml

Group: 1-M : 0 mg base/kg/day		
MEAN	6	1.074
SD	0.5	0.0423
N	4	4

Group: 2-M : 0.1 mg base/kg/day		
MEAN	7	1.033
SD	1.0	0.0253
N	4	4

Group: 3-M : 1.0 mg base/kg/day		
MEAN	6	1.040
SD	0.0	0.0220
N	4	4

Group: 4-M : 4.0 mg base/kg/day		
MEAN	7	1.068
SD	1.4	0.0159
N	4	4

Table 9.5

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF URINALYSIS TESTS
PERIOD: WEEK -1

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): PH SG
UNITS: - g/ml

Group: 1-F : 0 mg base/kg/day
MEAN 7 1.052
SD 1.0 0.0288
N 4 4

Group: 2-F : 0.1 mg base/kg/day
MEAN 7 1.053
SD 0.8 0.0035
N 4 4

Group: 3-F : 1.0 mg base/kg/day
MEAN 6 1.059
SD 0.5 0.0198
N 4 4

Group: 4-F : 4.0 mg base/kg/day
MEAN 7 1.051
SD 0.6 0.0270
N 4 4

Table 9.6
ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF URINALYSIS TESTS
PERIOD: WEEK 13

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): PH SG
UNITS: - g/ml

Group: 1-F : 0 mg base/kg/day
MEAN 7 1.090
SD 1.3 0.0814
N 4 4

Group: 2-F : 0.1 mg base/kg/day
MEAN 7 1.069
SD 1.3 0.0204
N 4 4

Group: 3-F : 1.0 mg base/kg/day
MEAN 6 1.064
SD 0.5 0.0138
N 4 4

Group: 4-F : 4.0 mg base/kg/day
MEAN 6 1.114
SD 0.5 0.0606
N 4 4

Table 9.7

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF URINALYSIS TESTS
PERIOD: WEEK 26

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): PH SG
UNITS: - g/ml

Group: 1-F : 0 mg base/kg/day
MEAN 7 1.059
SD 0.6 0.0257
N 4 4

Group: 2-F : 0.1 mg base/kg/day
MEAN 8 1.088
SD 1.3 0.0320
N 4 4

Group: 3-F : 1.0 mg base/kg/day
MEAN 7 1.083
SD 1.0 0.0337
N 4 4

Group: 4-F : 4.0 mg base/kg/day
MEAN 6 1.087
SD 0.0 0.0502
N 4 4

Table 9.8

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF URINALYSIS TESTS
PERIOD: WEEK 52

STUDY ID: UIC-9
STUDY NO: 219

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s):	PH	SG
UNITS:	-	g/ml

Group: 1-F : 0 mg base/kg/day		
MEAN	7	1.053
SD	1.4	0.0068
N	4	4

Group: 2-F : 0.1 mg base/kg/day		
MEAN	6	1.068
SD	1.0	0.0403
N	4	4

Group: 3-F : 1.0 mg base/kg/day		
MEAN	6	1.055
SD	0.0	0.0159
N	4	4

Group: 4-F : 4.0 mg base/kg/day		
MEAN	7	1.048
SD	1.0	0.0177
N	4	4

Table 10.1

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF ARTERIAL BLOOD GASES DATA
PERIOD: WEEK 53

STUDY ID: UIC-9
STUDY NO: 219BG

SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	PCO2 mmHg	PH -	HCO3- mmol/L	O2 SAT %	PO2 mmHg	TOTAL CO2 mmol/L
Group: 1-M : 0 mg base/kg/day						
MEAN	44.3	7.333	23.7	88.3	63	25.1
SD	2.49	0.0080	1.22	6.25	13.3	1.26
N	4	4	4	4	4	4
Group: 2-M : 0.1 mg base/kg/day						
MEAN	43.7	7.327	23.2	87.9	61	24.5
SD	2.51	0.0152	1.86	5.01	10.3	1.97
N	4	4	4	4	4	4
Group: 3-M : 1.0 mg base/kg/day						
MEAN	43.1	7.333	23.1	81.4	53	24.5
SD	2.45	0.0316	1.23	11.35	13.9	1.30
N	4	4	4	4	4	4
Group: 4-M : 4.0 mg base/kg/day						
MEAN	42.9	7.363	24.6	66.7	43	25.9
SD	4.58	0.0360	0.95	35.52	21.5	1.07
N	4	4	4	4	4	4

Table 10.2

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

SUMMARY OF ARTERIAL BLOOD GASES DATA
PERIOD: WEEK 53

STUDY ID: UIC-9
STUDY NO: 2198G

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

TEST(s): UNITS:	PCO2 mmHg	PH -	HCO3- mmol/L	O2 SAT %	PO2 mmHg	TOTAL CO2 mmol/L
Group: 1-F : 0 mg base/kg/day						
MEAN	44.9	7.348	24.8	85.8	61	26.2
SD	6.13	0.0536	1.65	10.89	19.4	1.69
N	4	4	4	4	4	4
Group: 2-F : 0.1 mg base/kg/day						
MEAN	44.2	7.342	24.2	86.4	57	25.6
SD	2.22	0.0163	1.24	4.51	8.8	1.27
N	4	4	4	4	4	4
Group: 3-F : 1.0 mg base/kg/day						
MEAN	46.0	7.323	24.1	75.8	52	25.5
SD	5.35	0.0361	2.00	24.83	19.6	2.18
N	4	4	4	4	4	4
Group: 4-F : 4.0 mg base/kg/day						
MEAN	43.0	7.319	22.2	84.0	56	23.5
SD	5.48	0.0524	0.30	9.49	12.0	0.37
N	4	4	4	4	4	4

Table 11.1

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

ORGAN WEIGHT SUMMARY (% BRAIN WEIGHT)

STUDY: 219
STUDY NO: 219
SEX: MALE

ALL FATES DAYS: 365-366 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

GROUP:	(1) 1-M	(2) 2-M	(3) 3-M	(4) 4-M
Adrenal Glands(% BRAIN WEIGHT)				
MEAN	1.74	1.72	1.94	1.81
SD	0.310	0.220	0.382	0.367
N	4	4	4	4
Heart(% BRAIN WEIGHT)				
MEAN	127.26	127.08	133.91	138.89
SD	7.972	16.981	7.711	12.078
N	4	4	4	4
Kidneys(% BRAIN WEIGHT)				
MEAN	83.74	78.42	69.21	75.54
SD	13.006	13.132	6.885	7.970
N	4	4	4	4
Liver(% BRAIN WEIGHT)				
MEAN	391.06	373.16	427.54	509.82*
SD	57.371	58.303	17.364	74.414
N	4	4	4	4
Lungs(% BRAIN WEIGHT)				
MEAN	128.70	119.21	163.74	311.82*
SD	12.126	12.322	25.409	55.199
N	4	4	4	4
Pituitary(% BRAIN WEIGHT)				
MEAN	0.12	0.09	0.09	0.11
SD	0.042	0.024	0.032	0.016
N	4	4	4	4
Spleen(% BRAIN WEIGHT)				
MEAN	53.76	43.62	59.85	72.66*
SD	10.179	2.146	9.449	4.547
N	4	4	4	4
Testes + Epididymides(% BRAIN WEIGHT)				
MEAN	28.51	26.04	20.52	22.63
SD	6.277	3.923	4.126	1.932
N	4	4	4	4
Thyroid + Parathyroids(% BRAIN WEIGHT)				
MEAN	1.16	1.25	1.10	1.30
SD	0.318	0.436	0.151	0.323
N	4	4	4	4

(1)-0 mg base/kg/day
(2)-0.1 mg base/kg/day

(3)-1.0 mg base/kg/day
(4)-4.0 mg base/kg/day

*-Significant Difference from Control P < .05

Table 11.2

DRAFTONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

ORGAN WEIGHT SUMMARY (% BRAIN WEIGHT)

STUDY: 219
STUDY NO: 219
SEX: FEMALEALL FATES DAYS: 365-366 ALL BALANCES
ANALYSIS OF VARIANCE USING DUNNETT'S PROCEDURE

GROUP:	(5) 1-F	(6) 2-F	(7) 3-F	(8) 4-F
Adrenal Glands(% BRAIN WEIGHT)				
MEAN	1.87	2.20	2.03	1.83
SD	0.130	0.442	0.278	0.152
N	4	4	4	4
Heart(% BRAIN WEIGHT)				
MEAN	113.48	118.46	103.58	112.78
SD	14.148	7.157	20.630	13.335
N	4	4	4	4
Kidneys(% BRAIN WEIGHT)				
MEAN	57.13	63.21	54.24	61.91
SD	5.990	5.645	7.161	8.844
N	4	4	4	4
Liver(% BRAIN WEIGHT)				
MEAN	364.53	447.36	422.58	522.50
SD	106.982	100.641	124.950	65.180
N	4	4	4	4
Lungs(% BRAIN WEIGHT)				
MEAN	113.44	113.88	132.16	232.74*
SD	18.379	5.807	32.715	52.880
N	4	4	4	4
Ovaries(% BRAIN WEIGHT)				
MEAN	2.02	1.82	1.54	1.78
SD	0.876	0.541	0.531	0.188
N	4	4	4	4
Pituitary(% BRAIN WEIGHT)				
MEAN	0.16	0.13	0.10	0.13
SD	0.054	0.055	0.016	0.068
N	4	4	4	4
Spleen(% BRAIN WEIGHT)				
MEAN	51.91	52.72	53.26	172.31*
SD	22.106	9.832	4.929	115.660
N	4	4	4	4
Thyroid + Parathyroids(% BRAIN WEIGHT)				
MEAN	1.09	1.43	1.08	1.18
SD	0.081	0.103	0.389	0.301
N	4	4	4	4

(5)-0 mg base/kg/day
(6)-0.1 mg base/kg/day(7)-1.0 mg base/kg/day
(8)-4.0 mg base/kg/day

*-Significant Difference from Control P < .05

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Table 12

ONE YEAR ORAL TOXICITY STUDY OF
 WR238605 SUCCINATE IN DOGS

Summary of Microscopic Lesions

ORGAN - lesion	Sex	Dose Group (Dose Level)			
		Control (0 mg base/kg/day)	Low (0.1 mg base/kg/day)	Mid (1.0 mg base/kg/day)	High (4.0 mg base/kg/day)
LUNG					
- Inflammation, chronic, interstitium	M	0/4	0/4	4/4 (1.25)*	4/4 (2.75)
	F	0/4	0/4	4/4 (1.25)	4/4 (2.25)
- Accumulation, foamy macrophage	M	0/4	0/4	4/4 (2.00)	4/4 (3.00)
	F	0/4	0/4	4/4 (1.50)	4/4 (2.75)
LIVER					
- Pigmentation, Kupffer cell	M	0/4	0/4	3/4 (0.75)	4/4 (2.50)
	F	0/4	2/4 (0.50)	4/4 (2.00)	4/4 (2.00)
- Inflammation, subacute, centrilobular	M	0/4	0/4	0/4	3/4 (0.75)
	F	0/4	0/4	0/4	2/4 (0.50)
KIDNEY					
- Pigmentation, epithelium, cortex	M	0/4	0/4	2/4 (0.50)	4/4 (2.50)
	F	0/4	1/4 (0.25)	0/4	2/4 (0.75)
SPLEEN					
- Pigmentation	M	2/4 (1.00)	1/4 (0.25)	3/4 (1.25)	4/4 (2.50)
	F	1/4 (0.25)	2/4 (0.50)	4/4 (2.00)	4/4 (2.00)
BONE MARROW, RIB					
- Hyperplasia	M	0/4	0/4	1/4 (0.25)	3/4 (1.25)
	F	0/4	0/4	1/4 (0.25)	4/4 (1.75)
GALLBLADDER					
- Pigmentation, macrophage, submucosa	M	0/4	0/4	0/4	2/4 (1.00)
	F	0/4	0/4	0/4	1/4 (0.25)
TONSIL					
- Pigmentation, macrophage	M	0/4	0/4	3/4 (0.75)	4/4 (2.50)
	F	0/4	0/4	1/4 (0.75)	4/4 (3.00)
LYMPH NODE, MANDIBULAR					
- Pigmentation, macrophage	M	4/4 (1.00)	2/4 (0.50)	4/4 (1.00)	4/4 (2.50)
	F	2/4 (0.50)	2/4 (0.75)	4/4 (1.00)	4/4 (1.75)
LYMPH NODE, MESENTERIC					
- Pigmentation, macrophage	M	0/4	0/4	3/4 (0.75)	4/4 (2.00)
	F	0/4	0/4	4/4 (1.25)	4/4 (1.75)

* Incidence (mean group severity score)

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Table 12 (contd.)

ONE YEAR ORAL TOXICITY STUDY OF
 WR238605 SUCCINATE IN DOGS

Summary of Microscopic Lesions

ORGAN - lesion	Sex	Dose Group (Dose Level)			
		Control (0 mg base/kg/day)	Low (0.1 mg base/kg/day)	Mid (1.0 mg base/kg/day)	High (4.0 mg base/kg/day)
LYMPH NODE, BRONCHIAL					
- Accumulation, pigmented macrophage	M	-	-	2/2 (2.50)*	4/4 (3.00)
	F	-	-	1/1 (3.00)	4/4 (3.00)
- Hemorrhage	M	-	-	-	1/4 (0.50)
	F	-	-	1/1 (1.00)	1/4 (0.25)
LYMPH NODE, MEDIASTINAL					
- Accumulation, pigmented macrophage	M	-	0/1	-	2/2 (2.00)
	F	-	-	-	2/2 (2.00)
- Hemorrhage	M	-	1/1 (2.00)	-	2/2 (2.00)
	F	-	-	-	2/2 (2.50)

* Incidence (mean group severity score)

- Not examined

Figure 1

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

Summary of Male Body Weights

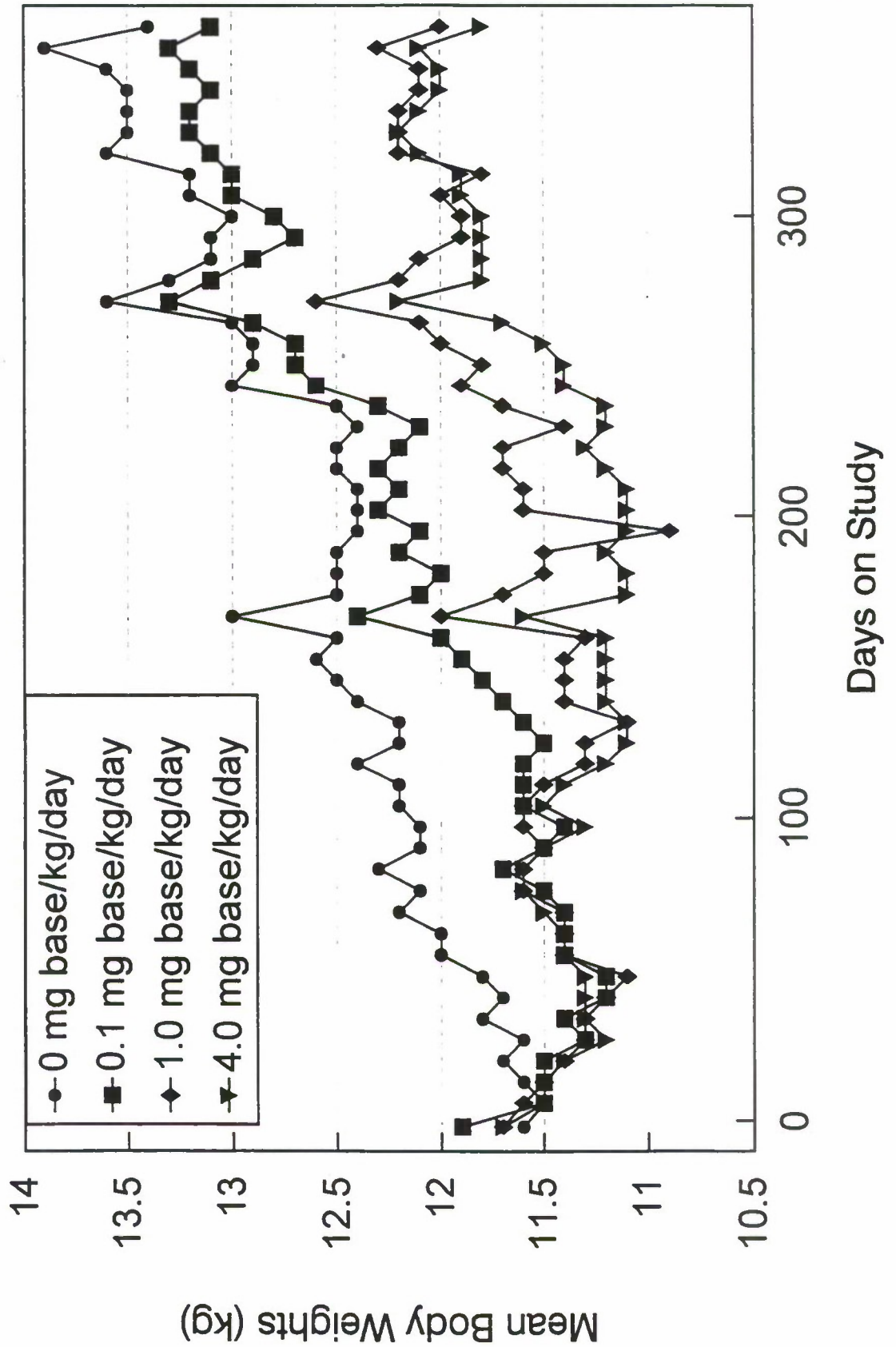
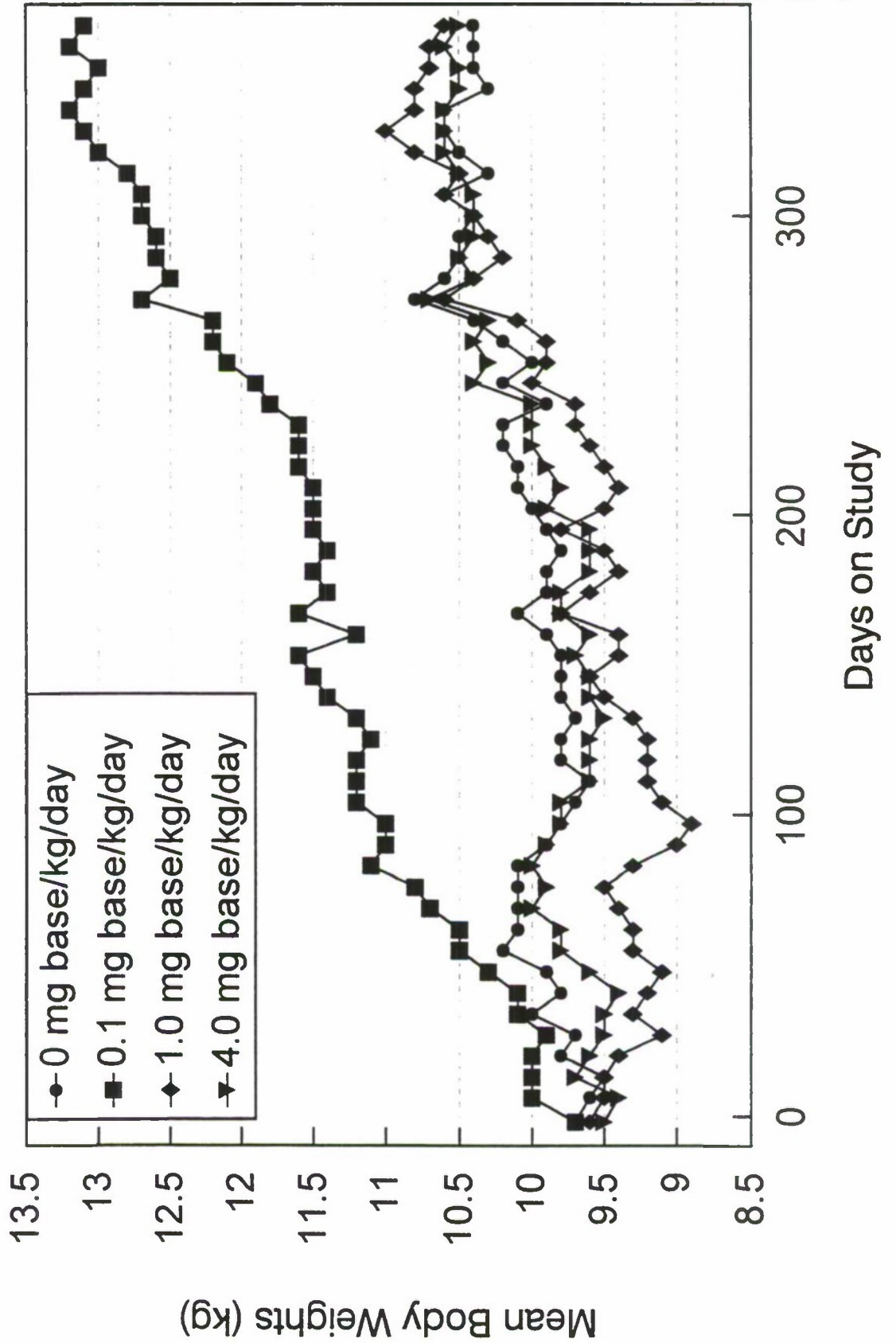


Figure 2
ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

Summary of Female Body Weights



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APPENDIX A
Analytical Chemistry Report

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ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS

UIC/TRL STUDY NUMBER 219

Part I: Identity and Purity of 8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline Succinate (WR238605 Succinate)

Part II: Dosing Formulation Analysis of WR238605

Analyst: Thomas Tolhurst, B. S.
A. Karl Larsen, Jr., Ph. D.

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

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

Report prepared by: Thomas Tolhurst, B. S.

Report Prepared: September 22, 1997

Approved: October 1, 1997
Eugene F. Woods, Ph. D.
Director, Drug Disposition Research Laboratory

Part I: Identity and Purity of 8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline Succinate (WR238605 Succinate)

Objective

The objectives of this investigation were to confirm the identity and establish the purity of 8-[(4-amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline succinate (WR238605 Succinate).

Experimental

The subject sample (WR238605 Succinate, lot no. KB-02-201) was supplied by the Toxicology Research Laboratory (TRL) and stored at -20°C.

Description

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

Purity

HPLC System

Solvent Delivery System:	Waters 501 Pump
Injector:	Rheodyne 7125 with 20 μ L sample loop
Analytical column:	Phenomenex 10 μ m, C ₁₈ , 300 x 3.9 mm
Detector:	Kratos, SpectraFlow 773, UV set at 268 nm
Integrator:	Spectra-Physics SP 4270
Mobile Phase:	9.0 mL <i>o</i> -phosphoric acid (85%) and 6.9 g sodium acetate per liter of methanol:water (75:25, v/v); flow rate 1.5 mL/minute

Procedure

Five solutions of WR238605 Succinate were prepared as follows. Ten mg of subject sample were weighed into a 10 mL volumetric flask. The sample was dissolved in and the volume brought to the mark with mobile phase. A 20 μ L aliquot of each solution was immediately chromatographed. Purity of WR238605 Succinate was determined prior to dosing initiation, after six months of dosing and after completion of dosing for Study No. 219.

Calculations

Quantitations were based on the assumption of equal detector response per unit weight of all UV-absorbing components.

Areas of WR238605 and other detectable components in the subject sample chromatograms were employed in the following equation to calculate the percentage of WR238605 present in the subject sample.

$$\% \text{ Purity} = \{ \text{area of WR238605} / (\text{total area} - \text{mobile phase area}) \} \times 100$$

Results

Typical chromatograms are shown in Figures 1, 2 and 3. The samples submitted for purity analysis were found to contain < 0.01% of UV-absorbing impurities at 268 nm. Percent purity of the initial sample of WR238605 Succinate was found to be $99.99 \pm 0.004\%$; the six-month and terminal purities were each $100.00 \pm 0.000\%$. These results are presented in Tables 1, 2 and 3.

Identification**GC-MS System**

Gas Chromatograph:	Hewlett Packard Model 5890 Series II
Mass Selective Detector (MSD):	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. 270° C, carrier gas, helium with a flow rate of 2 mL/minute and a 10:1 split ratio

Procedure

Subject sample (WR238605 Succinate) was submitted prior to the start of Study No. 219 for GC-MS analysis. The sample was dissolved in hexane:ethanol (4:1) to a concentration of 1 µg/mL and a 2 µL aliquot was injected on column. The MSD scanned from 40 amu to 475 amu at a rate of 1 scan per second.

Results

The mass spectrum indicates a molecular ion = 463 (M^+ free base) and $m/e = 405$ [M^+ free base minus $(CH_2)_3NH_2$]. This pattern is consistent with the structural formula of WR238605 and corresponds to the finding observed by SRI International (See Report No. 469, 9 May, 1984).

Figure 4 shows the mass spectrum for WR238605 sample submitted prior to initiation of Study No. 219.

Figure 1

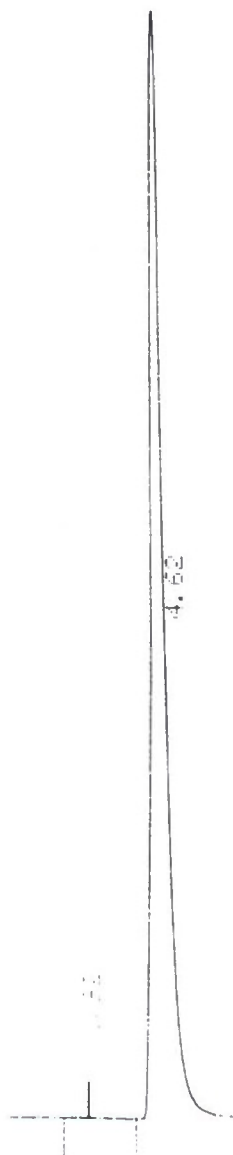
Initial purity chromatogram for WR238605 Succinate



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Figure 2

Six month purity chromatogram for WR238605



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Figure 3

Terminal purity chromatogram for WP238605 Succinate

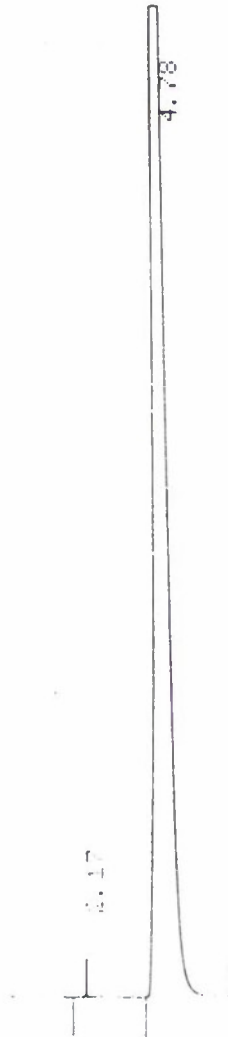


Table 1

Initial purity data obtained as areas for WR238605 Succinate solutions

Peak I. D.	~Retention Time (mins)	1	2	3	4	5
A*	2.1	-	-	6084	-	5821
B	2.4	-	-	-	-	206
C	2.9	-	-	-	434	-
D	3.4	-	-	-	345	-
E	4.3	2459	-	2678	2935	2633
F ^a	4.7	27638512	27147723	27847832	26962969	27922933
% Purity per Run ^b		99.99	100.00	99.99	99.99	99.99

* Mobile phase area

^a WR238605 peak

^b % Purity per run = {area of WR238605 Succinate/(total area - mobile phase area)} x 100

Table 2

Six-month purity data obtained as areas for WR238605 Succinate solutions

Peak I. D.	~Retention Time (mins)	1	2	3	4	5
A*	2.1	9791	2474	-	1794	8216
B ^a	4.6	48604597	32113968	31067410	29875691	29636466
% Purity per Run ^b		100.00	100.00	100.00	100.00	100.00

* Mobile phase area

^a WR238605 peak

^b % Purity per run = {area of WR238605 Succinate/(total area - mobile phase area)} x 100

Table 3

Terminal purity data obtained as areas for WR238605 Succinate solutions

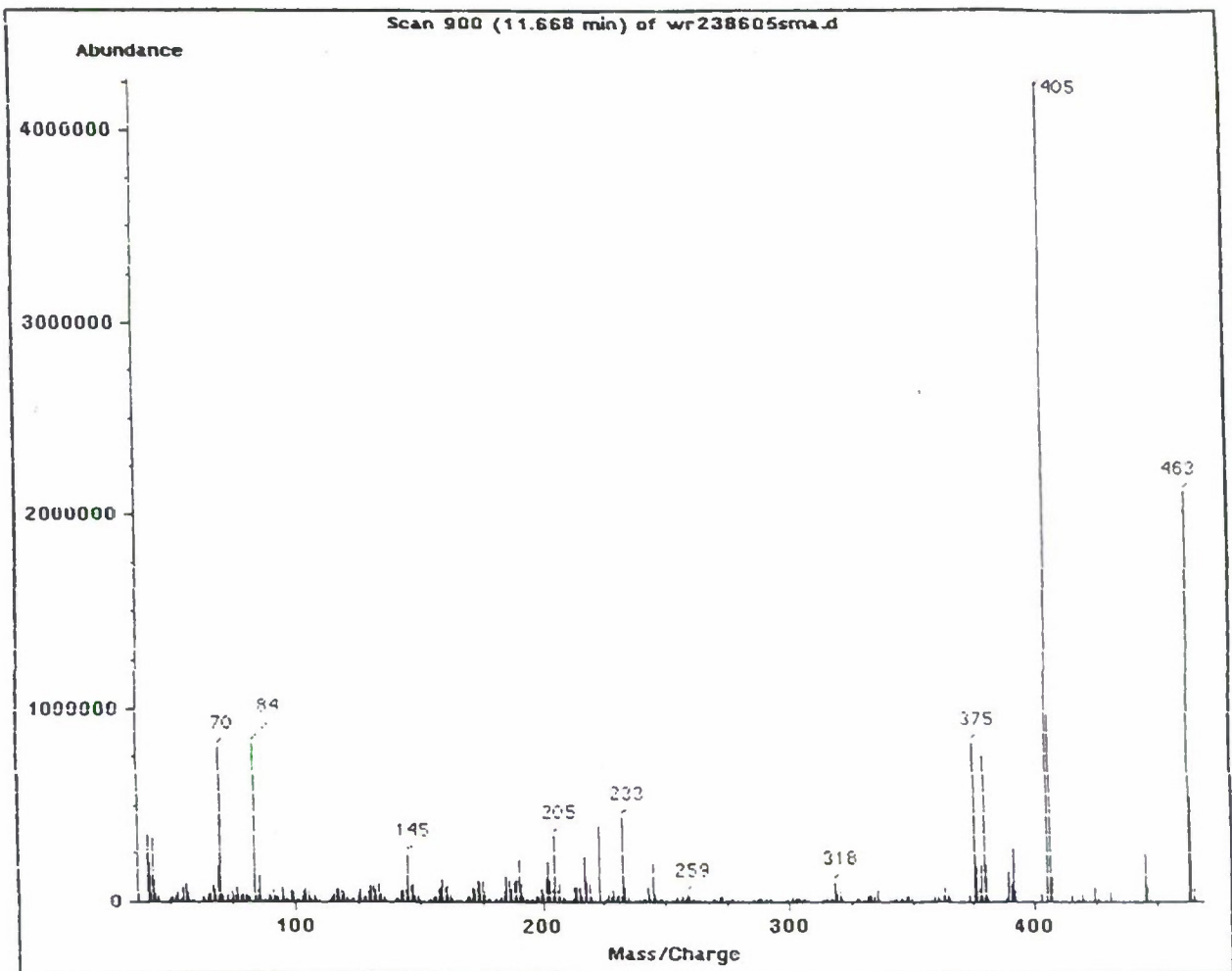
Peak I. D.	~Retention Time (mins)	1	2	3	4	5
A*	2.2	9229	4589	-	1481	1432
B ^a	4.8	28599795	30051351	29636330	30392161	29970617
% Purity per Run ^b		100.00	100.00	100.00	100.00	100.00

* Mobile phase area

^a WR238605 peak^b % Purity per run = {area of WR238605 Succinate/(total area - mobile phase area)} x 100

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Figure 4
Mass Spectrum of WR238605



Part II: Analytical Method for Determination of WR238605 in Dosing Suspensions

Introduction

Samples from UIC/TRL Study Number 219 were submitted by the Toxicology Research Laboratory (UIC/TRL) to the Drug Disposition Laboratory for quantitation of WR238605 in dosing formulations. All samples were analyzed according to Standard Operating Procedure Number 01MA10-01, titled Quantitation of WR238605 in Suspension using HPLC and is briefly described below. The concentrations of WR238605 were determined by high performance liquid chromatography (HPLC) using a reverse phase column for separation and UV detection at 268 nm. A standard curve was analyzed at the beginning and end of each assay run and replicate analysis of controls were performed during each assay run.

Reagents

The subject sample (WR238605 Succinate, mole fraction = 0.8) was supplied by the Toxicology Research Laboratory. HPLC grade sodium acetate, *o*-phosphoric acid and methanol were purchased from Fisher Scientific. HPLC grade water was supplied by a Millipore, Milli-Q^{UF} Plus Water System.

Standard Solutions

A 0.8 mg/mL WR238605 stock solution (mole fraction = 0.8) was prepared by weighing 100 mg of WR238605 Succinate into a 100 mL volumetric flask. The content was dissolved in and the volume was brought to the mark with mobile phase. A WR238605 working standard solution (80 µg/mL) was prepared by transferring 10 mL of the 0.8 mg/mL solution to a 100 mL volumetric flask and diluting to the mark with mobile phase. Calibration standard solutions were prepared in mobile phase using the 80 µg/mL working stock solution as follows:

<u>Volume Transferred (mL)</u>	<u>Final Volume (mL)</u>	<u>Final Concentration (µg/mL)</u>
1.0	10	8
2.0	10	16
4.0	10	32
6.0	10	48
8.0	10	64

Control Solutions

Control A (0.8 mg/mL) and Control B (2.4 mg/mL) were prepared by weighing 25 mg and 30 mg of WR238605 Succinate (mole fraction 0.8) into 25 mL and 10 mL volumetric flasks, respectively. The drug quantities were dissolved in and diluted to the mark with mobile phase. Working control solutions were prepared by diluting Control A 1:25 and Control B 1:62.5 with mobile phase.

HPLC System

Solvent Delivery System:	Waters 510 Pump
Injector:	Rheodyne 7125 with 20 μ L sample loop
Analytical column:	Phenomenex, Bondacclone 10 μ , C ₁₈ , 300 x 3.9 mm
Detector:	Kratos, Spectroflow 773 UV at 268 nm
Integrator:	Spectra-Physics SP4270
Mobile Phase:	9.0 mL of <i>o</i> -phosphoric acid (85%) and 6.9 g of sodium acetate per liter of methanol:water (75:25, v/v); flow rate 1.5 mL/minute

Dosing Formulations

Dosing formulations submitted for analysis were diluted with mobile phase prior to analysis such that the final concentration of WR238605 was within the range of the standard curve (8 to 80 μ g/mL). Received dosing formulation samples at WR238605 concentrations of 0.00 mg base/mL and 0.625 mg base/mL were diluted 1:10, the 6.250 mg base/mL dosing formulation was diluted 1:100 and the 25.000 mg base/mL dosing formulation was diluted 1:625. The dosing formulations were diluted in triplicate and each dilution was analyzed for WR238605 concentration.

Results

The standard curves were linear over the range of WR238605 assayed (8 μ g/mL to 80 μ g/mL). A representative standard curve is shown in Figure 5. Dosing formulation analysis from UIC/TRL Study Number 219 is found in Table 4. All samples except the post dose 6.25 mg base/mL formulation on 09/26/96 and 10/24/96 were within 10% of their target concentration.

Figure 5

Representative Standard Curve for WR238605

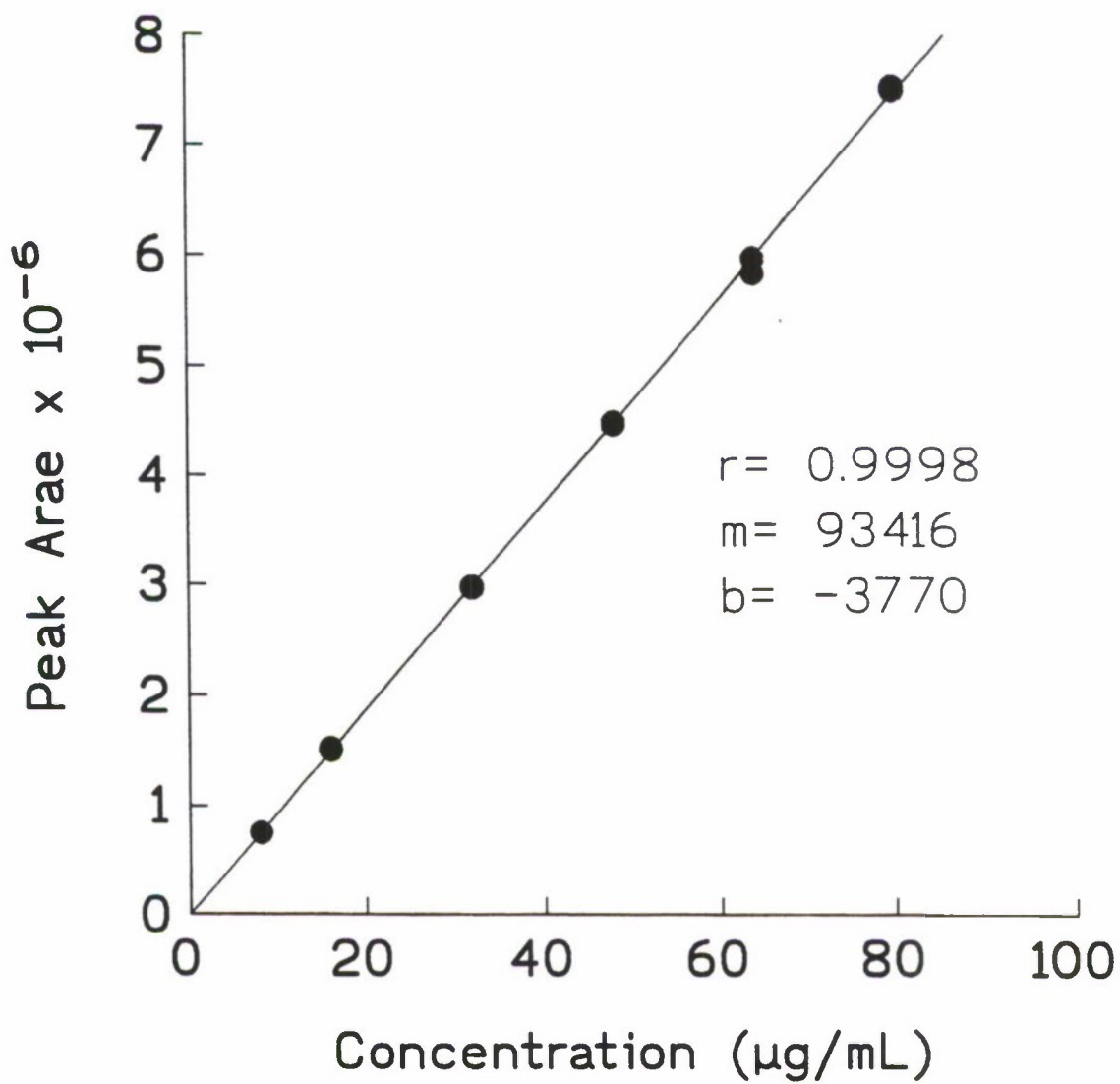


Table 4

ONE YEAR ORAL TOXICITY STUDY OF WR238605 SUCCINATE IN DOGS

Study Weeks	Target Concentration (mg base/ml)	Predose Analysis ^a			Postdose Analysis ^a		
		Date	(mg base/ml)	% Target	Date	(mg base/ml)	% Predose
1 & 2	0.000	07/16/96	0	-	08/01/96	0	-
	0.625		0.650 ± 0.005	104.0		0.593 ± 0.010	91.2
	6.250		6.468 ± 0.278	103.5		6.409 ± 0.027	99.1
	25.000		25.406 ± 0.278	101.6		27.330 ± 0.179	107.6
5 & 6	0.000	08/13/96	0	-	08/29/96	0	-
	0.625		0.593 ± 0.006	94.9		0.598 ± 0.019	100.8
	6.250		6.267 ± 0.031	100.3		6.192 ± 0.020	98.8
	25.000		25.000 ± 0.080	100.0		24.286 ± 0.524	97.1
9 & 10	0.000	09/10/96	0	-	09/26/96	0	-
	0.625		0.592 ± 0.012	94.7		0.579 ± 0.001	97.8
	6.250		6.047 ± 0.058	96.8		4.341 ± 0.022 ^b	71.8
	25.000		24.928 ± 0.111	99.7		24.963 ± 0.804	99.9
11 & 12*	0.000	-	-	-	10/08/96	0	-
	0.625		-	-		0.594 ± 0.004	95.0 ^c
	6.250		-	-		6.326 ± 0.249	101.2 ^c
	25.000		-	-		25.775 ± 0.061	103.1 ^c
13 & 14	0.000	10/08/96	0	-	10/24/96	0	-
	0.625		0.564 ± 0.017	90.2		0.593 ± 0.004	105.1
	6.250		6.352 ± 0.049	101.6		4.897 ± 0.063	77.1
	25.000		24.521 ± 1.577	98.1		25.923 ± 0.186	105.7
17 & 18	0.000	11/05/96	0	-	11/21/96	0	-
	0.625		0.625 ± 0.019	100.0		0.580 ± 0.013	92.8
	6.250		6.120 ± 0.254	97.9		6.415 ± 0.069	104.8
	25.000		25.318 ± 0.550	101.3		25.227 ± 0.252	99.6
21 & 22	0.000	12/03/96	0	-	12/19/96	0	-
	0.625		0.623 ± 0.007	99.7		0.603 ± 0.033	96.8
	6.250		6.395 ± 0.109	102.3		5.974 ± 0.305	93.4
	25.000		26.038 ± 0.215 ^d	104.2		25.876 ± 1.238	99.4
25 & 26	0.000	12/30/96	0	-	01/16/97	0	-
	0.625		0.611 ± 0.002	97.8		0.595 ± 0.001	97.4
	6.250		6.302 ± 0.155	100.8		6.024 ± 0.026	95.6
	25.000		24.773 ± 0.072	99.1		25.489 ± 0.112	102.9
31&32	0.000	02/11/97	0	-	02/27/97	0	-
	0.625		0.609 ± 0.003	97.4		0.622 ± 0.013	102.1
	6.250		6.336 ± 0.033	101.4		6.548 ± 0.091	103.3
	25.000		23.906 ± 1.070	95.6		25.534 ± 0.193	106.8
37 & 38	0.000	03/25/97	0	-	04/10/97	0	-
	0.625		0.602 ± 0.002	96.3		0.602 ± 0.003	100.0
	6.250		6.021 ± 0.093	96.3		6.206 ± 0.041	103.1
	25.000		24.987 ± 0.192	99.9		24.993 ± 0.175	100.0
43 & 44	0.000	05/06/97	0	-	05/22/97	0	-
	0.625		0.636 ± 0.003	101.8		0.600 ± 0.001	94.3
	6.250		6.159 ± 0.284	98.5		5.975 ± 0.040	97.0
	25.000		26.471 ± 0.427	105.9		25.958 ± 0.003	98.1
49 & 50	0.000	06/17/97	0	-	07/03/97	0	-
	0.625		0.602 ± 0.021	96.3		0.593 ± 0.003	98.5
	6.250		6.300 ± 0.078 ^d	100.8		6.299 ± 0.085	100.0
	25.000		25.256 ± 1.138	101.0		25.162 ± 1.278	99.6

^an=3^bn=6^c% Target^dn=2

*Predose samples not submitted for analysis

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APPENDIX B
Clinical Pathology Methodology

CLINICAL CHEMISTRYAlanine Aminotransferase (ALT/GPT)

Modified Wroblewski & La Due procedure
Ciba-Corning 550 Express Clinical Chemistry System
Henry, R.J., Chiamori, N., Golub, O.J. and Berkman, S.
Am. J. Clin. Path., 34, 381, 1960.

Aspartate Aminotransferase

Modified Karmen procedure
Ciba-Corning 550 Clinical Chemistry System
Bergmeyer, H.V., Scheibe, P., and Wahlefeld, A.W.
Clin. Chem., 24, 68, 1978.

Total Protein

Biuret technique
Ciba-Corning 550 Express Clinical Chemistry System
Kingsley, G.R.
J. Biol. Chem. 131, 197, 1939.

Albumin

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

Total Bilirubin

Modified Walters and Gerard method
Ciba-Corning 550 Express Clinical Chemistry System
Ertinghausen, G., Fabiny-Byrd, D.L., Tiffany, T.O., and Carey, S.J.
Clin. Chem. 19, 1366, 1973.

Alkaline Phosphatase

Modified Bessey-Lowry procedure
Ciba-Corning 550 Express Clinical Chemistry System
Neumann, H. and Von Vreedendaal
M. Clin. Chem. Acta., 17, 183, 1967.

Gamma Glutamyl Transferase (GGT)

JFCC Methods for Gamma Glutamyl Transferase
Shaw, L.M., Stromme, J.H., London, J.L., Theodorsen, L.
J. Clin. Chem. C; in, Biochem. 21 (1983) 633-646.

Cholesterol

Cholesterol esterase-oxidase method
Ciba-Corning 550 Express Clinical Chemistry System
Rosechlow, P., et. al
Z.F. Klin. Chem. V. Klin. Biochem. 12, 226, 1974.

CLINICAL CHEMISTRY (Contd.)Triglycerides

Tetrazolium salt reduction method

Ciba-Corning 550 Express Clinical Chemistry System

Klotzsch, S., *et. al.*

Advances Automated Analysis, Vol. 1, Mediad Inc., Tarrytown, N.Y., p. 111, 1973.

Lactate Dehydrogenase

L → P technique

Ciba-Corning 550 Express Clinical Chemistry System

Wacker, W.E.C., Ulmer, D.D., Valle, B.L.

New England J Med. 225, 449, 1956.

Creatine Kinase

Modification of Szasz *et al.* procedure

Ciba-Corning 550 Express Clinical Chemistry System

Clin. Chem. 22, 650-656, 1976.

Urea Nitrogen (BUN)

Modified urease technique

Ciba-Corning 550 Express Clinical Chemistry System

Talke, H. and Schubert, G.E.

Klin. Wehnschr. 43, 174, 1965.

Creatinine

Jaffe method

Ciba-Corning 550 Express Clinical Chemistry System

Larsen. K.

Clin. Chem. Acta, 41, 209, 1972

Na+, K+

Ion specific electrodes

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

Chloride

Mecuric thiocyanate procedure

Ciba-Corning 550 Express Clinical Chemistry System

Zall, O.M., Fisher, D. and Garner, M.Q.

Anal. Chem, 28, 1065, 1956.

Calcium

Modified alizarin procedure

Ciba-Corning 550 Express Clinical Chemistry System

Frings, C.S., *et. al.*

Clin. Chem., 16, 816, 1970.

CLINICAL CHEMISTRY (Contd.)Phosphorus, Inorganic

Ammonium molybdate method
Ciba-Corning 550 Express Clinical Chemistry System
Fiske, C.H. and Subbarow, Y.
J. Biol. Chem. 66, 325, 1925.

Glucose

Hexokinase method
Ciba-Corning 550 Express Clinical Chemistry System
Bondar, J.L. and Mead, D.C.
Clin. Chem. 20, 586, 1974.

Haptoglobin

Antigen-antibody method
Ciba-Corning 550 Express Clinical Chemistry System
Atlantic Antibodies Test Kit

HEMATOLOGYErythrocyte Count

Electronic counting procedure
Sysmex K1000 Hematology Analyzer

Hemoglobin

Cyanomethemoglobin method
Sysmex K1000 Hematology Analyzer

Hematocrit

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

Mean Corpuscular Volume (MCV)

Indirect method; calculated value based on hematocrit and red blood cell count

Mean Corpuscular Hemoglobin (MCH)

Indirect method; calculated value based on erythrocyte count and hemoglobin

Mean Corpuscular Hemoglobin Concentration (MCHC)

Indirect method; calculated value based on hematocrit and hemoglobin

Reticulocyte Count

New methylene blue staining procedure
Brecher, G., Am. J. Clin. Path., 19, 895, 1949.

Platelet Count

Electronic counting procedure
Sysmex K1000 Hematology Analyzer

Activated Partial Thromboplastin Time (APTT)

Electra 700 coagulation machine

Prothrombin Time (PT)

Electra 700 coagulation machine

Leukocyte Count

Electronic counting procedure
Sysmex K1000 Hematology Analyzer

Leukocyte Differential Count

Neutrophils - Immature (bands)

Neutrophils - Mature (segs)

Monocytes

Basophils

Lymphocytes

Eosinophils

Wright stain procedure

Schalm, O.W., Jain, N.C. and Carroll, E.J. Veterinary Hematology, Color Plates Chapter, 3rd Edition, Lee and Febiger, 1975.

HEMATOLOGY (Contd.)

Nucleated RBCs

Wright stain procedure

Schalm, O.W., Jain, N.C. and Carroll, E.J. Veterinary Hematology, Color Plates Chapter, 3rd Edition, Lee and Febiger, 1975.

RBC Morphology

Wright stain procedure

Schalm, O.W., Jain, N.C. and Carroll, E.J. Veterinary Hematology, Color Plates Chapter, 3rd Edition, Lee and Febiger, 1975.

Heinz Bodies

Methyl violet staining technique

Methemoglobin

Co-oximeter (Instrumentation Laboratory Model 282)

URINALYSIS

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Qualitative Measurements

Ketones, Protein, Glucose, Blood, Bilirubin, Urobilinogen,
Nitrite, Leukocytes, pH
Boehringer Mannheim Chemstrip 9 Reagent Strips

Specific Gravity

Optical temperature compensated refractometer

Microscopic Evaluation

Urinary sediment stained with kova-stain and evaluated using the Ames Atlas of Urine Sediment, Ames Co., Division Miles Laboratories, Elkhart, Indiana.

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APPENDIX C

Individual Clinical Signs and Clinical Observations

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ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL CLINICAL SIGNS

STUDY: 219
DAY 1-DAY 366

GROUP: 1-M
DOSE: 0 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8922	Normal Scheduled Sacrifice			DAY 1-DAY 364 DAY 365
8915	Normal Scheduled Sacrifice			DAY 1-DAY 364 DAY 365
8911	Diarrhea Diarrhea Normal Normal Normal Scheduled Sacrifice	1 1		DAY 202 DAY 281 DAY 1-DAY 201 DAY 203-DAY 280 DAY 282-DAY 365 DAY 366
8909	Normal Scheduled Sacrifice			DAY 1-DAY 364 DAY 365

Severity Codes

<u>Observation</u>	<u>Severity</u>	<u>Description</u>
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

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ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL CLINICAL SIGNS

STUDY: 219
DAY 1-DAY 366

GROUP: 2-M
DOSE: 0.1 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8923	Normal Scheduled Sacrifice			DAY 1-DAY 365 DAY 366
8907	Normal Scheduled Sacrifice			DAY 1-DAY 365 DAY 366
8919	Normal Scheduled Sacrifice			DAY 1-DAY 364 DAY 365
8924	Diarrhea Normal Normal Scheduled Sacrifice	1		DAY 217 DAY 1-DAY 216 DAY 218-DAY 364 DAY 365

Severity Codes

<u>Observation</u>	<u>Severity</u>	<u>Description</u>
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 219
DAY 1-DAY 366

GROUP: 3-M
DOSE: 1.0 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8917	Diarrhea	1		DAY 90
	Diarrhea	1		DAY 271
	Diarrhea w/Red Material			DAY 348
	Normal			DAY 1-DAY 89
	Normal			DAY 91-DAY 270
	Normal			DAY 272-DAY 347
	Normal			DAY 349-DAY 364
	Scheduled Sacrifice			DAY 365
8910	Diarrhea	1		DAY 334
	Normal			DAY 1-DAY 333
	Normal			DAY 335-DAY 364
	Scheduled Sacrifice			DAY 365
8913	Diarrhea	1		DAY 37
	Diarrhea	1		DAY 68
	Diarrhea	1		DAY 84
	Diarrhea	1		DAY 287
	Normal			DAY 1-DAY 36
	Normal			DAY 38-DAY 67
	Normal			DAY 69-DAY 83
	Normal			DAY 85-DAY 286
	Normal			DAY 288-DAY 364
	Scheduled Sacrifice			DAY 365
8914	Diarrhea	1		DAY 27
	Diarrhea	1		DAY 103
	Diarrhea	1		DAY 153
	Diarrhea	1		DAY 230
	Diarrhea	1		DAY 271
	Normal			DAY 1-DAY 26
	Normal			DAY 28-DAY 102
	Normal			DAY 104-DAY 152
	Normal			DAY 154-DAY 229
	Normal			DAY 231-DAY 270
	Normal			DAY 272-DAY 365
		Scheduled Sacrifice		

Severity Codes

Observation	Severity	Description
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 219
DAY 1-DAY 366

GROUP: 4-M
DOSE: 4.0 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8918	Blue Tongue	1		DAY 120
	Diarrhea	1		DAY 27
	Diarrhea	1		DAY 49
	Diarrhea	1		DAY 181
	Diarrhea	2		DAY 209
	Diarrhea	2		DAY 350
	Normal			DAY 1-DAY 26
	Normal			DAY 28-DAY 48
	Normal			DAY 50-DAY 119
	Normal			DAY 121-DAY 180
	Normal			DAY 182-DAY 208
	Normal			DAY 210-DAY 349
	Normal			DAY 351-DAY 365
	Scheduled Sacrifice			DAY 366
8908	Blue Tongue	1		DAY 20
	Blue Tongue	1		DAY 51
	Blue Tongue	1		DAY 147
	Blue Tongue	1		DAY 170
	Blue Tongue	1		DAY 197
	Diarrhea	1		DAY 362
	Diarrhea	2		DAY 181
	Normal			DAY 1-DAY 19
	Normal			DAY 21-DAY 50
	Normal			DAY 52-DAY 146
	Normal			DAY 148-DAY 153
	Normal			DAY 155-DAY 169
	Normal			DAY 171-DAY 180
	Normal			DAY 182-DAY 196
	Normal			DAY 198-DAY 361
Scheduled Sacrifice			DAY 366	
Vomit Seen In Run			DAY 154	
8926	Blue Tongue	1		DAY 71
	Blue Tongue	1		DAY 120
	Blue Tongue	1		DAY 124

Severity Codes

Observation	Severity	Description
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 219
DAY 1-DAY 366

GROUP: 4-M
DOSE: 4.0 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
	Blue Tongue	1		DAY 126
	Blue Tongue	1		DAY 152
	Blue Tongue	1		DAY 170
	Blue Tongue	1		DAY 260
	Blue Tongue	1		DAY 293
	Diarrhea	1		DAY 28
	Diarrhea	1		DAY 32
	Diarrhea	1		DAY 34
	Normal			DAY 1-DAY 27
	Normal			DAY 29-DAY 31
	Normal			DAY 33
	Normal			DAY 35-DAY 70
	Normal			DAY 72-DAY 119
	Normal			DAY 121-DAY 123
	Normal			DAY 125
	Normal			DAY 127-DAY 151
	Normal			DAY 153-DAY 168
	Normal			DAY 171-DAY 259
	Normal			DAY 261-DAY 292
	Normal			DAY 294-DAY 319
	Normal			DAY 321-DAY 364
	Scheduled Sacrifice			DAY 365
	Vomit Seen In Run			DAY 169
	Vomit Seen In Run			DAY 320
8921	Blue Tongue	1		DAY 41
	Diarrhea	1		DAY 132
	Normal			DAY 1-DAY 40
	Normal			DAY 42-DAY 131
	Normal			DAY 133-DAY 188
	Normal			DAY 190-DAY 365
	Scheduled Sacrifice			DAY 366
	Vomit Seen In Run			DAY 189

Severity Codes

Observation	Severity	Description
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INDIVIDUAL CLINICAL SIGNS

STUDY: 219
DAY 1-DAY 366

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

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8929	Normal Scheduled Sacrifice			DAY 1-DAY 365 DAY 366
8942	Diarrhea Normal Normal Scheduled Sacrifice	1		DAY 188 DAY 1-DAY 187 DAY 189-DAY 365 DAY 366
8930	Normal Scheduled Sacrifice			DAY 1-DAY 364 DAY 365
8938	Normal Scheduled Sacrifice			DAY 1-DAY 364 DAY 365

Severity Codes

<u>Observation</u>	<u>Severity</u>	<u>Description</u>
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 219
DAY 1-DAY 366

GROUP: 2-F
DOSE: 0.1 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8935	Diarrhea Normal Normal Scheduled Sacrifice	2		DAY 223 DAY 1-DAY 222 DAY 224-DAY 365 DAY 366
8937	Normal Scheduled Sacrifice			DAY 1-DAY 365 DAY 366
8934	Diarrhea Diarrhea Normal Normal Normal Scheduled Sacrifice	1 1		DAY 21 DAY 55 DAY 1-DAY 20 DAY 22-DAY 54 DAY 56-DAY 365 DAY 366
8945	Normal Scheduled Sacrifice			DAY 1-DAY 365 DAY 366

Severity Codes

<u>Observation</u>	<u>Severity</u>	<u>Description</u>
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INDIVIDUAL CLINICAL SIGNS

STUDY: 219
DAY 1-DAY 366

GROUP: 3-F
DOSE: 1.0 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8928	Normal Scheduled Sacrifice			DAY 1-DAY 365 DAY 366
8940	Diarrhea Normal Normal Scheduled Sacrifice	1		DAY 62 DAY 1-DAY 61 DAY 63-DAY 364 DAY 365
8931	Diarrhea Normal Normal Scheduled Sacrifice	1		DAY 211 DAY 1-DAY 210 DAY 212-DAY 365 DAY 366
8943	Blue Tongue Diarrhea Normal Normal Normal Normal Scheduled Sacrifice Vomit Seen In Run	1 1		DAY 20 DAY 83 DAY 1-DAY 19 DAY 21-DAY 37 DAY 39-DAY 82 DAY 84-DAY 364 DAY 365 DAY 38

Severity Codes

<u>Observation</u>	<u>Severity</u>	<u>Description</u>
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

DRAFT

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

INDIVIDUAL CLINICAL SIGNS

STUDY: 219
DAY 1-DAY 366

GROUP: 4-F
DOSE: 4.0 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8941	Diarrhea	1		DAY 34
	Diarrhea	1		DAY 202
	Diarrhea	1		DAY 300
	Diarrhea	1		DAY 343
	Normal			DAY 1-DAY 33
	Normal			DAY 35-DAY 201
	Normal			DAY 203-DAY 299
	Normal			DAY 301-DAY 342
	Normal			DAY 344-DAY 364
		Scheduled Sacrifice		
8933	Blue Tongue	1		DAY 120
	Blue Tongue	1		DAY 141
	Blue Tongue	1		DAY 146-DAY 147
	Blue Tongue	1		DAY 149
	Blue Tongue	1		DAY 169-DAY 170
	Blue Tongue	1		DAY 198
	Blue Tongue	1		DAY 215
	Blue Tongue	1		DAY 243
	Diarrhea	1		DAY 27-DAY 30
	Diarrhea	1		DAY 46
	Diarrhea	1		DAY 49
	Diarrhea	1		DAY 55
	Diarrhea	1		DAY 75
	Diarrhea	1		DAY 88
	Diarrhea	1		DAY 90
	Diarrhea	1		DAY 95-DAY 96
	Diarrhea	1		DAY 105-DAY 106
	Diarrhea	1		DAY 108
	Diarrhea	1		DAY 127
	Diarrhea	1		DAY 134
	Diarrhea	1		DAY 143
	Diarrhea	1		DAY 148-DAY 149
	Diarrhea	1		DAY 186-DAY 187
	Diarrhea	1		DAY 200
	Diarrhea	1		DAY 205
	Diarrhea	1		DAY 207

Severity Codes

Observation	Severity	Description
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 219
DAY 1-DAY 366

GROUP: 4-F
DOSE: 4.0 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
	Diarrhea	1	DAY	212
	Diarrhea	1	DAY	221
	Diarrhea	1	DAY	230
	Diarrhea	1	DAY	240-DAY 241
	Diarrhea	1	DAY	251
	Diarrhea	1	DAY	281
	Diarrhea	1	DAY	338
	Diarrhea	2	DAY	21
	Diarrhea	2	DAY	89
	Diarrhea	2	DAY	168
	Diarrhea	2	DAY	174
	Normal		DAY	1-DAY 20
	Normal		DAY	22-DAY 26
	Normal		DAY	31-DAY 45
	Normal		DAY	47-DAY 48
	Normal		DAY	50-DAY 54
	Normal		DAY	56-DAY 74
	Normal		DAY	76-DAY 87
	Normal		DAY	91-DAY 94
	Normal		DAY	97-DAY 104
	Normal		DAY	107
	Normal		DAY	109-DAY 119
	Normal		DAY	121-DAY 126
	Normal		DAY	128-DAY 133
	Normal		DAY	135-DAY 140
	Normal		DAY	142
	Normal		DAY	144-DAY 145
	Normal		DAY	150-DAY 156
	Normal		DAY	158-DAY 167
	Normal		DAY	171-DAY 173
	Normal		DAY	175-DAY 185
	Normal		DAY	188-DAY 197
	Normal		DAY	199
	Normal		DAY	201-DAY 204
	Normal		DAY	206
	Normal		DAY	208-DAY 211
	Normal		DAY	213-DAY 214
	Normal		DAY	216-DAY 220

Severity Codes

Observation	Severity	Description
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 219
DAY 1-DAY 366

GROUP: 4-F
DOSE: 4.0 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
	Normal			DAY 222-DAY 229
	Normal			DAY 231-DAY 239
	Normal			DAY 242
	Normal			DAY 244-DAY 250
	Normal			DAY 252-DAY 280
	Normal			DAY 282-DAY 337
	Normal			DAY 339-DAY 364
	Scheduled Sacrifice			DAY 365
	Vomit Seen In Run			DAY 157
8936	Blue Tongue	1		DAY 28
	Blue Tongue	1		DAY 73-DAY 74
	Blue Tongue	1		DAY 91-DAY 92
	Blue Tongue	1		DAY 110-DAY 111
	Blue Tongue	1		DAY 115
	Blue Tongue	1		DAY 118
	Blue Tongue	1		DAY 122-DAY 125
	Blue Tongue	1		DAY 128-DAY 129
	Blue Tongue	1		DAY 132
	Blue Tongue	1		DAY 134
	Blue Tongue	1		DAY 136-DAY 137
	Blue Tongue	1		DAY 141
	Blue Tongue	1		DAY 143
	Blue Tongue	1		DAY 169-DAY 170
	Blue Tongue	1		DAY 173-DAY 175
	Blue Tongue	1		DAY 191
	Blue Tongue	1		DAY 198
	Blue Tongue	1		DAY 208
	Blue Tongue	1		DAY 225
	Diarrhea	1		DAY 125
	Diarrhea	1		DAY 197
	Diarrhea	1		DAY 202
	Diarrhea	1		DAY 233
	Diarrhea	1		DAY 253
	Diarrhea	1		DAY 287
	Diarrhea	1		DAY 307-DAY 308
	Normal			DAY 1-DAY 27
	Normal			DAY 29-DAY 72

Severity Codes

Observation	Severity	Description
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semj-solid to liquid feces

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 219
DAY 1-DAY 366

GROUP: 4-F
DOSE: 4.0 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
	Normal			DAY 75-DAY 90
	Normal			DAY 93-DAY 109
	Normal			DAY 112-DAY 114
	Normal			DAY 116-DAY 117
	Normal			DAY 119-DAY 121
	Normal			DAY 126-DAY 127
	Normal			DAY 130-DAY 131
	Normal			DAY 133
	Normal			DAY 135
	Normal			DAY 138-DAY 140
	Normal			DAY 142
	Normal			DAY 144-DAY 168
	Normal			DAY 171-DAY 172
	Normal			DAY 176-DAY 190
	Normal			DAY 192-DAY 196
	Normal			DAY 199-DAY 201
	Normal			DAY 203-DAY 207
	Normal			DAY 209-DAY 224
	Normal			DAY 226-DAY 232
	Normal			DAY 234-DAY 252
	Normal			DAY 254-DAY 286
	Normal			DAY 288-DAY 306
	Normal			DAY 309-DAY 364
	Scheduled Sacrifice			DAY 365
8944	Blue Tongue	1		DAY 18
	Blue Tongue	1		DAY 20
	Blue Tongue	1		DAY 61
	Blue Tongue	1		DAY 65
	Blue Tongue	1		DAY 74-DAY 75
	Blue Tongue	1		DAY 120
	Blue Tongue	1		DAY 126
	Blue Tongue	1		DAY 128
	Blue Tongue	1		DAY 131
	Blue Tongue	1		DAY 136-DAY 137
	Blue Tongue	1		DAY 147
	Blue Tongue	1		DAY 152
	Blue Tongue	1		DAY 161

Severity Codes

Observation	Severity	Description
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

INDIVIDUAL CLINICAL SIGNS

STUDY: 219
DAY 1-DAY 366

GROUP: 4-F
DOSE: 4.0 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
	Blue Tongue	1		DAY 167
	Blue Tongue	1		DAY 170
	Blue Tongue	1		DAY 172
	Blue Tongue	1		DAY 180
	Blue Tongue	1		DAY 183
	Blue Tongue	1		DAY 188
	Blue Tongue	1		DAY 192-DAY 193
	Blue Tongue	1		DAY 211
	Blue Tongue	1		DAY 252
	Blue Tongue	1		DAY 278
	Diarrhea	1		DAY 42
	Diarrhea	1		DAY 57
	Diarrhea	1		DAY 76
	Diarrhea	1		DAY 90
	Diarrhea	1		DAY 123-DAY 124
	Diarrhea	1		DAY 231
	Diarrhea	1		DAY 308
	Diarrhea	2		DAY 194
	Diarrhea	2		DAY 225
	Normal			DAY 1-DAY 17
	Normal			DAY 19
	Normal			DAY 21-DAY 41
	Normal			DAY 43-DAY 56
	Normal			DAY 58-DAY 60
	Normal			DAY 62-DAY 64
	Normal			DAY 66-DAY 73
	Normal			DAY 77-DAY 89
	Normal			DAY 91-DAY 119
	Normal			DAY 121-DAY 122
	Normal			DAY 125
	Normal			DAY 127
	Normal			DAY 129-DAY 130
	Normal			DAY 132-DAY 135
	Normal			DAY 138-DAY 146
	Normal			DAY 148-DAY 151
	Normal			DAY 153-DAY 160
	Normal			DAY 162-DAY 166
	Normal			DAY 168-DAY 169

Severity Codes

Observation	Severity	Description
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLINICAL SIGNS

STUDY: 219
DAY 1-DAY 366

GROUP: 4-F
DOSE: 4.0 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
	Normal			DAY 171
	Normal			DAY 173-DAY 179
	Normal			DAY 181-DAY 182
	Normal			DAY 184-DAY 187
	Normal			DAY 189-DAY 191
	Normal			DAY 196-DAY 210
	Normal			DAY 212-DAY 224
	Normal			DAY 226-DAY 230
	Normal			DAY 232-DAY 251
	Normal			DAY 253-DAY 277
	Normal			DAY 279-DAY 307
	Normal			DAY 309-DAY 365
	Scheduled Sacrifice			DAY 366
	Vomit Seen In Run			DAY 195

Severity Codes

<u>Observation</u>	<u>Severity</u>	<u>Description</u>
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
DAY 1					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 2					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 3					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 4					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 5					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 6					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 7					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 8					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 9					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 10					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
DAY 11					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 12					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 13					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 14					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 15					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 16					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 17					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 18					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 19					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 20					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV					

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0			
		1-M	2-M	3-M	4-M
Day 20 (contd.)	1	0	0	0	1 25%
DAY 21					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 22					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 23					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 24					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 25					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 26					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 27					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	3 75%	3 75%
Diarrhea					
SEV					
1		0	0	1 25%	1 25%
DAY 28					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
1		0	0	0	1 25%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	DOSE: (mg/kg)			
		0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
Day 29	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 30	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 31	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 32	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Diarrhea				
	SEV				
	1	0	0	0	1 25%
DAY 33	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 34	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Diarrhea				
	SEV				
	1	0	0	0	1 25%
DAY 35	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 36	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 37	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	3 75%	4 100%
	Diarrhea				

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0				0.1				1.0				4.0			
		1-M		2-M		3-M		4-M		3-M		4-M		4-M			
Day 37 (contd.)	SEV 1	0		0		1 25%		0									
DAY 38	No. Observed	4		4		4		4									
	Normal	4 100%		4 100%		4 100%		4 100%									
DAY 39	No. Observed	4		4		4		4									
	Normal	4 100%		4 100%		4 100%		4 100%									
DAY 40	No. Observed	4		4		4		4									
	Normal	4 100%		4 100%		4 100%		4 100%									
DAY 41	No. Observed	4		4		4		4									
	Normal	4 100%		4 100%		4 100%		4 100%									
	Blue Tongue											3 75%					
	SEV 1	0		0		0		1 25%									
DAY 42	No. Observed	4		4		4		4									
	Normal	4 100%		4 100%		4 100%		4 100%									
DAY 43	No. Observed	4		4		4		4									
	Normal	4 100%		4 100%		4 100%		4 100%									
DAY 44	No. Observed	4		4		4		4									
	Normal	4 100%		4 100%		4 100%		4 100%									
DAY 45	No. Observed	4		4		4		4									
	Normal	4 100%		4 100%		4 100%		4 100%									
DAY 46	No. Observed	4		4		4		4									
	Normal	4 100%		4 100%		4 100%		4 100%									

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
DAY 47					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 48					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 49					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
1		0	0	0	1 25%
DAY 50					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 51					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV					
1		0	0	0	1 25%
DAY 52					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 53					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 54					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 55					
No. Observed		4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
Day 55 (contd.)	Normal	4 100%	4 100%	4 100%	4 100%
DAY 56					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 57					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 58					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 59					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 60					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 61					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 62					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 63					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 64					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 65					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
DAY 66					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 67					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 68					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	3 75%	4 100%
Diarrhea					
SEV					
1		0	0	1 25%	0
DAY 69					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 70					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 71					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV					
1		0	0	0	1 25%
DAY 72					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 73					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 74					
No. Observed		4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD		DOSE:(mg/kg) GROUP:	0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
Day 74 (contd.)	Normal		4 100%	4 100%	4 100%	4 100%
DAY 75	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 76	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 77	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 78	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 79	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 80	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 81	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 82	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 83	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 84	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	3 75%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	SEX: MALE			
		0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
Day 84 (contd.)	Diarrhea SEV 1	0	0	1 25%	0
DAY 85	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 86	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 87	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 88	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 89	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 90	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	3 75%	4 100%
	Diarrhea SEV 1	0	0	1 25%	0
DAY 91	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 92	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 93	No. Observed	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
Day 93 (contd.)	Normal	4 100%	4 100%	4 100%	4 100%
DAY 94	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 95	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 96	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 97	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 98	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 99	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 100	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 101	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 102	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 103	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	3 75%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	SEX: MALE			
		0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
Day 103 (contd.)	Diarrhea				
	SEV				
	1	0	0	1 25%	0
DAY 104					
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 105					
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 106					
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 107					
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 108					
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 109					
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 110					
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 111					
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 112					
	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0				0.1				1.0				4.0			
		1-M		2-M		3-M		4-M		3-M		4-M		3-M		4-M	
Day 113	No. Observed	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 114	No. Observed	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 115	No. Observed	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 116	No. Observed	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 117	No. Observed	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 118	No. Observed	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 119	No. Observed	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 120	No. Observed	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	2	50%		
	Blue Tongue																
	SEV																
	1	0		0		0		0		0		0		2	50%		
DAY 121	No. Observed	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 122	No. Observed	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	SEX: MALE			
		0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
DAY 123					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 124					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV					
1		0	0	0	1 25%
DAY 125					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 126					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV					
1		0	0	0	1 25%
DAY 127					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 128					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 129					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 130					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 131					
No. Observed		4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	SEX: MALE			
		0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
Day 131 (contd.)	Normal	4 100%	4 100%	4 100%	4 100%
DAY 132	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Diarrhea				
	SEV				
	1	0	0	0	1 25%
DAY 133	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 134	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 135	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 136	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 137	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 138	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 139	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 140	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
DAY 141					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 142					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 143					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 144					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 145					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 146					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 147					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV					
1		0	0	0	1 25%
DAY 148					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 149					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 150					
No. Observed		4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	SEX: MALE			
		0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
Day 150 (contd.)	Normal	4 100%	4 100%	4 100%	4 100%
DAY 151	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 152	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Blue Tongue				
	SEV				
	1	0	0	0	1 25%
DAY 153	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	3 75%	4 100%
	Diarrhea				
	SEV				
	1	0	0	1 25%	0
DAY 154	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Vomit Seen In Run	0	0	0	1 25%
DAY 155	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 156	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 157	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 158	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
DAY 159					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 160					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 161					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 162					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 163					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 164					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 165					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 166					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 167					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 168					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
Day 169	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Vomit Seen In Run	0	0	0	1 25%
DAY 170	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	2 50%
	Blue Tongue				
	SEV				
	1	0	0	0	2 50%
DAY 171	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 172	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 173	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 174	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 175	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 176	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 177	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 178	No. Observed	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0				0.1				1.0				4.0			
		1-M		2-M		3-M		4-M		3-M		4-M		3-M		4-M	
Day 178 (contd.)	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 179	No. Observed	4		4		4		4		4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 180	No. Observed	4		4		4		4		4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 181	No. Observed	4		4		4		4		4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	2	50%	2	50%	2	50%
	Diarrhea																
	SEV																
	1	0		0		0		0		0		1	25%	1	25%	1	25%
	2	0		0		0		0		0		1	25%	1	25%	1	25%
DAY 182	No. Observed	4		4		4		4		4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 183	No. Observed	4		4		4		4		4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 184	No. Observed	4		4		4		4		4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 185	No. Observed	4		4		4		4		4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 186	No. Observed	4		4		4		4		4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 187	No. Observed	4		4		4		4		4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
DAY 188					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 189					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Vomit Seen In Run		0	0	0	1 25%
DAY 190					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 191					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 192					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 193					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 194					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 195					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 196					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 197					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0				0.1				1.0				4.0			
		1-M		2-M		3-M		4-M		3-M		4-M		3-M		4-M	
Day 197 (contd.)	Blue Tongue SEV 1	0	0	0	0	0	0	0	0	1	25%						
DAY 198	No. Observed	4	4	4	4	4	4	4	4	4		4	4	4	4		
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%		
DAY 199	No. Observed	4	4	4	4	4	4	4	4	4		4	4	4	4		
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%		
DAY 200	No. Observed	4	4	4	4	4	4	4	4	4		4	4	4	4		
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%		
DAY 201	No. Observed	4	4	4	4	4	4	4	4	4		4	4	4	4		
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%		
DAY 202	No. Observed	4	4	4	4	4	4	4	4	4		4	4	4	4		
	Normal	3	75%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%		
	Diarrhea SEV 1	1	25%	0		0		0		0							
DAY 203	No. Observed	4	4	4	4	4	4	4	4	4		4	4	4	4		
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%		
DAY 204	No. Observed	4	4	4	4	4	4	4	4	4		4	4	4	4		
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%		
DAY 205	No. Observed	4	4	4	4	4	4	4	4	4		4	4	4	4		
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%		
DAY 206	No. Observed	4	4	4	4	4	4	4	4	4		4	4	4	4		

ONE YEAR ORAL TOXICITY STUDY OF
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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
Day 206 (contd.)	Normal	4 100%	4 100%	4 100%	4 100%
DAY 207	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 208	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 209	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Diarrhea				
	SEV				
	2	0	0	0	1 25%
DAY 210	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 211	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 212	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 213	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 214	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 215	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
DAY 216					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 217					
No. Observed		4	4	4	4
Normal		4 100%	3 75%	4 100%	4 100%
Diarrhea					
SEV					
1		0	1 25%	0	0
DAY 218					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 219					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 220					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 221					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 222					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 223					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 224					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 225					
No. Observed		4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	SEX: MALE			
		0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
Day 225 (contd.)	Normal	4 100%	4 100%	4 100%	4 100%
DAY 226	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 227	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 228	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 229	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 230	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	3 75%	4 100%
	Diarrhea				
	SEV				
	1	0	0	1 25%	0
DAY 231	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 232	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 233	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 234	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
DAY 235					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 236					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 237					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 238					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 239					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 240					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 241					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 242					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 243					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 244					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
Day 245	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 246	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 247	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 248	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 249	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 250	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 251	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 252	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 253	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 254	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 255	No. Observed	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
Day 255 (contd.)	Normal	4 100%	4 100%	4 100%	4 100%
DAY 256	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 257	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 258	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 259	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 260	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Blue Tongue				
	SEV				
	1	0	0	0	1 25%
DAY 261	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 262	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 263	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 264	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
DAY 265					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 266					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 267					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 268					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 269					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 270					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 271					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	2 50%	4 100%
Diarrhea					
SEV					
1		0	0	2 50%	0
DAY 272					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 273					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 274					
No. Observed		4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0				0.1				1.0				4.0			
		1-M		2-M		3-M		4-M		3-M		4-M		3-M		4-M	
Day 274 (contd.)	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 275	No. Observed	4		4		4		4		4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 276	No. Observed	4		4		4		4		4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 277	No. Observed	4		4		4		4		4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 278	No. Observed	4		4		4		4		4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 279	No. Observed	4		4		4		4		4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 280	No. Observed	4		4		4		4		4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 281	No. Observed	4		4		4		4		4		4		4		4	
	Normal	3	75%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
	Diarrhea																
	SEV																
	1	1	25%	0		0		0		0		0		0		0	
DAY 282	No. Observed	4		4		4		4		4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%
DAY 283	No. Observed	4		4		4		4		4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%	4	100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
DAY 284					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 285					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 286					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 287					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	3 75%	4 100%
Diarrhea					
SEV					
1		0	0	1 25%	0
DAY 288					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 289					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 290					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 291					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 292					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 293					
No. Observed		4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0		0.1		1.0		4.0	
		1-M		2-M		3-M		4-M	
Day 293 (contd.)	Normal	4	100%	4	100%	4	100%	3	75%
	Blue Tongue								
	SEV								
	1	0		0		0		1	25%
DAY 294	No. Observed	4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%
DAY 295	No. Observed	4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%
DAY 296	No. Observed	4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%
DAY 297	No. Observed	4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%
DAY 298	No. Observed	4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%
DAY 299	No. Observed	4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%
DAY 300	No. Observed	4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%
DAY 301	No. Observed	4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%
DAY 302	No. Observed	4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
DAY 303					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 304					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 305					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 306					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 307					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 308					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 309					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 310					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 311					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 312					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0			
		1-M	2-M	3-M	4.0 4-M
Day 313	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 314	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 315	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 316	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 317	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 318	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 319	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 320	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Vomit Seen In Run	0	0	0	1 25%
DAY 321	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 322	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	SEX: MALE			
		0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
Day 323	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 324	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 325	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 326	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 327	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 328	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 329	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 330	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 331	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 332	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 333	No. Observed	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE: (mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
Day 333 (contd.)	Normal	4 100%	4 100%	4 100%	4 100%
DAY 334	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	3 75%	4 100%
	Diarrhea				
	SEV				
	1	0	0	1 25%	0
DAY 335	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 336	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 337	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 338	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 339	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 340	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 341	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 342	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
DAY 343					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 344					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 345					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 346					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 347					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 348					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	3 75%	4 100%
Diarrhea w/Red Material		0	0	1 25%	0
DAY 349					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 350					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
2		0	0	0	1 25%
DAY 351					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD		DOSE:(mg/kg) GROUP:	0 1-M	0.1 2-M	1.0 3-M	4.0 4-M
Day 352	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 353	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 354	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 355	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 356	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 357	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 358	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 359	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 360	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 361	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 362	No. Observed		4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: MALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-M	2-M	3-M	4-M
Day 362 (contd.)	Normal	4 100%	4 100%	4 100%	3 75%
	Diarrhea				
	SEV				
	1	0	0	0	1 25%
DAY 363	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 364	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 365	No. Observed	4	4	4	4
	Scheduled Sacrifice	3 75%	2 50%	3 75%	1 25%
	Normal	1 25%	2 50%	1 25%	3 75%
DAY 366	No. Observed	1	2	1	3
	Scheduled Sacrifice	1 100%	2 100%	1 100%	3 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
DAY 1					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 2					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 3					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 4					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 5					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 6					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 7					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 8					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 9					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 10					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
DAY 11					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 12					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 13					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 14					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 15					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 16					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 17					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 18					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV					
1		0	0	0	1 25%
DAY 19					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 20					
No. Observed		4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
Day 20 (contd.)	Normal	4 100%	4 100%	3 75%	3 75%
	Blue Tongue				
	SEV				
	1	0	0	1 25%	1 25%
DAY 21	No. Observed	4	4	4	4
	Normal	4 100%	3 75%	4 100%	3 75%
	Diarrhea				
	SEV				
	1	0	1 25%	0	0
	2	0	0	0	1 25%
DAY 22	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 23	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 24	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 25	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 26	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 27	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Diarrhea				
	SEV				
	1	0	0	0	1 25%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
Day 28 (contd.)	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	2 50%
	Blue Tongue				
	SEV				
	1	0	0	0	1 25%
	Diarrhea				
	SEV				
	1	0	0	0	1 25%
DAY 29	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Diarrhea				
	SEV				
	1	0	0	0	1 25%
DAY 30	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Diarrhea				
	SEV				
	1	0	0	0	1 25%
DAY 31	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 32	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 33	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 34	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Diarrhea				
	SEV				
	1	0	0	0	1 25%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
DAY 35					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 36					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 37					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 38					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	3 75%	4 100%
Vomit Seen In Run		0	0	1 25%	0
DAY 39					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 40					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 41					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 42					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
1		0	0	0	1 25%
DAY 43					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
DAY 44					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 45					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 46					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
1		0	0	0	1 25%
DAY 47					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 48					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 49					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
1		0	0	0	1 25%
DAY 50					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 51					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 52					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
DAY 53					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 54					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 55					
No. Observed		4	4	4	4
Normal		4 100%	3 75%	4 100%	3 75%
Diarrhea					
SEV					
1		0	1 25%	0	1 25%
DAY 56					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 57					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
1		0	0	0	1 25%
DAY 58					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 59					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 60					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 61					
No. Observed		4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0		0.1		1.0		4.0	
		1-F	2-F	3-F	4-F	3-F	4-F		
Day 61 (contd.)	Normal	4	100%	4	100%	4	100%	3	75%
	Blue Tongue								
	SEV								
	1	0		0		0		1	25%
DAY 62	No. Observed	4		4		4		4	
	Normal	4	100%	4	100%	3	75%	4	100%
	Diarrhea								
	SEV								
	1	0		0		1	25%	0	
DAY 63	No. Observed	4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%
DAY 64	No. Observed	4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%
DAY 65	No. Observed	4		4		4		4	
	Normal	4	100%	4	100%	4	100%	3	75%
	Blue Tongue								
	SEV								
	1	0		0		0		1	25%
DAY 66	No. Observed	4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%
DAY 67	No. Observed	4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%
DAY 68	No. Observed	4		4		4		4	
	Normal	4	100%	4	100%	4	100%	4	100%
DAY 69	No. Observed	4		4		4		4	

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
Day 69 (contd.)	Normal	4 100%	4 100%	4 100%	4 100%
DAY 70	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 71	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 72	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 73	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Blue Tongue				
	SEV				
	1	0	0	0	1 25%
DAY 74	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	2 50%
	Blue Tongue				
	SEV				
	1	0	0	0	2 50%
DAY 75	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	2 50%
	Blue Tongue				
	SEV				
	1	0	0	0	1 25%
	Diarrhea				
	SEV				
	1	0	0	0	1 25%
DAY 76	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
Day 76 (contd.)	Diarrhea SEV 1	0	0	0	1 25%
DAY 77	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 78	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 79	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 80	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 81	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 82	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 83	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	3 75%	4 100%
	Diarrhea SEV 1	0	0	1 25%	0
DAY 84	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 85	No. Observed	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0		0.1		1.0		4.0	
		1-F	2-F	3-F	4-F	3-F	4-F	3-F	4-F
Day 85 (contd.)	Normal	4	4	4	4	4	4	4	4
		100%	100%	100%	100%	100%	100%	100%	100%
DAY 86	No. Observed	4	4	4	4	4	4	4	4
	Normal	4	4	4	4	4	4	4	4
		100%	100%	100%	100%	100%	100%	100%	100%
DAY 87	No. Observed	4	4	4	4	4	4	4	4
	Normal	4	4	4	4	4	4	4	4
		100%	100%	100%	100%	100%	100%	100%	100%
DAY 88	No. Observed	4	4	4	4	4	4	4	4
	Normal	4	4	4	4	4	3	3	3
	Diarrhea								
	SEV								
	1	0	0	0	0	0	1	1	1
									25%
DAY 89	No. Observed	4	4	4	4	4	4	4	4
	Normal	4	4	4	4	4	3	3	3
	Diarrhea								
	SEV								
	2	0	0	0	0	0	1	1	1
									25%
DAY 90	No. Observed	4	4	4	4	4	4	4	4
	Normal	4	4	4	4	4	2	2	2
	Diarrhea								
	SEV								
	1	0	0	0	0	0	2	2	2
									50%
DAY 91	No. Observed	4	4	4	4	4	4	4	4
	Normal	4	4	4	4	4	3	3	3
	Blue Tongue								
	SEV								
	1	0	0	0	0	0	1	1	1
									25%
DAY 92	No. Observed	4	4	4	4	4	4	4	4
	Normal	4	4	4	4	4	3	3	3
		100%	100%	100%	100%	100%	75%	75%	75%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD		DOSE:(mg/kg) GROUP:	0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
Day 92 (contd.)	Blue Tongue SEV 1		0	0	0	1 25%
DAY 93	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 94	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 95	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4
	Diarrhea					3 75%
	SEV 1		0	0	0	1 25%
DAY 96	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4
	Diarrhea					3 75%
	SEV 1		0	0	0	1 25%
DAY 97	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 98	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 99	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 100	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
DAY 101					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 102					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 103					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 104					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 105					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
1		0	0	0	1 25%
DAY 106					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
1		0	0	0	1 25%
DAY 107					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 108					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
1		0	0	0	1 25%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
DAY 109					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 110					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV					
1		0	0	0	1 25%
DAY 111					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV					
1		0	0	0	1 25%
DAY 112					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 113					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 114					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 115					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV					
1		0	0	0	1 25%
DAY 116					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
DAY 117					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 118					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV					
1		0	0	0	1 25%
DAY 119					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 120					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	2 50%
Blue Tongue					
SEV					
1		0	0	0	2 50%
DAY 121					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 122					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV					
1		0	0	0	1 25%
DAY 123					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	2 50%
Blue Tongue					
SEV					
1		0	0	0	1 25%
Diarrhea					

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
Day 123 (contd.)	SEV 1	0	0	0	1 25%
DAY 124	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	2 50%
	Blue Tongue				
	SEV 1	0	0	0	1 25%
	Diarrhea				
	SEV 1	0	0	0	1 25%
DAY 125	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Blue Tongue				
	SEV 1	0	0	0	1 25%
	Diarrhea				
	SEV 1	0	0	0	1 25%
DAY 126	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Blue Tongue				
	SEV 1	0	0	0	1 25%
DAY 127	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Diarrhea				
	SEV 1	0	0	0	1 25%
DAY 128	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	2 50%
	Blue Tongue				

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
Day 128 (contd.) SEV 1		0	0	0	2 50%
DAY 129					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV 1		0	0	0	1 25%
DAY 130					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 131					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV 1		0	0	0	1 25%
DAY 132					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV 1		0	0	0	1 25%
DAY 133					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 134					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	2 50%
Blue Tongue					
SEV 1		0	0	0	1 25%
Diarrhea					
SEV 1		0	0	0	1 25%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
DAY 135					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 136					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	2 50%
Blue Tongue					
SEV					
1		0	0	0	2 50%
DAY 137					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	2 50%
Blue Tongue					
SEV					
1		0	0	0	2 50%
DAY 138					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 139					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 140					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 141					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	2 50%
Blue Tongue					
SEV					
1		0	0	0	2 50%
DAY 142					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
DAY 143					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	2 50%
Blue Tongue					
SEV					
1		0	0	0	1 25%
Diarrhea					
SEV					
1		0	0	0	1 25%
DAY 144					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 145					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 146					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV					
1		0	0	0	1 25%
DAY 147					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	2 50%
Blue Tongue					
SEV					
1		0	0	0	2 50%
DAY 148					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
1		0	0	0	1 25%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
Day 149	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Blue Tongue				
	SEV				
	1	0	0	0	1 25%
	Diarrhea				
	SEV				
	1	0	0	0	1 25%
DAY 150	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 151	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 152	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Blue Tongue				
	SEV				
	1	0	0	0	1 25%
DAY 153	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 154	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 155	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 156	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
Day 157	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Vomit Seen In Run	0	0	0	1 25%
DAY 158	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 159	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 160	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 161	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Blue Tongue SEV 1	0	0	0	1 25%
DAY 162	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 163	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 164	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 165	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 166	No. Observed	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
Day 166 (contd.)	Normal	4 100%	4 100%	4 100%	4 100%
DAY 167					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV					
1		0	0	0	1 25%
DAY 168					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
2		0	0	0	1 25%
DAY 169					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	2 50%
Blue Tongue					
SEV					
1		0	0	0	2 50%
DAY 170					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	1 25%
Blue Tongue					
SEV					
1		0	0	0	3 75%
DAY 171					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 172					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV					
1		0	0	0	1 25%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
DAY 173					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV					
1		0	0	0	1 25%
DAY 174					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	2 50%
Blue Tongue					
SEV					
1		0	0	0	1 25%
Diarrhea					
SEV					
2		0	0	0	1 25%
DAY 175					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV					
1		0	0	0	1 25%
DAY 176					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 177					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 178					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 179					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
Day 180	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Blue Tongue SEV 1	0	0	0	1 25%
DAY 181	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 182	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 183	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Blue Tongue SEV 1	0	0	0	1 25%
DAY 184	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 185	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 186	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Diarrhea SEV 1	0	0	0	1 25%
DAY 187	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Diarrhea SEV				

ONE YEAR ORAL TOXICITY STUDY OF
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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0				0.1				1.0				4.0			
		1-F		2-F		3-F		4-F		3-F		4-F		3-F		4-F	
Day 187 (contd.)	1	0		0		0		0		1		25%					
DAY 188																	
No. Observed		4		4		4		4		4		4		4		4	
Normal		3		75%		4		100%		4		100%		3		75%	
Blue Tongue																	
SEV																	
1		0		0		0		0		1		25%					
Diarrhea																	
SEV																	
1		1		25%		0		0		0		0					
DAY 189																	
No. Observed		4		4		4		4		4		4		4		4	
Normal		4		100%		4		100%		4		100%		4		100%	
DAY 190																	
No. Observed		4		4		4		4		4		4		4		4	
Normal		4		100%		4		100%		4		100%		4		100%	
DAY 191																	
No. Observed		4		4		4		4		4		4		4		4	
Normal		4		100%		4		100%		4		100%		3		75%	
Blue Tongue																	
SEV																	
1		0		0		0		0		1		25%					
DAY 192																	
No. Observed		4		4		4		4		4		4		4		4	
Normal		4		100%		4		100%		4		100%		3		75%	
Blue Tongue																	
SEV																	
1		0		0		0		0		1		25%					
DAY 193																	
No. Observed		4		4		4		4		4		4		4		4	
Normal		4		100%		4		100%		4		100%		3		75%	
Blue Tongue																	
SEV																	
1		0		0		0		0		1		25%					

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0		0.1		1.0		4.0	
		1-F	2-F	3-F	4-F	3-F	4-F	3-F	4-F
DAY 194									
No. Observed		4	4	4	4	4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%	4 100%	3 75%	4	4
Diarrhea									
SEV									
2		0	0	0	0	0	1 25%		
DAY 195									
No. Observed		4	4	4	4	4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%	4 100%	3 75%	4	4
Vomit Seen In Run		0	0	0	0	0	1 25%		
DAY 196									
No. Observed		4	4	4	4	4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%	4 100%	4 100%	4	4
DAY 197									
No. Observed		4	4	4	4	4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%	4 100%	3 75%	4	4
Diarrhea									
SEV									
1		0	0	0	0	0	1 25%		
DAY 198									
No. Observed		4	4	4	4	4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%	4 100%	2 50%	4	4
Blue Tongue									
SEV									
1		0	0	0	0	0	2 50%		
DAY 199									
No. Observed		4	4	4	4	4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%	4 100%	4 100%	4	4
DAY 200									
No. Observed		4	4	4	4	4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%	4 100%	3 75%	4	4
Diarrhea									
SEV									
1		0	0	0	0	0	1 25%		

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
DAY 201					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 202					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	2 50%
Diarrhea					
SEV					
1		0	0	0	2 50%
DAY 203					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 204					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 205					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
1		0	0	0	1 25%
DAY 206					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 207					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
1		0	0	0	1 25%
DAY 208					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0		0.1		1.0		4.0	
		1-F	2-F	3-F	4-F	3-F	4-F	3-F	4-F
Day 208 (contd.)	SEV 1	0	0	0	1	25%			
DAY 209	No. Observed	4	4	4	4				
	Normal	4 100%	4 100%	4 100%	4 100%				
DAY 210	No. Observed	4	4	4	4				
	Normal	4 100%	4 100%	4 100%	4 100%				
DAY 211	No. Observed	4	4	4	4				
	Normal	4 100%	4 100%	3 75%	3 75%				
	Blue Tongue								
	SEV								
	1	0	0	0	1	25%			
	Diarrhea								
	SEV								
	1	0	0	1	25%		0		
DAY 212	No. Observed	4	4	4	4				
	Normal	4 100%	4 100%	4 100%	3 75%				
	Diarrhea								
	SEV								
	1	0	0	0	1	25%			
DAY 213	No. Observed	4	4	4	4				
	Normal	4 100%	4 100%	4 100%	4 100%				
DAY 214	No. Observed	4	4	4	4				
	Normal	4 100%	4 100%	4 100%	4 100%				
DAY 215	No. Observed	4	4	4	4				
	Normal	4 100%	4 100%	4 100%	3 75%				
	Blue Tongue								
	SEV								

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD		DOSE: (mg/kg) GROUP:	0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
Day 215 (contd.)	1		0	0	0	1 25%
DAY 216						
No. Observed			4	4	4	4
Normal			4 100%	4 100%	4 100%	4 100%
DAY 217						
No. Observed			4	4	4	4
Normal			4 100%	4 100%	4 100%	4 100%
DAY 218						
No. Observed			4	4	4	4
Normal			4 100%	4 100%	4 100%	4 100%
DAY 219						
No. Observed			4	4	4	4
Normal			4 100%	4 100%	4 100%	4 100%
DAY 220						
No. Observed			4	4	4	4
Normal			4 100%	4 100%	4 100%	4 100%
DAY 221						
No. Observed			4	4	4	4
Normal			4 100%	4 100%	4 100%	3 75%
Diarrhea						
SEV						
1			0	0	0	1 25%
DAY 222						
No. Observed			4	4	4	4
Normal			4 100%	4 100%	4 100%	4 100%
DAY 223						
No. Observed			4	4	4	4
Normal			4 100%	3 75%	4 100%	4 100%
Diarrhea						
SEV						
2			0	1 25%	0	0

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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
Day 224	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 225	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	2 50%
	Blue Tongue SEV 1	0	0	0	1 25%
	Diarrhea SEV 2	0	0	0	1 25%
DAY 226	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 227	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 228	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 229	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 230	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Diarrhea SEV 1	0	0	0	1 25%
DAY 231	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Diarrhea SEV				

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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	SEX: FEMALE			
		0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
Day 231 (contd.)	1	0	0	0	1 25%
DAY 232					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 233					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
1		0	0	0	1 25%
DAY 234					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 235					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 236					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 237					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 238					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 239					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 240					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					

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INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
Day 240 (contd.)	SEV 1	0	0	0	1 25%
DAY 241	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Diarrhea				
	SEV 1	0	0	0	1 25%
DAY 242	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 243	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Blue Tongue				
	SEV 1	0	0	0	1 25%
DAY 244	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 245	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 246	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 247	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 248	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
DAY 249					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 250					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 251					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
1		0	0	0	1 25%
DAY 252					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Blue Tongue					
SEV					
1		0	0	0	1 25%
DAY 253					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
1		0	0	0	1 25%
DAY 254					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 255					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 256					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
DAY 257					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 258					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 259					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 260					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 261					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 262					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 263					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 264					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 265					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 266					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE: (mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
Day 267	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 268	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 269	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 270	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 271	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 272	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 273	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 274	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 275	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 276	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 277	No. Observed	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
Day 277 (contd.)	Normal	4 100%	4 100%	4 100%	4 100%
DAY 278	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Blue Tongue				
	SEV				
	1	0	0	0	1 25%
DAY 279	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 280	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 281	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Diarrhea				
	SEV				
	1	0	0	0	1 25%
DAY 282	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 283	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 284	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 285	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD		DOSE:(mg/kg) GROUP:	0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
Day 286	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 287	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	3 75%
	Diarrhea					
	SEV					
	1		0	0	0	1 25%
DAY 288	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 289	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 290	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 291	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 292	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 293	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 294	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 295	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
DAY 296					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 297					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 298					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 299					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 300					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	3 75%
Diarrhea					
SEV					
1		0	0	0	1 25%
DAY 301					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 302					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 303					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 304					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD		DOSE:(mg/kg) GROUP:	0 1-F	0.1 2-F	1.0 3-F	4.0 4-F
Day 305	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 306	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 307	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	3 75%
	Diarrhea					
	SEV					
	1		0	0	0	1 25%
DAY 308	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	2 50%
	Diarrhea					
	SEV					
	1		0	0	0	2 50%
DAY 309	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 310	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 311	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 312	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%
DAY 313	No. Observed		4	4	4	4
	Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
DAY 314					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 315					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 316					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 317					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 318					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 319					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 320					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 321					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 322					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 323					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
Day 324	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 325	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 326	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 327	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 328	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 329	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 330	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 331	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 332	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 333	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 334	No. Observed	4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
Day 334 (contd.)	Normal	4 100%	4 100%	4 100%	4 100%
DAY 335	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 336	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 337	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 338	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Diarrhea				
	SEV				
	1	0	0	0	1 25%
DAY 339	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 340	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 341	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 342	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 343	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	3 75%
	Diarrhea				

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
Day 343 (contd.) SEV 1		0	0	0	1 25%
DAY 344					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 345					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 346					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 347					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 348					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 349					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 350					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 351					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 352					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 353					
No. Observed		4	4	4	4

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
Day 353 (contd.)	Normal	4 100%	4 100%	4 100%	4 100%
DAY 354	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 355	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 356	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 357	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 358	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 359	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 360	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 361	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 362	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%
DAY 363	No. Observed	4	4	4	4
	Normal	4 100%	4 100%	4 100%	4 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INCIDENCE OF OBSERVATIONS

STUDY: 219

SEX: FEMALE

PERIOD	DOSE:(mg/kg) GROUP:	0	0.1	1.0	4.0
		1-F	2-F	3-F	4-F
DAY 364					
No. Observed		4	4	4	4
Normal		4 100%	4 100%	4 100%	4 100%
DAY 365					
No. Observed		4	4	4	4
Scheduled Sacrifice		2 50%	0	2 50%	3 75%
Normal		2 50%	4 100%	2 50%	1 25%
DAY 366					
No. Observed		2	4	2	1
Scheduled Sacrifice		2 100%	4 100%	2 100%	1 100%

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLIN. OBSERVATIONS^a

STUDY: 219B
DAY 1-DAY 363

GROUP: 1-M
DOSE: 0 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8922	Diarrhea Normal Normal	1		DAY 167 DAY 1-DAY 160 DAY 174-DAY 363
8915	Normal			DAY 1-DAY 363
8911	Diarrhea Normal	1		DAY 363 DAY 1-DAY 356
8909	Diarrhea Normal Normal	1		DAY 27 DAY 1-DAY 20 DAY 34-DAY 363

Severity Codes

<u>Observation</u>	<u>Severity</u>	<u>Description</u>
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

^aIndividual weekly observations

INDIVIDUAL CLIN. OBSERVATIONS^a

STUDY: 219B
DAY 1-DAY 363

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

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8929	Normal			DAY 1-DAY 363
8942	Normal			DAY 1-DAY 363
8930	Blue Mammary Area			DAY 76
	Firm Mammary Area			DAY 76
	Normal			DAY 1-DAY 69
	Normal			DAY 83-DAY 363
8938	Normal			DAY 1-DAY 363

Severity Codes

<u>Observation</u>	<u>Severity</u>	<u>Description</u>
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

^aIndividual weekly observations

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLIN. OBSERVATIONS^a

STUDY: 219B
DAY 1-DAY 363

GROUP: 2-M
DOSE: 0.1 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8923	Normal			DAY 1-DAY 363
8907	Blue Tongue	1		DAY 132
	Normal			DAY 1-DAY 125
	Normal			DAY 139-DAY 363
8919	Normal			DAY 1-DAY 363
8924	Diarrhea	1		DAY 307
	Normal			DAY 1-DAY 300
	Normal			DAY 314-DAY 363

Severity Codes

<u>Observation</u>	<u>Severity</u>	<u>Description</u>
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

^aIndividual weekly observations

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLIN. OBSERVATIONS^a

STUDY: 219B
DAY 1-DAY 363

GROUP: 2-F
DOSE: 0.1 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8935	Normal			DAY 1-DAY 363
8937	Normal			DAY 1-DAY 363
8934	Blue Tongue Normal Normal	1		DAY 125 DAY 1-DAY 118 DAY 132-DAY 363
8945	Normal			DAY 1-DAY 363

Severity Codes

<u>Observation</u>	<u>Severity</u>	<u>Description</u>
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

^aIndividual weekly observations

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLIN. OBSERVATIONS^a

STUDY: 219B
DAY 1-DAY 363

GROUP: 3-M
DOSE: 1.0 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8917	Blue Tongue	1		DAY 279
	Diarrhea	1		DAY 97
	Diarrhea	1		DAY 125
	Diarrhea	1		DAY 174
	Diarrhea	1		DAY 356
	Diarrhea w/Red Material	1		DAY 349
	Normal			DAY 1-DAY 90
	Normal			DAY 104-DAY 118
	Normal			DAY 132-DAY 167
	Normal			DAY 181-DAY 272
	Normal			DAY 286-DAY 342
	Normal			DAY 363
	8910	Blue Tongue	1	
Blue Tongue		1		DAY 188
Blue Tongue		1		DAY 251
Diarrhea		1		DAY 174
Normal				DAY 1-DAY 118
Normal				DAY 132-DAY 167
Normal				DAY 181
Normal				DAY 195-DAY 244
Normal				DAY 258-DAY 363
Normal				
8913	Blue Tongue	1		DAY 118
	Blue Tongue	1		DAY 139
	Diarrhea	1		DAY 83
	Diarrhea	1		DAY 153
	Diarrhea	1		DAY 251
	Diarrhea	1		DAY 293
	Normal			DAY 1-DAY 76
	Normal			DAY 90-DAY 111
	Normal			DAY 125-DAY 132
	Normal			DAY 146
	Normal			DAY 160-DAY 244
	Normal			DAY 258-DAY 286
Normal			DAY 300-DAY 363	

Severity Codes

Observation	Severity	Description
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

^aIndividual weekly observations

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLIN. OBSERVATIONS^a

STUDY: 219B
DAY 1-DAY 363

GROUP: 3-M
DOSE: 1.0 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8914	Blue Tongue	1		DAY 90
	Blue Tongue	1		DAY 139
	Blue Tongue	1		DAY 195
	Blue Tongue	1		DAY 209
	Diarrhea	1		DAY 111
	Diarrhea	1		DAY 300
	Diarrhea	1		DAY 321
	Diarrhea	2		DAY 342
	Normal			DAY 1-DAY 83
	Normal			DAY 97-DAY 104
	Normal			DAY 118-DAY 132
	Normal			DAY 146-DAY 188
	Normal			DAY 202
	Normal			DAY 216-DAY 293
	Normal			DAY 307-DAY 314
	Normal			DAY 328-DAY 335
	Normal			DAY 349-DAY 363

Severity Codes

<u>Observation</u>	<u>Severity</u>	<u>Description</u>
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

^aIndividual weekly observations

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLIN. OBSERVATIONS^a

STUDY: 219B
DAY 1-DAY 363

GROUP: 3-F
DOSE: 1.0 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8928	Blue Mammary Area	1		DAY 55-DAY 76
	Blue Tongue			DAY 195
	Firm Mammary Area			DAY 55
	Firm Mammary Area			DAY 69-DAY 76
	Normal			DAY 1-DAY 48
	Normal			DAY 83-DAY 188
	Normal			DAY 202-DAY 363
8940	Blue Tongue	1		DAY 90-DAY 97
	Blue Tongue	1		DAY 139
	Blue Tongue	1		DAY 153
	Blue Tongue	1		DAY 167
	Blue Tongue	1		DAY 181-DAY 188
	Blue Tongue	1		DAY 202
	Blue Tongue	1		DAY 216-DAY 223
	Blue Tongue	1		DAY 237
	Blue Tongue	1		DAY 258
	Blue Tongue	1		DAY 272-DAY 279
	Blue Tongue	1		DAY 349-DAY 363
	Diarrhea	1		DAY 181
	Normal			DAY 1-DAY 83
	Normal			DAY 104-DAY 132
	Normal			DAY 146
	Normal			DAY 160
	Normal			DAY 174
	Normal			DAY 195
	Normal			DAY 209
	Normal			DAY 230
	Normal			DAY 244-DAY 251
	Normal			DAY 265
	Normal			DAY 286-DAY 342
8931	Diarrhea	1		DAY 349
	Normal			DAY 1-DAY 342
	Normal			DAY 356-DAY 363
8943	Blue Tongue	1		DAY 20

Severity Codes

Observation	Severity	Description
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

^aIndividual weekly observations

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLIN. OBSERVATIONS^a

STUDY: 219B
DAY 1-DAY 363

GROUP: 3-F
DOSE: 1.0 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
	Blue Tongue	1		DAY 41
	Blue Tongue	1		DAY 62-DAY 97
	Blue Tongue	1		DAY 118-DAY 132
	Blue Tongue	1		DAY 160-DAY 195
	Blue Tongue	1		DAY 216
	Blue Tongue	1		DAY 258-DAY 265
	Blue Tongue	1		DAY 279
	Blue Tongue	1		DAY 307
	Blue Tongue	1		DAY 328
	Blue Tongue	1		DAY 342
	Blue Tongue	1		DAY 356-DAY 363
	Excess Salivation			DAY 111-DAY 118
	Normal			DAY 1-DAY 13
	Normal			DAY 27-DAY 34
	Normal			DAY 48-DAY 55
	Normal			DAY 104
	Normal			DAY 139-DAY 153
	Normal			DAY 202-DAY 209
	Normal			DAY 223-DAY 251
	Normal			DAY 272
	Normal			DAY 286-DAY 300
	Normal			DAY 314-DAY 321
	Normal			DAY 335
	Normal			DAY 349

Severity Codes

<u>Observation</u>	<u>Severity</u>	<u>Description</u>
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

^aIndividual weekly observations

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLIN. OBSERVATIONS^a

STUDY: 219B
DAY 1-DAY 363

GROUP: 4-M
DOSE: 4.0 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8918	Blue Tongue	1		DAY 83
	Blue Tongue	1		DAY 97
	Blue Tongue	1		DAY 132-DAY 167
	Blue Tongue	1		DAY 195-DAY 202
	Blue Tongue	1		DAY 216
	Blue Tongue	1		DAY 237-DAY 244
	Blue Tongue	1		DAY 272
	Blue Tongue	1		DAY 286-DAY 293
	Blue Tongue	1		DAY 307
	Blue Tongue	1		DAY 321-DAY 328
	Blue Tongue	1		DAY 356-DAY 363
	Normal			DAY 1-DAY 76
	Normal			DAY 90
	Normal			DAY 104-DAY 125
	Normal			DAY 174-DAY 188
	Normal			DAY 209
	Normal			DAY 223-DAY 230
	Normal			DAY 251-DAY 265
	Normal			DAY 279
	Normal			DAY 300
Normal			DAY 314	
Normal			DAY 335-DAY 349	
8908	Blue Tongue	1		DAY 69
	Blue Tongue	1		DAY 97
	Blue Tongue	1		DAY 111
	Blue Tongue	1		DAY 132-DAY 153
	Blue Tongue	1		DAY 174-DAY 195
	Blue Tongue	1		DAY 230-DAY 251
	Blue Tongue	1		DAY 265-DAY 279
	Blue Tongue	1		DAY 293-DAY 307
	Blue Tongue	1		DAY 349
	Blue Tongue	1		DAY 363
	Diarrhea	1		DAY 125
	Diarrhea	1		DAY 335
	Normal			DAY 1-DAY 62
	Normal			DAY 76-DAY 90

Severity Codes

<u>Observation</u>	<u>Severity</u>	<u>Description</u>
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

^aIndividual weekly observations

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLIN. OBSERVATIONS^a

STUDY: 219B
DAY 1-DAY 363

GROUP: 4-M
DOSE: 4.0 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
	Normal			DAY 104
	Normal			DAY 118
	Normal			DAY 160-DAY 167
	Normal			DAY 202-DAY 223
	Normal			DAY 258
	Normal			DAY 286
	Normal			DAY 314-DAY 328
	Normal			DAY 342
	Normal			DAY 356
8926	Blue Tongue	1		DAY 34-DAY 55
	Blue Tongue	1		DAY 76-DAY 118
	Blue Tongue	1		DAY 146
	Blue Tongue	1		DAY 160-DAY 167
	Blue Tongue	1		DAY 181-DAY 237
	Blue Tongue	1		DAY 258-DAY 300
	Blue Tongue	1		DAY 314-DAY 349
	Blue Tongue	1		DAY 363
	Blue Tongue	2		DAY 307
	Dehydrated			DAY 174
	Normal			DAY 1-DAY 27
	Normal			DAY 62-DAY 69
	Normal			DAY 125-DAY 139
	Normal			DAY 153
	Normal			DAY 244-DAY 251
	Normal			DAY 356
8921	Blue Tongue	1		DAY 34-DAY 48
	Blue Tongue	1		DAY 76
	Blue Tongue	1		DAY 118-DAY 125
	Blue Tongue	1		DAY 153
	Blue Tongue	1		DAY 174
	Blue Tongue	1		DAY 202
	Blue Tongue	1		DAY 216-DAY 223
	Blue Tongue	1		DAY 237
	Blue Tongue	1		DAY 251-DAY 293
	Blue Tongue	1		DAY 307-DAY 314
	Blue Tongue	1		DAY 328-DAY 335

Severity Codes

Observation	Severity	Description
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

^aIndividual weekly observations

INDIVIDUAL CLIN. OBSERVATIONS^a

STUDY: 219B
 DAY 1-DAY 363

GROUP: 4-M
 DOSE: 4.0 (mg/kg)

SEX: MALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
	Blue Tongue	1		DAY 356-DAY 363
	Normal			DAY 1-DAY 27
	Normal			DAY 90-DAY 111
	Normal			DAY 139-DAY 146
	Normal			DAY 181-DAY 195
	Normal			DAY 209
	Normal			DAY 230
	Normal			DAY 244
	Normal			DAY 300
	Normal			DAY 321
	Normal			DAY 342-DAY 349
	Respiratory Rate Increased			DAY 55-DAY 83
	Respiratory Rate Increased			DAY 132
	Respiratory Rate Increased			DAY 153-DAY 174

Severity Codes

<u>Observation</u>	<u>Severity</u>	<u>Description</u>
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

^aIndividual weekly observations

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLIN. OBSERVATIONS^a

STUDY: 219B
DAY 1-DAY 363

GROUP: 4-F
DOSE: 4.0 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8941	Blue Mammary Area			DAY 69
	Blue Tongue	1		DAY 118-DAY 125
	Blue Tongue	1		DAY 146
	Blue Tongue	1		DAY 160
	Blue Tongue	1		DAY 174-DAY 195
	Blue Tongue	1		DAY 209-DAY 216
	Blue Tongue	1		DAY 230-DAY 244
	Blue Tongue	1		DAY 265-DAY 307
	Blue Tongue	1		DAY 349
	Diarrhea	1		DAY 188
	Diarrhea	1		DAY 321-DAY 328
	Firm Mammary Area			DAY 69
	Normal			DAY 1-DAY 62
	Normal			DAY 76-DAY 111
	Normal			DAY 132-DAY 139
	Normal			DAY 153
	Normal			DAY 167
	Normal			DAY 202
	Normal			DAY 223
	Normal			DAY 251-DAY 258
Normal			DAY 314	
Normal			DAY 335-DAY 342	
Normal			DAY 356-DAY 363	
8933	Blue Mammary Area			DAY 69
	Blue Tongue	1		DAY 76
	Blue Tongue	1		DAY 97-DAY 118
	Blue Tongue	1		DAY 146
	Blue Tongue	1		DAY 160-DAY 216
	Blue Tongue	1		DAY 237-DAY 251
	Blue Tongue	1		DAY 265-DAY 300
	Blue Tongue	1		DAY 314
	Blue Tongue	1		DAY 335
	Blue Tongue	1		DAY 349-DAY 363
	Diarrhea	1		DAY 41
	Diarrhea	1		DAY 104
	Diarrhea	1		DAY 132

Severity Codes

Observation	Severity	Description
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

^aIndividual weekly observations

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLIN. OBSERVATIONS^a

STUDY: 219B
DAY 1-DAY 363

GROUP: 4-F
DOSE: 4.0 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
	Diarrhea	1		DAY 202
	Diarrhea	1		DAY 230
	Diarrhea	1		DAY 356
	Diarrhea	2		DAY 27
	Excess Salivation			DAY 111
	Firm Mammary Area			DAY 69
	Normal			DAY 1-DAY 20
	Normal			DAY 34
	Normal			DAY 48-DAY 62
	Normal			DAY 83-DAY 90
	Normal			DAY 125
	Normal			DAY 139
	Normal			DAY 153
	Normal			DAY 223
	Normal			DAY 258
	Normal			DAY 307
	Normal			DAY 321-DAY 328
	Normal			DAY 342
8936	Blue Tongue	1		DAY 48-DAY 55
	Blue Tongue	1		DAY 76-DAY 111
	Blue Tongue	1		DAY 125-DAY 146
	Blue Tongue	1		DAY 160-DAY 174
	Blue Tongue	1		DAY 188-DAY 230
	Blue Tongue	1		DAY 244
	Blue Tongue	1		DAY 265-DAY 314
	Blue Tongue	1		DAY 349-DAY 363
	Diarrhea	1		DAY 230
	Diarrhea	1		DAY 356-DAY 363
	Normal			DAY 1-DAY 41
	Normal			DAY 62-DAY 69
	Normal			DAY 118
	Normal			DAY 153
	Normal			DAY 181
	Normal			DAY 237
	Normal			DAY 251-DAY 258
	Normal			DAY 321-DAY 342

Severity Codes

Observation	Severity	Description
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

^aIndividual weekly observations

ONE YEAR ORAL TOXICITY STUDY OF
WR238605 SUCCINATE IN DOGS

DRAFT

INDIVIDUAL CLIN. OBSERVATIONS^a

STUDY: 219B
DAY 1-DAY 363

GROUP: 4-F
DOSE: 4.0 (mg/kg)

SEX: FEMALE

ANIMAL #	OBSERVATIONS	SEVERITY	LOC	TIME OCCURRED
8944	Blue Tongue	1		DAY 20
	Blue Tongue	1		DAY 34-DAY 118
	Blue Tongue	1		DAY 132-DAY 160
	Blue Tongue	1		DAY 181-DAY 265
	Blue Tongue	1		DAY 279-DAY 293
	Blue Tongue	1		DAY 307-DAY 328
	Blue Tongue	1		DAY 342-DAY 363
	Blue Tongue	2		DAY 272
	Blue Tongue	2		DAY 335
	Diarrhea	1		DAY 251
	Diarrhea	1		DAY 307
	Normal			DAY 1-DAY 13
	Normal			DAY 27
	Normal			DAY 125
	Normal			DAY 167-DAY 174
	Normal			DAY 300

Severity Codes

Observation	Severity	Description
Blue Tongue	1	Slight (slight blue tinged color)
Diarrhea	1	Semi-solid feces
	2	Semi-solid to liquid feces

^aIndividual weekly observations