

**UNITED STATES AIR FORCE
RESEARCH LABORATORY**

**90-DAY ORAL GAVAGE TOXICITY
STUDY OF C9-C16 AROMATIC
FRACTION JET-A IN FEMALE
SPRAGUE-DAWLEY CD RATS AND
MALE C57BL/6 MICE**

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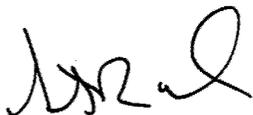
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The animal use described in this study was conducted in accordance with the principles stated in the "Guide for the Care and Use of Laboratory Animals", National Research Council, 1996, and the Animal Welfare Act of 1966, as amended.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE DIRECTOR



STEPHEN R. CHANNEL, Maj, USAF, BSC
Branch Chief, Operational Toxicology Branch
Air Force Research Laboratory

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13. ABSTRACT (Maximum 200 words) This study was conducted to characterize the potential toxic effects of C9-C16 aromatic fraction of Jet-a in female Sprague-Dawley CD rats and male C57BL/6 mice following daily oral administration for 90 days. Four groups of 15 female/rats group and 15 male mice/group were administered a daily oral gavage dose of the test substance at 0 (vehicle control), 20, 100, and 500 mg/kg in a corn oil vehicle. Mean hemoglobin, hematocrit, and red blood cell counts were decreased in the mid- and high-dose female rats. Necropsy examinations revealed enlarged livers in the high-dose rats. This correlated with the organ weight measurements indicating significant liver weight increases (absolute and relative to brain and body weight) in the high-dose rats compared with their controls. There were no pathological lesions observed or changes in serum chemistry parameters which were related to the test substance. Clinical observations included hunched posture in all groups of mice, with the frequency of the observation increasing with higher doses. Lethargy was recorded from all of the high-dose mice and half of the high-dose rats. Lethargy was also observed in 5/15 low-dose and 12/15 mid-dose mice. Salivation was observed in all of the high-dose rats and from 6/15 from the mid-dose rats. Rats in the mid- and high-dose groups were observed shoveling their contact bedding with their noses within minutes after being dosed. The shoveling and salivation observed in the rats is consistent with an irritation response in the mouth. There were no apparent effects of the test substance on the body weights during the study. Increased food consumption was observed in the rats that received test substance, with significant increases observed during most of the study in the high-dose group.

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QUALITY ASSURANCE STATEMENT

This study was inspected by the Quality Assurance Unit and reports were submitted to the Study Director and management as follows:

<u>Phase Inspected</u>	<u>Inspection Date</u>	<u>Date Reported to Study Director/Management</u>
Formulation preparation	7/30/98	8/3/98
Training records review	7/30/98	8/3/98
Formulation analysis	8/3/98	9/1/98
Body weights	8/4/98	9/1/98
Clinical observations	8/4/98	9/1/98
Protocol review	8/4/98	8/4/98
Test substance administration	8/4/98	9/1/98
Food consumption measurements	8/4/98	9/1/98
Blood collection	11/2/98	12/1/98
Clinical observations	11/2/98	12/1/98
Body weights	11/2/98	12/1/98
Tissue harvest	11/2/98	12/1/98
Test substance administration	11/2/98	12/1/98
Organ weights	11/2/98	12/1/98
Clinical lab blood processing/analysis	11/2/98	12/1/98
Audit study file	11/3/98	11/3/98
Audit study file	11/16/98	11/16/98
Audit study file	12/15/98	12/15/98
Audit draft report	12/16/98	12/16/98
Audit report tables and/or appendices	1/14/99	1/14/99
Audit study file	8/23/99	8/23/99
Audit draft final report	8/23/99	8/23/99
Audit final report	8/30/99	8/30/99

 Quality Assurance Unit

Date

COMPLIANCE STATEMENT

This study was conducted in compliance with the U.S. Environmental Protection Agency (EPA) TSCA Good Laboratory Practice regulations, 40 CFR Part 792, August 17, 1989 with the exception that neither the stability evaluation conducted by Equilon Enterprises, L.L.C. nor the histopathology tissue preparation conducted by the United States Air Force were performed in full compliance with these practices. This study was listed on Battelle's Master List of regulated studies.

Peter B. Smith, M.S.
Study Director

Date

STUDY SCHEDULE

Protocol Approval by Battelle.....	July 16, 1998
Protocol Approval by Sponsor	July 23, 1998
Animal Arrival at Battelle	July 23, 1998
Quarantine Release.....	July 29, 1998
Start of Dosing	August 4, 1998
Final Necropsy	November 3, 1998

SUMMARY

This study was conducted to characterize the potential toxic effects of C₉-C₁₆ aromatic fraction of Jet-A in female Sprague-Dawley CD Rats and male C57BL/6 Mice following daily oral administration over 90 days. Four groups of 15 rats/group and four groups of 15 mice/group were administered a daily oral gavage dose of the test substance at 0 (vehicle control), 20, 100, and 500 mg/kg. During the study, body weights and food consumption were evaluated prior to initiation of dosing and weekly thereafter. In addition the body weights were measured prior to necropsy (Day 91). Clinical observations were conducted within 1 to 2 hours following dosing and again at least 6 hours after dosing (with twice-daily mortality and morbidity observations). Clinical pathology evaluations for hematology, coagulation and serum chemistry parameters were conducted on fasted rats on the day of necropsy. Clinical pathology evaluations for hematology and serum chemistry parameters were conducted on non-fasted mice on the day of necropsy. Following the 90-day dosing period, all surviving animals were subjected to a complete necropsy with organ weight measurement and tissue collection on Day 91. The collected tissues were processed histologically and examined microscopically by pathologists of the United States Air Force.

One rat died and one mouse was euthanized in a moribund condition in their respective high dose groups (500 mg/kg). Both of these early deaths were attributed to injury from gavage error. The remaining mice and rats survived until scheduled necropsy.

Clinical observations included hunched posture in all groups of mice, with increasing frequency of the observation with increasing test substance dose. Rough coat was observed at least once for every animal on study (including controls). There was an increase in the frequency of this rough coat observation with increasing test substance dose, but it is not clear that this is an effect of the test substance. Lethargy was recorded from 15/15 of the high dose mice (500 mg/kg) and 7/15 of the high dose rats (500 mg/kg). Lethargy was also observed in 5/15 low dose (20 mg/kg) and 12/15 mid dose mice (100 mg/kg). At least 2 mice from each group (including controls) appeared thin during at least one of the observations; this was not believed to be an effect of the test substance. Salivation was observed in 15/15 of the high dose rats (500 mg/kg) and from 6/15 from the mid dose rats (100 mg/kg). Shoveling behavior was observed throughout the study in rats in both the mid and high dose groups (100 and 500 mg/kg). The shoveling behavior was observed incidentally, shortly after dosing, but was not present at the 1 to 2 hour post dose observation. The shoveling and salivation observed in the rats is consistent with an irritation response in the mouth.

There were no effects of the test substance on the body weights during the study. Increased group mean food consumption values were observed in the groups of rats which received test substance. These increases were statistically significant occasionally in the low dose group (20 mg/kg) and were significant during 9 of the last 10 weeks of the study in the high dose group (500 mg/kg). The mice showed an

opposite pattern, with mildly decreased food consumption, which was occasionally statistically significant in the high dose group (500 mg/kg).

Clinical pathology evaluations revealed mean hemoglobin, hematocrit, and red blood cell counts (HGB/HCT/RBC) were minimally decreased in the mid- and high-dose female rats. Based on the dose-dependency and frequent statistical significance of these decreases, they were interpreted to be treatment-related. HGB/HCT/RBC results of the low-dose female rats and all three treated groups of male mice were similar to controls. No other differences in hematology or serum chemistry parameters were interpreted to be related to treatment with the test substance.

Of the two animals that died prior to scheduled necropsy, both were observed to have antemortem and gross necropsy observations consistent with accidental gavage injury. Necropsy examinations revealed enlarged livers in the high dose group rats (500 mg/kg). This gross observation was confirmed by organ weight measurements indicating highly significant liver weight increases (absolute and relative to brain and body weight) in the 500 mg/kg rats compared with their controls. The kidney weights relative to body weight and relative to brain weight were increased in the 500 mg/kg/day rats. However, there were no lesions of the kidney or liver which correspond to the increased organ weights, nor were there any changes in serum markers which normally relate to functional changes in the liver or kidney. There were no other test substance effects observed at necropsy or in the comparison of organ weights. Microscopic examination of tissues found several lesions, but none of these was attributed to a test substance effect.

Daily oral administration of up to 20 mg/kg/day C₉-C₁₆ aromatic fraction of Jet-A was well-tolerated by female Sprague-Dawley (CD) rats and male C57BL/6 mice during a ninety day period. Doses of 500 mg/kg/day produced increased liver and kidney weights in the rats, hemoglobin, hematocrit and red blood cell counts were decreased in the rats, clinical signs of lethargy in both species, hunched posture in the mice and shoveling and salivation in the rats. Doses of 100 mg/kg results in decreased hemoglobin, hematocrit and red blood cell counts in the rats, hunched posture and lethargy in the mice and shoveling and salivation in the rats. Based on these findings, the no-observed adverse effect level (NOAEL) of C₉-C₁₆ aromatic fraction of Jet-A at dosages of 0, 20, 100 and 500 mg/kg/day was 20 mg/kg/day.

1.0 INTRODUCTION

The objective of this study was to characterize the potential toxic effects elicited by the daily oral administration of C₉-C₁₆ aromatic fraction of Jet-A in female rats and male mice for 90 days. Menzie-Cura & Associates, Inc. was the Sponsor of the study. Donna Vorhees was the Sponsor's Study Monitor. Menzie-Cura & Associates, Inc. were acting as the agent of their primary client, the U.S. Air Force's Occupational Toxicology Branch of the Air Force Research Laboratory. The study protocol, amendments to the protocol, and protocol deviations are contained in Appendix A.

Rodents are the preferred species for general toxicity testing (EPA, 1990). Members of the total petroleum hydrocarbon criteria working group (TPHCWG) evaluated the "data gaps" on animal toxicity of petroleum hydrocarbons and suggested that data from two species (rats and mice) would be of greater value than data from a single species for establishing a test substance reference dose. However, toxicity data from male rats may be difficult to interpret due to the development of α -2-microglobulin nephropathy, induced by most hydrocarbons. To keep animal numbers to a minimum, one sex of each species was considered appropriate for meeting the objectives of this study. Thus, female rats and male mice were selected. Except for the development of α -2-microglobulin nephropathy in male rats, differences between the sexes were not observed in the biological endpoints monitored. Both the Fischer 344 rat and the C57BL/6 mouse were used extensively for the toxicity testing of jet fuels from 1973 to 1983 by the Air Force.

The study was performed at Battelle (Columbus, OH) under the direction of Peter B. Smith, Study Director. The experimental start date (first day of dosing) was August 4, 1998 and the in-life phase was completed (final necropsy) on November 3, 1998.

2.0 EXPERIMENTAL DESIGN

Sixty Sprague-Dawley (CD) female rats and sixty Charles River C57BL/6 male mice were each allocated into 4 treatment groups comprised of fifteen animals. Each animal received a daily oral gavage administration of vehicle or test substance as specified below. All animals were necropsied after a 90-day treatment period.

Study Design Summary Table

Group Number	Number of Animals	Treatment	Dose Level (mg/kg/day)
1	15 female rats	Carrier Control	0
2	15 female rats	Jet-A ^a	20
3	15 female rats	Jet-A ^a	100
4	15 female rats	Jet-A ^a	500
5	15 male mice	Carrier Control	0
6	15 male mice	Jet-A ^a	20
7	15 male mice	Jet-A ^a	100
8	15 male mice	Jet-A ^a	500

a. Jet-A = C₉-C₁₆ aromatic fraction of Jet-A.

Data collection included:

- detailed clinical observations for signs of toxicity approximately one to two hours after dosing and a second observation at least six hours after dosing, twice-daily mortality and morbidity observations
- body weights at time of group assignment (Day 4 for rats and Day 5 for mice), prior to initiation of dosing (Day 1), weekly during the study and prior to necropsy (Day 91)
- weekly total food consumption measurements
- hematology and serum chemistry evaluations of animals at study termination
- complete necropsy of all animals
- measurement of organ weights and calculation of organ weights relative to brain and body weight
- microscopic examination of histologically prepared tissue samples

The study protocol, amendments and deviations are provided in Appendix A. Detailed methods for all phases of the study are specified in subsequent sections of this report.

3.0 MATERIALS AND METHODS

3.1 Test Substance

The test substance for this study was C₉-C₁₆ aromatic fraction of Jet-A and was supplied by BDM Petroleum Technologies in two separate shipments. Both shipments were of Lot 97-POSF-3404-AR916. The first shipment contained 100 mL of C₉-C₁₆ aromatic fraction of Jet-A was sent in a 120 mL amber glass vial, and was received at Battelle on 4/21/98. The second shipment contained 1 L of the test substance in a 3 L metal canister, and was received at Battelle on 8/6/98. No expiration date was provided for this lot of material, but analyses performed by Equilon Enterprises, L.L.C. showed no significant change in the neat material over the course of six months (Appendix G).

The carrier for this study was corn oil manufactured by Mazola, Ltd. (Lot Feb 1699A - expires 8/29/98, 9/12/98, 9/19/98; Lot Sep 1299A - expires 10/3/98, 10/10/98, 10/24/98, 10/31/98; Lot Dec 3099A - expires 11/14/98, 11/21/98 where expiration date was based on when an individual container of corn oil was first opened).

3.2 Test Substance Identity, Purity, and Stability Analyses

The identity, purity, stability, method of synthesis, and other formulated drug characterization data of the bulk test substance were the responsibility of the Sponsor. Battelle conducted 20 day stability evaluations and concentration analyses of the low, mid and high concentration dosing solutions used for weeks 1, 8 and 12, using a method supplied by the Sponsor and validated at Battelle prior to dose preparation. Results of these analyses are reported in Appendix G.

3.3 Dose Preparation

C₉-C₁₆ aromatic fraction of Jet-A was formulated for oral gavage administration at concentrations of 0, 2, 10 and 50 mg/mL in corn oil for the mice and 0, 8, 40 and 200 mg/mL in corn oil for the rats. The appropriate quantity of C₉-C₁₆ aromatic fraction of Jet-A was added to a volumetric flask, and the solution was diluted to the final volume by adding corn oil. The mixture was stirred, and the formulated solutions were then dispensed into amber glass vials with Teflon® septa and aluminum seals. Formulated doses were stored at -5 to 4°C, and used within 15 days of preparation. Carrier control dose (0 mg/mL) was also stored at -5 to 4°C and used within 15 days of preparation.

3.4 Dose Analysis

The C₉-C₁₆ aromatic fraction of Jet-A concentration of the dosing solutions was determined by a gas chromatographic method. A complete description of the dose analysis method is provided in Appendix E.

3.5 Test System

Sixty male C57BL/6 mice and 60 female Sprague-Dawley (CD) rats were used for this study. The animals were received in good condition as part of a larger shipment of animals received at Battelle on July 23, 1998 from Charles River Laboratories (Portage, MI). Colony health monitoring records were furnished by the supplier and are maintained in the study file. All rats were approximately 5 weeks of age at receipt and approximately 7 weeks of age at the initiation of dosing. All mice were approximately 7 weeks at receipt and approximately 9 weeks of age at the initiation of dosing. Body weights at the initiation of dosing ranged from 140.5 to 179.2 g for the rats and from 22.0 to 25.8 g for the mice.

Sprague-Dawley CD rats and C57BL/6 mice were chosen as the test system because these are accepted species, which are frequently used by the primary client to evaluate the safety of materials to which humans may be exposed. These two rodent species are frequently used for US EPA TSCA studies.

All housing and animal care conformed to the requirements stated in the "Guide for the Care and Use of Laboratory Animals" (National Academy of Sciences, 1996) and the U.S. Department of Agriculture through the Animal Welfare Act (Public Law 99-198). Battelle's Institutional Animal Care and Use Committee approved the study protocol.

3.5.1 Receipt and Quarantine

Upon receipt the animals were quarantined and observed twice daily for 7 days to evaluate the health of the animals. During the quarantine period, husbandry needs (i.e., housing, feed and water) were provided for each animal. Routine serological testing was conducted prior to release of the rats from quarantine for determination of antibody levels to pneumonia virus (PVM), Kilham rat virus (KRV), Toolan's H-1 virus (H-1), Sendai virus, and rat coronavirus-sialodacryoadenitis virus (RCV-SDA). Routine serological testing was also conducted prior to release of the mice from quarantine for determination of antibody levels to pneumonia virus (PVM), (Reo-3), (GDVII), (MVM), Polyoma, Ectromelia, Sendai; (MHV), (LCM), K Virus, (EDIM), and Mad-FL. All samples tested had no significant serum titers to these infectious agents. All animals were considered healthy and were released

from quarantine for use on the study following a health examination by a staff veterinarian. The animals were also closely monitored during the acclimation period that followed quarantine release and continued until the initiation of dosing.

3.5.2 Identification

All animals were identified by cage card with a pre-study number throughout the quarantine period. A unique study number was assigned to each animal at randomization and the animals were tattooed with their assigned study number. A cage card with the unique study identification number and study group assignment were displayed during the dosing period. Each animal's study identification number was used for the recording of raw data.

3.5.3 Housing and Environmental Conditions

The rats were individually housed in polycarbonate cages during quarantine and the in-life phase of the study. The mice were housed two to a cage during quarantine and then individually housed beginning July 28, 1998.

The environmental conditions of the animal study room during the study conformed to the following:

- The light/dark cycle was set to provide 12 hours of light and 12 hours of dark each day using fluorescent lighting
- The room temperature and relative humidity controls were set to provide from 64 to 79°F and 30 to 70 percent, respectively, and were monitored twice daily for conformance
- Fresh air was supplied to the room at a rate providing a minimum of ten changes of room air per hour.

3.5.4 Feed and Water

Each animal was allowed *ad libitum* access to Certified Rodent Lab Diet® 5002 (PMI Feeds, Inc.) during quarantine and study periods. Analysis reports of each feed lot were supplied by the vendor and are maintained in Battelle's archives. Water was provided *ad libitum* via an automatic watering system. The water source was the municipal potable supply from the City of Columbus, which conforms with EPA drinking water standards. The water supply is periodically monitored by chemical and microbial analyses; and the water analysis reports are maintained under the direction of Battelle. There

were no known contaminants in the food or water that could be expected to have an impact on the study results or interpretations.

3.6 Randomization

The animals were randomized to treatment groups 4 or 5 days (for rats and mice respectively) prior to the initiation of dosing. The Xybion PATH/TOX System randomly assigned the animals to treatment groups by body weight. The Xybion software algorithm assures homogeneity of mean body weights across all treatment groups.

3.7 Dose Administration

All dosing solutions were administered daily as a single bolus oral gavage. Dose volumes were based on the most recent body weights recorded weekly. Doses were administered using a gavage needle and syringe set according to the table below.

Dose Summary Table

Group Number	Treatment	Dose Level (mg/kg/day)	Dose Concentration (mg/mL)	Dose Delivery Volume (mL/kg/day)
1	Carrier Control	0	0	2.5
2	Jet-A ^a	20	8	2.5
3	Jet-A ^a	100	40	2.5
4	Jet-A ^a	500	200	2.5
5	Carrier Control	0	0	10
6	Jet-A ^a	20	2	10
7	Jet-A ^a	100	10	10
8	Jet-A ^a	500	50	10

a. Jet-A = C₉-C₁₆ aromatic fraction of Jet-A.

3.8 Clinical Observations

Each animal was observed approximately one to two hours following dosing and a second time at least 6 hours after dosing each day for overt signs of toxic or pharmacologic effect and change in general behavior and appearance during the study. All clinical observations were recorded whether findings were normal or abnormal.

3.9 Body Weights

Body weights were measured at time of randomization, on Day 1 prior to dosing, weekly during the study and prior to necropsy (Day 91).

3.10 Food Consumption

Individual food consumption was determined for all animals by measuring full and empty feeder weights weekly.

3.11 Clinical Pathology

Clinical pathology evaluations [hematology, coagulation (rats only) and serum chemistry] were performed for each animal as specified in the following sections. The rats (but not the mice) were fasted from food overnight for scheduled clinical pathology evaluations conducted on Day 91. Animals were anesthetized using a mixture of carbon dioxide/oxygen during the blood collection procedure. Blood for hematology evaluation was collected via cardiac puncture. Blood samples were collected in tubes both with and without anticoagulant (EDTA) for hematology and serum chemistry analyses, respectively. Tubes containing blood for serum chemistry were centrifuged, and the serum separated. Blood collected for coagulation parameters were collected into tubes containing sodium citrate.

3.11.1 Hematology

Samples for hematology analysis were collected from all surviving animals on Day 91. Coagulation parameters (Prothrombin Time and Activated Partial Thromboplastin Time) and Methemoglobin were evaluated only from the rats, due to the limited blood volume available from mice. The following parameters were evaluated.

Hematology
Erythrocyte count (RBC) - $10^6/\mu\text{L}$
Hemoglobin (HGB) - g/dL
Methemoglobin (MHG) - g/dL
Hematocrit (HCT) - %
Mean Corpuscular Volume (MCV) - fL
Mean Corpuscular Hemoglobin (MCH) - pg
Mean Corpuscular Hemoglobin Concentration (MCHC) - g/dL
Platelet Count (PLT) - $10^3/\mu\text{L}$
Reticulocyte Count (RET) - %
Total Leukocyte Count (WBC) - $10^3/\mu\text{L}$
Differential Leukocyte Count - $10^3/\mu\text{L}$
Prothrombin Time (PT) - sec
Activated Partial Thromboplastin Time (APTT) - sec

3.11.2 Serum Chemistry

Samples for clinical chemistry evaluations were collected from all surviving animals on Day 91. Blood samples were collected into tubes without anticoagulant. The serum was separated by centrifugation. The following parameters were evaluated.

Serum Chemistry
Blood Urea Nitrogen (BUN) - mg/dL
Creatinine (CREA) - mg/dL
Serum Aspartate Aminotransferase (AST) - IU/L
Serum Alanine Aminotransferase (ALT) - IU/L
Alkaline Phosphatase (ALP) - IU/L
Lactate Dehydrogenase (LDH) - IU/L
Creatine Kinase (CPK) - IU/L
gamma Glutamyltransferase (gGT) - IU/L
Sorbitol Dehydrogenase (SDH) - IU/L
Serum Glucose (GLU) - mg/dL
Cholesterol (CHOL) - mg/dL
Triglycerides (TRIG) - mg/dL
Sodium (Na) - mEq/L
Calcium (Ca) - mg/dL
Phosphorus (PHOS) - mg/dL
Potassium (K) - mEq/L
Chloride (Cl) - mEq/L
Total Protein (TP) - g/dL
Albumin (ALB) - g/dL
Globulin (GLOB) - g/dL
Albumin/Globulin ratio (AGR)

3.12 Anatomic Pathology

3.12.1 Necropsy

Necropsies were performed on all rats and mice. Each necropsy included an examination of the body; all orifices; the cranial, thoracic, abdominal and pelvic cavities; and collection of the protocol-required tissues. Selected organs were weighed and included the adrenal glands, heart, lungs, liver, spleen, kidneys, brain, testes, and ovaries at the time of necropsy. The thyroids and parathyroids were weighed post-fixation from rats only. With the exception of the eyes and testes that were preserved in Bouin's fixative, tissues collected at the time of necropsy were fixed in 10 percent neutral buffered formalin solution. For rats, the pituitary shelf was cut off at necropsy and placed in formalin prior to weighing. The remaining nasal bones were placed directly into Formical-4. Mouse nasal bones, including the pituitary, were placed into formalin. Mouse tissue was not placed into Formical-4. The rat nasal bones were left in Formical-4 and shipped in Formical-4.

Tissues preserved included: the tail tattoo for animal identification, adrenal glands, aorta, brain, cecum, colon, duodenum, epididymides, esophagus, femur/marrow, harderian glands, ileum, eyes with

optic nerve, jejunum, heart, kidneys, liver (with gallbladder for mice), lungs with bronchi, mandibular and mesenteric lymph nodes, mammary glands, nasal turbinates (nasopharyngeal), ovaries with oviducts, pancreas, pituitary gland, prostate, rectum, salivary glands, sciatic nerve, seminal vesicles, skeletal muscle (biceps femoris), skin (ventral), spinal cord, spleen, sternum, stomach, testes, thymus, thyroid gland (with parathyroids), tongue, trachea, urinary bladder, uterus (with cervix), vagina, carcass (mice only) and gross lesions. Gross observations were recorded on each animal's *Individual Animal Necropsy Record* and later entered into the Xybion Path/Tox Computer System.

3.12.2 Organ Weights

The adrenal glands, heart, lungs, liver, spleen, kidneys, brain, testes and ovaries were weighed fresh from all animals euthanized at the conclusion of the study (Day 91). The thyroid and pituitary glands were weighed following fixation from the rats only. These data were collected using the Xybion Path/Tox System.

3.12.3 Histopathology

Tissues were collected and sent in preservative to the primary client, where they were processed for histopathological evaluations from rodents in the high dose and control groups. Tissues from groups 1, 4, 5 and 8 were trimmed, dehydrated, embedded in paraffin, sectioned at 5 μm , stained with hematoxylin and eosin and reviewed microscopically by a board-certified veterinary pathologist employed by the primary client. Tissues from groups 2, 3, 6 and 7 were retained by the primary client for possible processing for histopathological evaluations, depending upon the presence of apparent test substance related lesions found in the high dose groups.

3.13 Statistics

All appropriate quantitative in-life, clinical pathology, and postmortem data collected at Battelle were analyzed statistically. All data were analyzed for test substance effects by analysis of variance. For data whose variances were considered homogeneous across test groups, as determined by Bartlett's test for homogeneity at the 0.05 level, tests for differences between the control and comparison groups were made using Dunnett's test. For nonhomogeneous data, as determined by Bartlett's test for homogeneity at the 0.05 level, tests for pairwise differences between the control and each of the comparison groups were made using Cochran and Cox's modified two-sample t-test. Statistical significance for each comparison are reported at the 0.05 level.

4.0 RESULTS

4.1 Quarantine

Based on the health evaluations conducted during the quarantine period, there were no abnormal clinical findings that precluded the use of any animals on this study.

4.2 Dose Administration

All doses administered to each animal were in agreement with the C₉-C₁₆ aromatic fraction of Jet-A target dosages.

4.3 Survival

One mouse was euthanized in a moribund condition and one rat died prior to scheduled necropsy from the high dose groups (500 mg/kg) on Study Days 8 and 41, respectively. All remaining mice and rats survived until scheduled termination.

4.4 Dose Analysis

All dosing solutions were within 10 percent of the target concentration. A complete dose analysis report is included in Appendix E. A report prepared by Equilon Enterprises, L. L. C. documenting the stability of the test substance is contained in Appendix G.

4.5 Clinical Observations

Clinical observations are summarized in Table 1. Clinical observations for individual animals are reported in Appendix B.

Clinical observations of mice included hunched posture in 4/15 of the control group, in 12/15 of the 20 mg/kg/day mice and all the 100 mg/kg/day and 500 mg/kg/day mice. This posture appears to be test substance related. Lethargy was recorded from 5/15 of the 20 mg/kg/day mice, from 12/15 of the 100 mg/kg/day mice and 15/15 of the 500 mg/kg/day mice. The correlation between dose level and incidence of lethargy strongly suggests a test substance effect. Rough coat was observed in every mouse. The widespread distribution of this rough coat observation suggests it is due to a vehicle effect.

Clinical observations of the rats included salivation in 6/15 of the mid dose (100 mg/kg/ day) and in 15/15 of the high dose (500 mg/kg/day) rats. Lethargy was seen in 7/15 of the high dose (500 mg/kg/day) rats. This reduced activity corresponds to the finding in the mice and is considered a test substance effect.

The Study Director was present to observe dosing several times over the course of the study. These visits ranged from the first day of dosing up through the final week. On every such occasion the rats exhibited a shoveling behavior shortly after dosing. This behavior was seen in a few animals from the mid dose group (100 mg/kg/day), and from most of the animals in the high dose group (500 mg/kg/day). The clinical observation records do not reflect this observation, because the clinical observations were keyed to an interval 1 to 2 hours after dosing. This behavior was always short-lived and began within minutes after dosing, and continued for approximately 10 to 20 minutes after dosing. The primary technician for the study, Laura Blessing, B.S., also observed this shoveling behavior. However, her observations were not systematic due to the fact that she was continuing to dose the remaining animals, and only incidentally observed this behavior when glancing back at animals she had recently dosed. The shoveling and salivation observed in the rats is consistent with an oral irritation response to the test substance.

There were no other clinical observations believed to be related to test substance or treatment effects.

4.6 Body Weights

Group mean body weights are summarized in Table 2. Individual body weights are provided in Appendix B.

No biological or statistical differences in group mean body weight values were identified for any treated groups in either the rats or mice.

4.7 Food Consumption

Group mean food consumption values are summarized in Table 3. Food consumption values for individual animals are reported in Appendix B.

The food consumption of the 500 mg/kg/day rats were significantly increased compared with their control group at week 4 and then from week 6 through the end of the study. The food consumption

of the 20 mg/kg/day rats were significantly increased compared to their control group at Weeks 4, 7 and 12. There was a general trend for the groups of rats treated with test substance to have greater food consumption than their control group. This clearly indicates a test substance effect.

For the mice, the 500 mg/kg/day group had significantly decreased food consumption compared with their controls at weeks 3, 9 and 10. During the weeks when these differences were not statistically significant, the amount of food consumed by the high dose was consistently lower than the controls. All other food consumption values for the treated groups of mice were similar to concurrent controls.

It is not clear why treatment with the test substance would increase the food consumed by rats, but decrease the food consumed by mice, especially since there were no substantial changes in body weights over the course of the study for either species.

4.8 Clinical Pathology

Group mean hematology values are summarized in Table 4. Group mean coagulation parameters are summarized in Table 5. Group mean serum chemistry values are summarized in Table 6. Hematology, coagulation and serum chemistry values for individual animals are reported in Appendix C.

Mean hemoglobin, hematocrit, and red blood cell counts (HGB/HCT/RBC) were minimally decreased in the mid- and high-dose female rats. Based on the dose-dependency and frequent statistical significance of these decreases, they were interpreted to be treatment-related. HGB/HCT/RBC results of the low-dose female rats and all three treated groups of male mice were similar to controls.

Other alterations of hematologic parameters, sometimes statistically significant, were noted in treated groups, but were interpreted to be unrelated to treatment. Some of these other alterations were interpreted to be unrelated to treatment because they involved small (relative to expected variation) differences from control values, such as increased mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration (MCHC) in high-dose male mice, and decreased MCHC in high-dose female rats. There was a treatment-related pattern of statistically significantly reduced activated partial thromboplastin times for all test article-treated rats, but these values all fall within the normal range seen in historical control data. Further, decreased clotting time is not normally considered a toxic change. Therefore the decreases in the activated partial thromboplastin times are not considered toxicologically significant. Other alterations involved small but noticeable changes from control in all dose groups, but the absence of dose-dependent pattern led to the conclusion that they were not treatment-related; for example the decreased platelet counts in all treated groups of male mice.

None of the clinical chemistry results were interpreted to indicate any treatment effects. A number of small-magnitude trends were noted in the data. Examples of these trends included the

increased serum cholesterol in treated male mice (with statistically significant difference in the high dose), and minimally decreased serum sodium and globulin and increased albumin/globulin ratio in treated female rats (often statistically significant). These changes were not interpreted to be treatment-related because the differences from control were small in comparison to the expected variation in the parameters involved.

4.9 Anatomic Pathology

4.9.1 Necropsy

Gross observations for individual rats and mice are presented in Table 7.

The livers of 13/15 of the 500 mg/kg/day rats were visibly enlarged at necropsy. This observation corresponds to the substantial increase noted in liver organ weights as discussed in section 4.9.2. The 500 mg/kg/day rat that was found dead was observed to have dark red discoloration of the lung and antemortem observations of ataxia and labored breathing, which are consistent with an accidental gavage error in dosing.

For the mice, one animal in the 100 mg/kg/day group had a white mass on the cardiac lobe of the lung. The 500 mg/kg/day mouse that was euthanized in a moribund condition had antemortem observations that included lethargy, hypothermia and labored respiration. At the necropsy of this animal, food was found around the lungs. These observations are all consistent with an accidental error in gavage dosing.

There were no other gross findings for either species that were believed to be a result of the test substance.

4.9.2 Organ Weights

The group mean organ weights are included as Table 8. The group mean organ-to-body weight and organ-to-brain weight ratio values are presented in Tables 9 and 10, respectively. The individual animal absolute organ weights, and the ratios of organ-to-body weight and organ-to-brain weight values were calculated and are included in Appendix D.

Organ weight measurements revealed highly significant liver weight increases (measured as absolute weights, as liver relative to brain weight, and liver relative to body weight) in the 500 mg/kg/day rats compared with their controls. This corresponds to the gross observation at necropsy that the livers

were enlarged. The 500 mg/kg/day mice had increased liver weights, but this increase was not statistically significantly different from their control group.

The 500 mg/kg/day rats also had statistically larger kidney-to-body weight and kidney-to-brain weight ratios. The absolute kidney weights were larger than the controls, but not significantly different. Since there are no corresponding kidney lesions nor significant changes in clinical pathology parameters normally related to changes in renal function, the elevated kidney weights do not seem to have any toxicologic relevance. There were no other organ weight differences between treated and control groups of either rats or mice.

4.9.3 Histopathology

While several lesions were observed microscopically in the various tissues of animals examined, none were attributed to a test substance effect. Most noteworthy is the lack of any microscopic lesions corresponding to the enlarged livers observed in the high dose group (500 mg/kg/day) rats. The full report from the United States Air Force pathologist is contained in Appendix F.

5.0 DISCUSSION/CONCLUSIONS

This study was conducted to characterize the potential toxic effects elicited by daily oral gavage administration of C₉-C₁₆ aromatic fraction of Jet-A in female rats and male mice during a 90-day test period. Test substance-related changes were assessed by monitoring clinical observations, body weight changes, food consumption, clinical pathology, necropsy and histopathology findings. Based on the data generated following daily oral gavage administration at dosages of 20, 100, and 500 mg/kg/day to female Sprague-Dawley (CD) rats and male C57BL/6 mice, it may be concluded that:

- Clinical observations included lethargy in the high dose (500 mg/kg/day) groups of both species as well as the low (20 mg/kg/day) and mid (100 mg/kg/day) groups of mice. Hunched posture was observed in all the test substance treated groups of mice. In addition, the high dose (500 mg/kg/day) and mid dose (100 mg/kg/day) rats were observed to shovel their bedding around the cage and salivate excessively after dosing. These last two observations were likely due to oral irritation caused by the test substance.
- C₉-C₁₆ aromatic fraction of Jet-A administration caused significantly increased mean food consumption in the 500 mg/kg/day rat group. There were also sporadic decreased mean food consumption values for the 500 mg/kg/day male mice; which were occasionally statistically significant. It is not clear why the food consumption of the two species react in opposite ways when treated with the test substance, especially since there were no significant differences between the body weights of the treated and control animals of either species.
- Liver weights (absolute, and relative to body and brain weights) were significantly increased in the high dose group (500 mg/kg/day) of the rats. The liver weights of the high dose (500 mg/kg/day) mice were also larger than controls, but this difference was not statistically significant.
- Mean hemoglobin, hematocrit, and red blood cell counts (HGB/HCT/RBC) were minimally decreased in the mid- and high-dose female rats (100 and 500 mg/kg/day, respectively). Based on the dose-dependency and frequent statistical significance of these decreases, they were interpreted to be treatment-related.
- Thirteen of the fourteen high dose (500 mg/kg/day) rats that survived to study completion were observed to have enlarged livers. C₉-C₁₆ aromatic fraction of Jet-A administration did not induce any other macroscopic changes in any tissue examined during necropsy at Day 91.
- There were no microscopic lesions attributed to test substance effect.

- Daily oral administration of up to 20 mg/kg/day C₉-C₁₆ aromatic fraction of Jet-A was well-tolerated by female Sprague-Dawley (CD) rats and male C57BL/6 mice during a ninety day period. Doses of 500 mg/kg/day produced increased liver and kidney weights in the rats, hemoglobin, hematocrit and red blood cell counts were decreased in the rats, clinical signs of lethargy in both species, hunched posture in the mice and shoveling and salivation in the rats. Doses of 100 mg/kg results in decreased hemoglobin, hematocrit and red blood cell counts in the rats, hunched posture and lethargy in the mice and shoveling and salivation in the rats.
- Based on these findings, the no-observed adverse effect level (NOAEL) of C₉-C₁₆ aromatic fraction of Jet-A at dosages of 0, 20, 100 and 500 mg/kg/day was 20 mg/kg/day.

6.0 REFERENCES

1. Good Laboratory Practices Regulations, United States Environmental Protection Agency, 40 CFR, Part 792.

7.0 SPECIMEN STORAGE AND RECORD ARCHIVES

All raw data as defined by the appropriate Good Laboratory Practice regulations generated in conjunction with this study will be maintained under the direction of Battelle. All test substance will either be used on subsequent studies, or will be returned to the Sponsor. Any remaining wet tissues will be stored at Battelle until transferred to a location specified by the Sponsor.

8.0 ACKNOWLEDGMENTS

Acknowledgment of principal contributors participating in the performance of this study is presented in the following list.

<u>Participant</u>	<u>Title</u>
Peter B. Smith, M.S.	Study Director
Richard W. Slauter, Ph.D., D.A.B.T.	Senior Program Director
Karen E. Veley, B.S.	Study Coordinator
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Tracy Peace, D.V.M., M.S., ACLAM	Clinical Veterinarian
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Jodi L. Putman	Necropsy Supervisor
Donna Browning, B.A., B.S.	Manager, Dose Formulation

Table 1-A. Summary of Abnormal Clinical Observations - Female Rats

Sex	Group Number	Category	Subcategory	Number of Animals Affected	Mean First Day Observed	Mean Last Day Observed	Total Number of Observations
Female	2	ABRASION/LESION	FOOT	1	44	62	16
	4	ABRASION/LESION	FOOT	1	77	78	4
Female	2	ABRASION/LESION	LEG	1	44	62	16
Female	3	ALOPECIA	BODY VENTRAL	1	40	91	103
Female	1	ALOPECIA	FOOT	3	38	91	323
	2	ALOPECIA	FOOT	3	18	54	191
	3	ALOPECIA	FOOT	4	16	60	357
	4	ALOPECIA	FOOT	7	40	83	516
Female	1	ALOPECIA	LEG	3	60	91	189
	2	ALOPECIA	LEG	2	42	71	119
	3	ALOPECIA	LEG	1	1	91	181
	4	ALOPECIA	LEG	2	79	91	51
Female	3	DIGESTIVE SYSTEM	SALIVATION	6	33	40	11
	4	DIGESTIVE SYSTEM	SALIVATION	15	9	70	361
Female	2	DISCOLORATION	FOOT	1	41	43	6
	4	DISCOLORATION	FOOT	1	31	34	8
Female	4	EYES/EARS	EYE DISCHARGE-CLEAR	1	31	31	1
Female	1	EYES/EARS	EYE DISCHARGE-RED	2	51	52	7
	3	EYES/EARS	EYE DISCHARGE-RED	1	76	86	3
	4	EYES/EARS	EYE DISCHARGE-RED	1	29	31	4
Female	4	GENERAL APPEARANCE	LETHARGIC	7	5	7	9
Female	4	NEURO/MUSCULOSKELETAL	ATAXIC (INCOORDINATION)	1	41	41	1
Female	4	RESPIRATORY SYSTEM	LABORED RESPIRATION	1	41	41	1
Female	1	RESPIRATORY SYSTEM	NASAL DISCHARGE-RED	1	32	32	1
	2	RESPIRATORY SYSTEM	NASAL DISCHARGE-RED	1	38	38	1
	4	RESPIRATORY SYSTEM	NASAL DISCHARGE-RED	5	32	32	6
Female	4	SWELLING	FOOT	1	32	34	6

Table 1-B. Summary of Abnormal Clinical Observations - Male Mice

Sex	Group Number	Category	Subcategory	Number of Animals Affected	Mean First Day Observed	Mean Last Day Observed	Total Number of Observations
Male	5	ALOPECIA	NECK	1	85	91	13
	6	ALOPECIA	NECK	1	73	91	37
Male	7	DIGESTIVE SYSTEM	FEW FECES	1	20	20	2
	8	DIGESTIVE SYSTEM	FEW FECES	3	15	15	7
Male	5	GENERAL APPEARANCE	HUNCHED POSTURE	4	51	58	11
	6	GENERAL APPEARANCE	HUNCHED POSTURE	12	23	58	97
	7	GENERAL APPEARANCE	HUNCHED POSTURE	15	23	66	131
	8	GENERAL APPEARANCE	HUNCHED POSTURE	15	8	74	305
Male	8	GENERAL APPEARANCE	HYPOTHERMIC	1	8	8	2
Male	6	GENERAL APPEARANCE	LETHARGIC	5	23	23	5
	7	GENERAL APPEARANCE	LETHARGIC	12	21	43	44
	8	GENERAL APPEARANCE	LETHARGIC	15	6	62	417
Male	5	GENERAL APPEARANCE	ROUGH COAT	15	3	80	876
	6	GENERAL APPEARANCE	ROUGH COAT	15	2	86	1194
	7	GENERAL APPEARANCE	ROUGH COAT	15	3	87	1286
	8	GENERAL APPEARANCE	ROUGH COAT	15	2	84	1793
Male	5	GENERAL APPEARANCE	THIN APPEARANCE	2	39	39	2
	6	GENERAL APPEARANCE	THIN APPEARANCE	4	18	18	7
	7	GENERAL APPEARANCE	THIN APPEARANCE	3	51	65	8
	8	GENERAL APPEARANCE	THIN APPEARANCE	8	20	26	16
Male	8	RESPIRATORY SYSTEM	LABORED RESPIRATION	2	5	5	3
Male	8	URINARY SYSTEM	UROGENITAL REGION-WET	2	58	59	4

Table 2. Group Mean Body Weights (g)

Group	Day of Study															
	-4 rats -5 mice	1	8	15	22	29	36	43	50	57	64	71	78	85	90	
Female Rats																
1	Means	142.04	161.69	185.72	207.57	224.04	237.43	250.35	255.43	267.11	262.93	274.59	281.97	287.61	292.11	293.93
	SD	8.19	8.96	9.71	14.36	17.46	17.61	21.17	20.69	19.12	19.79	21.21	22.53	24.86	26.11	26.64
	(N)	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
2	Means	141.43	160.39	180.95	205.39	224.73	236.45	248	254.97	265.73	264.12	273.93	283.31	289.99	293.94	295.63
	SD	7.68	9.11	8.97	11.07	14.92	15.71	13.93	15.97	16.59	16.6	19.33	16.44	15.84	18.51	21.94
	(N)	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
3	Means	141.41	160.59	183.27	208.05	225.92	240.19	253.53	261.81	270.75	268.25	279.72	288.82	294.97	301.95	297.83
	SD	7.52	9.54	10.70	13.17	12.19	16.65	19.83	17.47	21.38	20.92	21.24	23.97	25.84	28.43	28.65
	(N)	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
4	Means	141.82	157.61	177.68	199.81	216.70	231.04	240.97	251.14	257.94	257.11	271.94	279.81	283.80	290.07	285.88
	SD	7.62	9.55	11.15	14.03	15.49	16.24	19.41	19.3	21.95	23	26.87	27.98	28.51	30.59	28.62
	(N)	15	15	15	15	15	15	15	14	14	14	14	14	14	14	14
Male Mice																
5	Means	23.09	24.27	24.64	24.89	25.73	26.39	26.76	27.15	27.6	27.69	27.74	27.95	28.04	28.56	28.49
	SD	0.62	0.81	0.82	1.58	0.97	1.00	0.97	1.07	1.06	1.28	1.14	1.24	1.26	1.04	1.31
	(N)	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
6	Means	23.03	24.07	24.59	24.79	25.24	25.54	26.54	26.97	27.57	27.85	27.95	27.96	28.41	28.53	28.70
	SD	0.62	0.89	1.26	1.28	1.42	1.82	1.22	1.19	1.39	1.4	1.5	1.53	1.78	1.78	1.72
	(N)	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
7	Means	23.05	23.83	23.88	24.42	25.04	25.63	26.11	26.44	26.89	27.13	27.06	27.54	27.94	28.05	28.47
	SD	0.64	0.94	1.25	1.16	1.09	1.14	1.1	1.13	1.03	1.1	1.16	1.29	1.34	1.34	1.33
	(N)	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
8	Means	23.05	24.03	23.73	24.93	25.46	25.99	26.34	26.73	27.56	27.39	27.21	27.45	27.84	28.06	28.81
	SD	0.61	0.66	1.58	0.88	0.78	0.78	1.04	0.97	1.09	0.98	1.23	1.08	1.42	1.19	1.27
	(N)	15	15	15	14	14	14	14	14	14	14	14	14	14	14	14

Table 3. Group Mean Food Consumption (g)

Group	Day of Study													
	8	15	22	29	36	43	50	57	64	71	78	85	90	
Female Rats														
1	Means	15.50	16.52	15.79	15.37	15.78	15.20	14.09	12.94	14.55	15.01	14.93	15.27	15.72
	SD	1.23	2.00	1.64	1.39	1.84	1.42	1.03	1.66	1.35	1.62	1.56	1.27	1.19
	(N)	15	15	15	15	15	15	14	15	14	14	14	15	15
2	Means	15.37	16.94	17.26	16.47*	16.37	16.36	16.01*	14.36	14.81	16.57	16.32	16.54*	16.57
	SD	1.38	1.87	1.52	1.17	0.98	1.39	2.86	1.63	0.61	1.78	1.69	1.57	1.04
	(N)	15	14	12	14	12	12	13	15	10	13	13	15	15
3	Means	15.52	16.79	17.06	17.59	16.96	16.45	15.03	14.2	14.57	16.28	16.3	16.68	16.28
	SD	1.00	1.67	1.92	4.60	2.47	2.19	1.81	1.78	1.95	2.21	2.32	2.67	3.34
	(N)	15	14	14	13	13	14	14	15	14	14	14	15	15
4	Means	14.57	16.03	16.74	16.87*	16.79	16.96*	16.04*	15.17*	16.63*	16.95*	17.18*	17.56*	17.94*
	SD	1.60	1.23	1.45	1.77	1.88	2.00	1.86	2.06	2.09	2.1	2.27	2.19	2.47
	(N)	15	14	15	15	14	14	13	14	12	13	14	14	14
Male Mice														
5	Means	3.61	3.75	3.67	3.52	3.36	3.56	3.35	3.24	3.46	3.71	3.44	3.58	3.81
	SD	0.43	0.58	0.37	0.30	0.31	0.43	0.48	0.29	0.31	0.38	0.25	0.26	0.31
	(N)	15	15	15	15	15	15	15	15	15	15	15	15	15
6	Means	3.75	3.71	3.58	3.38	3.47	3.49	3.32	3.31	3.45	3.61	3.56	3.6	3.74
	SD	0.32	0.52	0.64	0.33	0.38	0.25	0.25	0.25	0.28	0.25	0.27	0.2	0.24
	(N)	15	15	15	15	15	15	15	15	15	15	15	15	15
7	Means	3.88	3.79	3.55	4.07	3.62	3.60	3.18	3.24	3.44	3.61	3.52	3.54	3.88
	SD	0.77	0.91	0.66	1.47	1.57	0.78	0.33	0.32	0.67	0.58	0.48	0.38	0.44
	(N)	15	15	15	15	15	15	15	15	15	15	14	15	15
8	Means	3.68	3.87	3.36*	3.46	3.12	3.53	3.34	3.04	3.21*	3.36*	3.36	3.5	3.74
	SD	0.48	0.76	0.37	0.31	0.52	1.24	0.51	0.48	0.26	0.27	0.32	0.36	0.37
	(N)	15	14	14	14	14	14	14	13	14	14	14	14	14

* Group mean values are significantly different from Groups 1 or 5 (vehicle) at p≤0.05.

Table 4. Group Mean Hematology Parameters, Day 91

Female Rats														
Group	Neutrophils (10 ³ /μL)	Lymphocytes (10 ³ /μL)	Monocytes (10 ³ /μL)	Eosinophils (10 ³ /μL)	Basophils (10 ³ /μL)	White Blood Cells (10 ³ /μL)	Red Blood Cells (10 ⁶ /μL)	Hemoglobin (g/dL)	Hematocrit (%)	Mean Corpuscular Volume (fL)	Mean Corpuscular Hemoglobin (pg)	Mean Corpuscular Hemoglobin Concentration (g/dL)	Platelets (10 ³ /μL)	Reticulocytes (%)
1	Mean	1.08	8.41	0.06	0.15	0.00	9.7	15.9	48.5	56.9	18.7	32.9	1025	0.5
	STD	0.30	2.07	0.05	0.07	0.01	2.1	0.8	2.4	1.5	0.7	0.5	135	0.3
	N	15	15	15	15	15	15	15	15	15	15	15	15	15
2	Mean	0.91	9.34	0.12	0.13	0.01	10.5	15.8	48.1	56.4	18.6	32.9	1013	0.4
	STD	0.33	2.09	0.18	0.03	0.01	2.3	0.8	2.1	1.9	0.8	0.6	223	0.2
	N	15	15	15	15	15	15	15	15	15	15	15	15	15
3	Mean	1.31	9.87	0.21	0.12	0.01	11.5	15.0*	45.8*	55.7	18.3	32.8	1013	0.4
	STD	1.47	2.65	0.35	0.05	0.02	2.7	0.8	2.5	1.6	0.5	0.4	168	0.2
	N	14	14	14	14	14	14	14	14	14	14	14	14	14
4	Mean	1.08	10.69	0.13*	0.14	0.01	12.0	14.4*	44.6*	57.7	18.6	32.4*	993	0.7
	STD	0.33	3.41	0.07	0.06	0.01	3.4	0.7	2	1.5	0.6	0.4	119	0.3
	N	13	13	13	13	13	13	13	13	13	13	13	13	13

* Group mean values are significantly different from Group 1 (vehicle) at p<0.05.

Table 4 continued. Group Mean Hematology Parameters, Day 91

Male Mice														
Group	Neutrophils (10 ³ /μL)	Lymphocytes (10 ³ /μL)	Monocytes (10 ³ /μL)	Eosinophils (10 ³ /μL)	Basophils (10 ³ /μL)	White Blood Cells (10 ³ /μL)	Red Blood Cells (10 ⁶ /μL)	Hemoglobin (g/dL)	Hematocrit (%)	Mean Corpuscular Volume (fL)	Mean Corpuscular Hemoglobin (pg)	Mean Corpuscular Hemoglobin Concentration (g/dL)	Platelets (10 ³ /μL)	Reticulocytes (%)
5	Mean	0.97	7.23	0.17	0.01	0.00	8.4	14.0	42.9	44.2	14.4	32.6	1123	0.8
	STD	0.59	1.94	0.11	0.01	0.00	2.2	0.6	1.8	0.5	0.2	0.4	239	0.2
	N	14	14	14	14	14	14	14	14	14	14	14	14	14
6	Mean	1.06	9.09*	0.16	0.02	0.01	10.3	14.3	43.3	43.9	14.5	33.2	887*	0.8
	STD	0.21	2.47	0.11	0.02	0.01	2.6	0.8	2.3	1.6	0.2	1.3	279	0.4
	N	13	13	13	13	13	13	13	13	13	13	13	13	13
7	Mean	0.83	7.79	0.16	0.02	0.00	8.8	14.1	43.2	44.4	14.5	32.6	860	0.9
	STD	0.23	1.86	0.12	0.02	0.00	2.0	0.8	2.5	0.4	0.2	0.4	479	0.5
	N	13	13	13	13	13	13	13	12	12	12	12	12	13
8	Mean	0.72	6.14	0.12	0.02	0.00	7.0	14.0	42.4	45.1*	14.8*	32.9*	984	0.9
	STD	0.29	1.46	0.09	0.03	0.00	1.6	0.6	1.7	0.5	0.2	0.4	230	0.2
	N	12	12	12	12	12	12	12	12	12	12	12	12	12

* Group mean values are significantly different from Group 5 (vehicle) at p≤0.05.

Table 5. Group Mean Coagulation Parameters

Female Rats			
Day 91			
Group		Prothrombin Time (seconds)	Activated Partial Thromboplastin Time (seconds)
1	Mean	11.3	14.6
	SD	0.3	1.2
	(N)	14	14
2	Mean	11.3	13.1*
	SD	0.4	1.5
	(N)	15	15
3	Mean	11.1	12.9*
	SD	0.3	1.6
	(N)	14	14
4	Mean	11.2	12.7*
	SD	0.3	1.2
	(N)	14	14

* Group mean values are significantly different from Group 1 (vehicle) at $p \leq 0.05$.

Table 6. Group Mean Serum Chemistry Parameters, Day 91

Group	Female Rats											Male Mice											
	Sorbitol Dehydrogenase (μ/L)	Alkaline Phosphatase (μ/L)	Aspartate Aminotransferase (μ/L)	Alanine Aminotransferase (μ/L)	Gamma Glutamyl Transferase (μ/L)	Total Protein (g/dL)	Albumin (g/dL)	Glucose (mg/dL)	Blood Urea Nitrogen (mg/dL)	Creatinine (mg/dL)	Calcium (mg/dL)	Sorbitol Dehydrogenase (μ/L)	Alkaline Phosphatase (μ/L)	Aspartate Aminotransferase (μ/L)	Alanine Aminotransferase (μ/L)	Gamma Glutamyl Transferase (μ/L)	Total Protein (g/dL)	Albumin (g/dL)	Glucose (mg/dL)	Blood Urea Nitrogen (mg/dL)	Creatinine (mg/dL)	Calcium (mg/dL)	
1	Mean	22	57	81	37	0	8.1	5.6	113	15	0.7	11.8											
	SD	6	20	17	11	0	0.6	0.4	11	3	0.1	0.3											
	N	15	15	15	15	15	15	15	15	15	15	15											
2	Mean	21	52	89	38	0	7.7	5.4	115	14	0.6*	11.8											
	SD	14	18	38	19	1	0.5	0.5	7	2	0.1	0.4											
	N	15	15	15	15	15	15	15	15	15	15	15											
3	Mean	25	42*	105	42	0	8.0	5.6	120	13*	0.6*	12.0											
	SD	29	11	61	33	0	0.8	0.6	10	2	0.1	0.5											
	N	15	15	15	15	15	15	15	15	15	15	15											
4	Mean	17*	46	80	39	0	7.9	5.7	118	14	0.6	11.8											
	SD	5	12	40	8	1	0.6	0.5	8	1	0.1	0.4											
	N	14	14	14	14	14	14	14	14	14	14	14											
5	Mean	47	86	70	25	1	5.6	3.8	169	24	0.3	9.7											
	SD	6	11	32	6	1	0.1	0.2	13	4	0.0	0.2											
	N	15	14	14	14	12	12	12	12	12	11	12											
6	Mean	56	89	87	28	0	5.7	3.9	174	24	0.3	9.8											
	SD	31	9	42	12	1	0.2	0.2	13	3	0.0	0.2											
	N	15	14	14	14	12	12	10	11	9	9	11											
7	Mean	50	85	86	24	0	5.5	3.9	178	23	0.3	9.7											
	SD	7	9	44	4	1	0.3	0.1	15	2	0.0	0.2											
	N	13	12	12	12	11	11	7	10	9	8	9											
8	Mean	44	85	65	22	0*	5.6	3.9	179	21	0.3	9.6											
	SD	3	10	22	5	0	0.1	0.1	12	2	0.1	0.3											
	N	13	11	11	10	10	10	7	10	9	8	10											

* Group mean values are significantly different from Groups 1 or 5 (vehicle) at p<0.05.

Table 6 continued. Group Mean Serum Chemistry Parameters, Day 91

Group	Female Rats											Male Mice											
	Phosphorus (mg/dL)	Creatine Kinase (μ/L)	Lactate Dehydrogenase (μ/L)	Triglycerides (mg/dL)	Cholesterol (mg/dL)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Globulin (g/dL)	Ag Ratio	Methemoglobin (g/dL)	Phosphorus (mg/dL)	Creatine Kinase (μ/L)	Lactate Dehydrogenase (μ/L)	Triglycerides (mg/dL)	Cholesterol (mg/dL)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Globulin (g/dL)	Ag Ratio	Methemoglobin (g/dL)	
1	Mean	193	146	54	72	152	7.2	104	2.5	2.22	0.3												
	SD	84	92	22	14	3	0.6	2	0.3	0.20	0.1												
	N	15	15	15	15	15	15	15	15	15	15												
2	Mean	208	134	44	74	150	6.9	103	2.3	2.40	0.3												
	SD	104	67	18	19	2	0.5	2	0.3	0.47	0.1												
	N	15	15	15	15	15	15	15	15	15	15												
3	Mean	329	162	43	81	149*	6.7	104	2.3	2.44*	0.3												
	SD	412	134	18	25	3	0.5	2	0.2	0.26	0.1												
	N	15	15	15	15	15	15	15	15	15	15												
4	Mean	170	157	38	85	149*	6.8	104	2.2*	2.54*	0.3												
	SD	97	202	13	13	3	0.7	2	0.2	0.24	0.1												
	N	14	14	14	14	14	14	14	14	14	14												
5	Mean	162	163	69	101	152	8.7	109	1.8	2.17													
	SD	106	31	15	13	2	0.4	1	0.2	0.31													
	N	12	12	12	12	15	15	15	12	12	12												
6	Mean	218	182	73	105	152	8.7	109	1.8	2.17													
	SD	149	42	24	17	2	0.4	1	0.1	0.18													
	N	12	12	11	9	15	15	15	10	10	10												
7	Mean	298	196	81	115	152	8.7	109	1.7	2.36													
	SD	247	71	25	9	2	0.4	2	0.1	0.19													
	N	11	11	8	8	14	14	14	7	7	7												
8	Mean	199	158	58	125*	153	8.5	109	1.7	2.27													
	SD	131	49	14	10	2	0.6	2	0.1	0.20													
	N	10	10	10	9	13	13	13	7	7	7												

* Group mean values are significantly different from Groups 1 or 5 (vehicle) at p≤0.05.

Table 7. Incidence Summary of Gross Necropsy Observations

	Group number	1	2	3	4
	Number in group	15	15	15	15
-- Female Rats --					
KIDNEY					
DILATATION		1	0	1	0
Total:		1	0	1	0
LIVER					
ENLARGED		0	0	1	13
Total:		0	0	1	13
LUNG					
DISCOLORATION		0	0	0	1
Total:		0	0	0	1
ANIMAL NOTE					
NO LESIONS FOUND AT NECROPSY		14	15	13	1
Total:		14	15	13	1
-- Male Mice --					
LUNG					
MASS		0	0	1	0
Total:		0	0	1	0
ANIMAL NOTE					
NO LESIONS FOUND AT NECROPSY		15	15	14	15
Total:		15	15	14	15

Table 8. Group Mean Organ Weights (g)

Group	Female Rats										Male Mice									
	Brain	Heart	Kidney	Liver	Lung	Ovary	Spleen	Adrenal Gland	Thyroid Gland	Pituitary Gland	Brain	Heart	Kidney	Liver	Lung	Testis	Spleen	Adrenal Gland		
1	Mean	1.046	1.935	8.439	1.497	0.125	0.537	0.064	0.023	0.020										
	SD	0.109	0.184	1.146	0.148	0.021	0.082	0.011	0.006	0.003										
	N	15	15	15	15	15	15	15	15	15										
2	Mean	1.880	1.014	8.159	1.453	0.122	0.494	0.065	0.023	0.023										
	SD	0.073	0.067	0.741	0.190	0.024	0.043	0.010	0.006	0.005										
	N	15	15	15	15	15	15	15	15	15										
3	Mean	1.849	1.033	8.803	1.417	0.118	0.503	0.066	0.024	0.023										
	SD	0.091	0.136	1.238	0.166	0.023	0.076	0.009	0.006	0.005										
	N	15	15	15	15	15	15	15	15	15										
4	Mean	1.850	1.040	11.166*	1.449	0.125	0.503	0.065	0.023	0.021										
	SD	0.085	0.136	1.272	0.157	0.028	0.097	0.010	0.004	0.007										
	N	14	14	14	14	14	14	14	14	14										
5	Mean	0.437	0.158	0.403	1.483	0.201	0.073	0.008												
	SD	0.019	0.014	0.028	0.107	0.028	0.012	0.003												
	N	15	15	15	15	15	15	15												
6	Mean	0.430	0.158	0.402	1.471	0.191	0.077	0.009												
	SD	0.020	0.016	0.039	0.141	0.023	0.012	0.004												
	N	15	15	15	15	15	15	15												
7	Mean	0.423	0.156	0.391	1.493	0.218	0.074	0.009												
	SD	0.019	0.012	0.026	0.152	0.106	0.023	0.005												
	N	15	15	15	15	15	15	15												
8	Mean	0.433	0.149	0.393	1.543	0.203	0.072	0.007												
	SD	0.018	0.014	0.030	0.141	0.039	0.009	0.003												
	N	14	14	14	14	14	14	14												

* Group mean values are significantly different from Groups 1 or 5 (vehicle) at p≤0.05.

Table 9. Group Mean Organ-to-Body Weight Ratios

Group	Female Rats										Male Mice								
	Brain	Heart	Kidney	Liver	Lung	Ovary	Spleen	Adrenal Gland	Thyroid Gland	Pituitary Gland	Brain	Heart	Kidney	Liver	Lung	Testis	Spleen	Adrenal Gland	
1	Mean	0.690	0.375	0.693	3.016	0.537	0.045	0.023	0.008	0.007									
	SD	0.062	0.043	0.052	0.291	0.058	0.008	0.005	0.003	0.001									
	N	15	15	15	15	15	15	15	15	15	15								
2	Mean	0.677	0.364	0.684	2.929	0.523	0.044	0.023	0.008	0.008									
	SD	0.050	0.024	0.063	0.223	0.075	0.009	0.004	0.002	0.002									
	N	15	15	15	15	15	15	15	15	15	15								
3	Mean	0.649	0.361	0.695	3.075	0.496	0.041	0.023	0.008	0.008									
	SD	0.054	0.036	0.063	0.354	0.057	0.009	0.003	0.002	0.002									
	N	15	15	15	15	15	15	15	15	15	15								
4	Mean	0.677	0.378	0.753*	4.059*	0.529	0.046	0.024	0.008	0.008									
	SD	0.062	0.034	0.051	0.296	0.065	0.011	0.004	0.002	0.002									
	N	14	14	14	14	14	14	14	14	14	14								
5	Mean	1.535	0.553	1.414	5.201	0.707	0.646	0.030											
	SD	0.092	0.039	0.075	0.313	0.106	0.089	0.011											
	N	15	15	15	15	15	15	15	15	15	15								
6	Mean	1.503	0.551	1.402	5.135	0.668	0.623	0.032											
	SD	0.081	0.039	0.105	0.419	0.083	0.106	0.013											
	N	15	15	15	15	15	15	15	15	15	15								
7	Mean	1.488	0.549	1.374	5.243	0.769	0.639	0.031											
	SD	0.083	0.045	0.075	0.451	0.389	0.080	0.015											
	N	15	15	15	15	15	15	15	15	15	15								
8	Mean	1.530	0.527	1.387	5.448	0.717	0.640	0.025											
	SD	0.055	0.045	0.089	0.405	0.128	0.099	0.010											
	N	14	14	14	14	14	14	14	14	14	14								

* Group mean values are significantly different from Groups 1 or 5 (vehicle) at p≤0.05.

Table 10. Group Mean Organ-to-Brain Weight Ratios

Female Rats										
Group	Heart	Kidney	Liver	Lung	Ovary	Spleen	Adrenal Gland	Thyroid Gland	Pituitary Gland	
1	Mean	54.56	101.05	440.00	78.18	6.55	28.01	3.37	1.22	1.04
	STD	5.64	10.21	56.64	8.36	1.25	4.14	0.56	0.33	0.16
	N	15	15	15	15	15	15	15	15	15
2	Mean	54.03	101.14	434.92	77.63	6.47	26.31	3.46	1.21	1.22
	STD	4.53	7.26	45.35	12.58	1.20	2.27	0.50	0.32	0.30
	N	15	15	15	15	15	15	15	15	15
3	Mean	55.91	107.69	476.50	76.73	6.36	27.20	3.59	1.28	1.23
	STD	6.98	12.46	63.86	8.99	1.13	3.84	0.45	0.34	0.29
	N	15	15	15	15	15	15	15	15	15
4	Mean	56.25	111.88*	603.92*	78.52	6.79	27.16	3.49	1.24	1.16
	STD	7.22	10.46	64.02	9.46	1.54	4.89	0.52	0.19	0.35
	N	14	14	14	14	14	14	14	14	14
Male Mice										
Group	Heart	Kidney	Liver	Lung	Testis	Spleen	Adrenal Gland			
5	Mean	36.12	92.39	339.81	46.20	42.19	16.71	1.95		
	STD	2.91	6.89	28.04	7.75	6.10	2.83	0.80		
	N	15	15	15	15	15	15	15		
6	Mean	36.74	93.47	342.90	44.44	41.53	17.83	2.11		
	STD	2.84	7.89	36.82	5.25	7.04	2.30	0.90		
	N	15	15	15	15	15	15	15		
7	Mean	37.01	92.64	354.17	52.16	42.97	17.69	2.07		
	STD	3.58	7.90	44.64	28.20	5.46	6.32	1.12		
	N	15	15	15	15	15	15	15		
8	Mean	34.42	90.71	356.27	46.94	41.88	16.74	1.64		
	STD	2.49	5.21	25.54	8.92	6.41	2.07	0.66		
	N	14	14	14	14	14	14	14		

* Group mean values are significantly different from Groups 1 or 5 (vehicle) at p≤0.05.

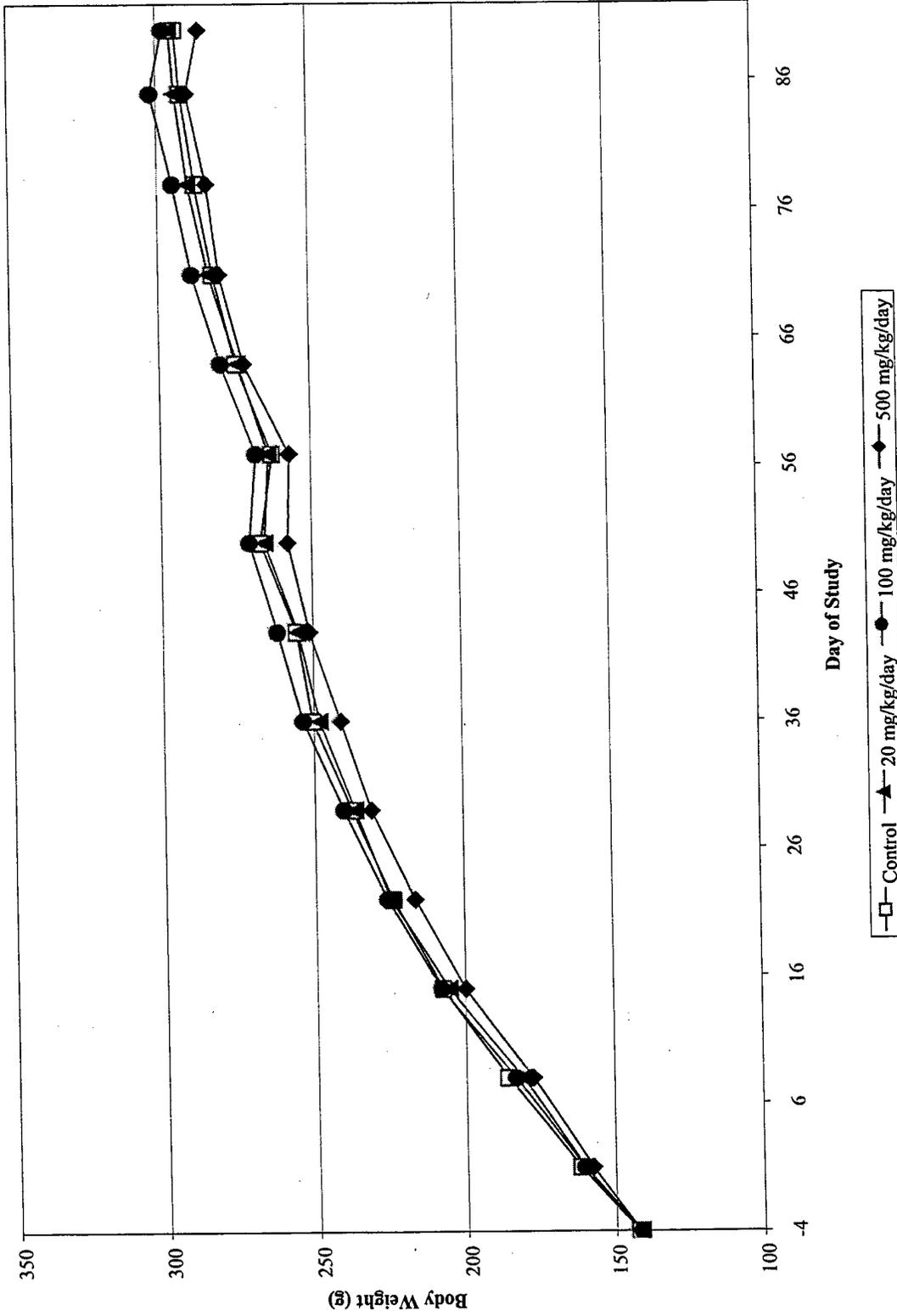


Figure 1. Group Mean Body Weights Female Rats

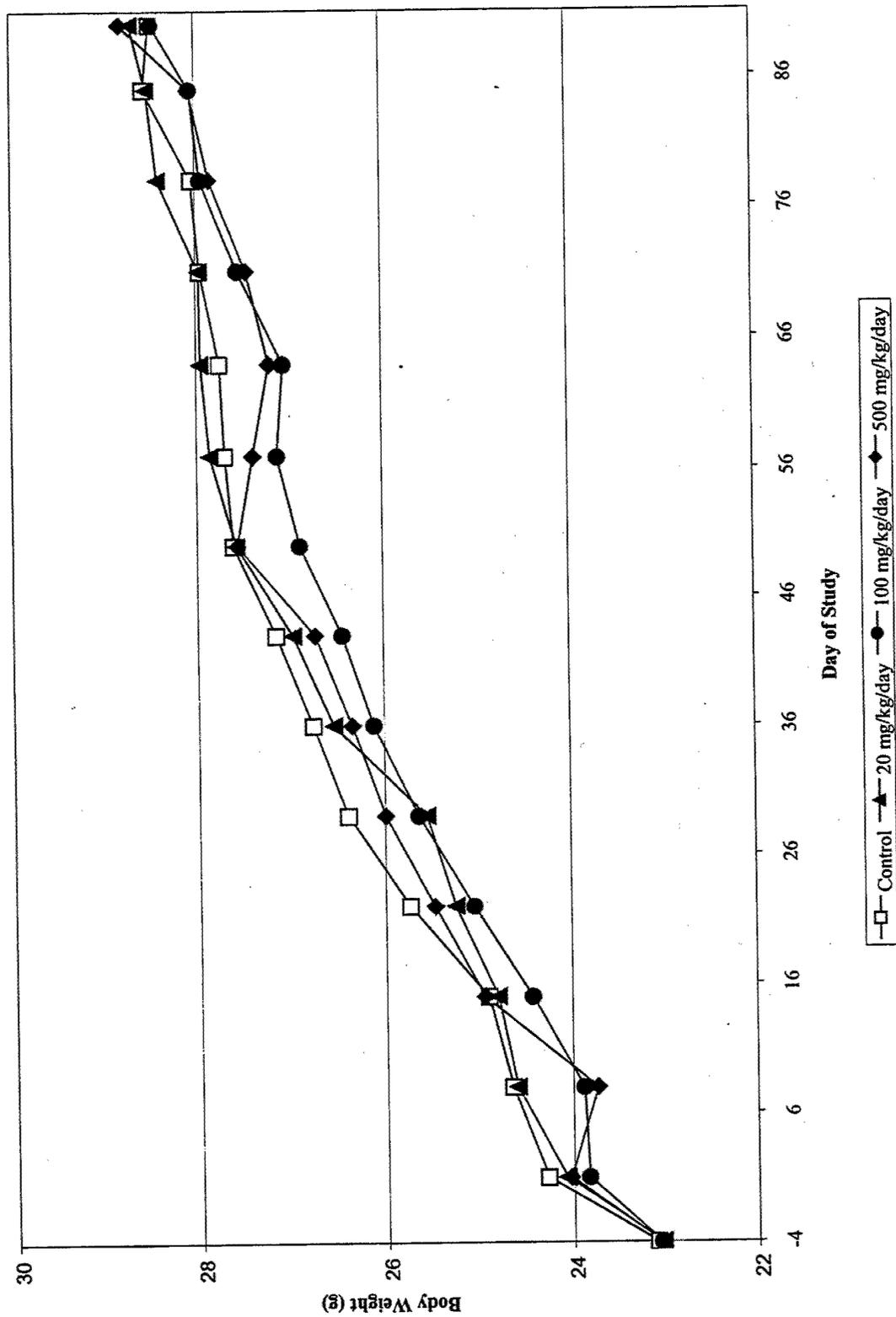


Figure 2. Group Mean Body Weights Male Mice

APPENDIX A

Protocol.....	A-2
Amendments.....	A-16
Deviations.....	A-20

BATTELLE STUDY PROTOCOL

90-DAY ORAL GAVAGE TOXICITY STUDY OF C₉-C₁₆ AROMATIC FRACTION OF JET-A IN FEMALE SPRAGUE- DAWLEY CD RATS AND MALE C57BL/6 MICE

Prepared For:

Menzie-Cura & Associates, Inc.



Battelle

... Putting Technology To Work

**90-DAY ORAL GAVAGE TOXICITY STUDY OF C₉-C₁₆
AROMATIC FRACTION OF JET-A IN FEMALE SPRAGUE-
DAWLEY CD RATS AND MALE C57BL/6 MICE**

APPROVED, BATTELLE:

Peter B. Smith, M.S.
Study Director

Date

Richard W. Slauter, Ph.D.
Senior Program Director

Date

APPROVED, SPONSOR:

Date

**90-DAY ORAL GAVAGE TOXICITY STUDY OF C₉-C₁₆ AROMATIC
FRACTION OF JET-A IN FEMALE SPRAGUE-DAWLEY CD RATS
AND MALE C57BL/6 MICE**

1.0 TITLE

90-Day Oral Gavage Toxicity Study of C₉-C₁₆ Aromatic Fraction of Jet-A in Female Sprague-Dawley CD Rats and Male C57BL/6 Mice

2.0 PURPOSE OF STUDY

The purpose of this study is to evaluate the potential toxicity of C₉-C₁₆ Aromatic Fraction of JET-A following oral gavage administrations in mice and rats once per day for 90 consecutive days. Assessment of potential toxicity will be based on clinical observations, body weight and food consumption changes, clinical pathology, gross necropsy findings, organ weight differences, and histopathology performed by the Primary Client.

3.0 PROPOSED STARTING AND COMPLETION DATES

Start of Treatment: TBD
In-Life Completion: TBD
Draft Final Report: TBD

4.0 ROUTE AND DURATION OF ADMINISTRATION

The test substance will be given once daily, 7 days/week, by oral gavage for 90 consecutive days.

5.0 SPONSOR AND SPONSOR'S REPRESENTATIVE

Menzie-Cura & Associates, Inc.
One Courthouse Lane, Suite 2
Chelmsford, MA 01824

Sponsor Project Monitor: Donna J. Vorhees
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Primary Client:
U.S. Air Force
Operational Toxicology Branch
Air Force Research Laboratory
Attn: Maj. Lana Harvey
AFRL/HEST Bldg. 79
Wright Patterson AFB, OH 45433
Telephone: (937) 255-5150; ext. 3194

6.0 TESTING LABORATORY

6.1 Facility

Battelle
505 King Avenue
Columbus, OH 43201-2693

6.2 Study Team

Program Director - Richard W. Slauter, Ph.D.
Study Director - Peter B. Smith, M.S.
Study Coordinator - Karen E. Veley, B.S.
Clinical Pathologist - Michael Ryan, D.V.M., Ph.D., A.C.V.P., D.A.B.T.

7.0 TEST SYSTEMS

- 7.1 Species: Rat
- 7.2 Breed: Sprague-Dawley CD, nulliparous and nonpregnant
- 7.3 Supplier: Charles River Laboratories
- 7.4 Age of animals at arrival: 4-6 weeks
- 7.5 Age of animals at start of study: 6-8 weeks
- 7.6 Expected weight range at randomization, Females: 90-150 g
- 7.7 Test system justification: This is an accepted species which is frequently used in toxicity studies for safety evaluation of drugs intended for human use.
- 7.8 Number of animals required for study: 60 females

- 7.9 Species: Mouse
- 7.10 Breed: C57BL/6
- 7.11 Supplier: Charles River Laboratories
- 7.12 Age of animals at arrival: 6-8 weeks
- 7.13 Age of animals at start of study: 8-10 weeks
- 7.14 Expected weight range at randomization, Males: 16-29 g
- 7.15 Test system justification: This is an accepted species which is frequently used in toxicity studies for safety evaluation of drugs intended for human use.
- 7.16 Number of animals required for study: 60 males

8.0 ANIMAL CARE, HOUSING, AND ENVIRONMENTAL CONDITIONS

8.1 Quarantine and Acclimatization

- Animals will be quarantined for a minimum of 7 days after receipt at Battelle during which time they will be acclimated to the environmental conditions that will be used for the study. Each animal will be observed twice daily during the quarantine period for clinical signs of abnormality that would make them unfit for study. All animals will be examined by a staff veterinarian and those of questionable health excluded from the study.

8.2 Animal Housing Conditions

- During the acclimation and study periods, the animals will be individually housed in standard polycarbonate cages. General procedures for animal care and housing will meet current AAALAC standards, current requirements stated in the NIH "Guide for Care and Use of Laboratory Animals" (National Academy of Sciences, 1996), and the U.S. Department of Agriculture through the Animal Welfare Act (Public Law 99-198).
- Temperature and relative humidity (RH) of the animal room will be maintained at 64-79°F and 30-70 percent, respectively. These measurements will be recorded twice daily and monitored for conformance. There will be at least 10 changes/hour of air in the rooms.
- Twelve hours of light and twelve hours of dark will be provided in the animal room. A fluorescent light source will be used, with lights turned on at approximately 0600 hours each day.

8.3 Feed

- Certified Rodent Diet® 5002 (PMI Feeds, Inc.) in pellet form will be used during the quarantine, acclimation period and throughout the study.
- Feed will be provided *ad libitum* to the animals, except during specified fasting periods.
- There are no known contaminants in the food that would affect the outcome of this study.

8.4 Water

- Fresh water from the Columbus Municipal Water Supply will be provided *ad libitum* to the animals via an automatic watering system.
- The water supply is periodically monitored by bacterial and chemical analyses. Results of these analyses are kept on file at Battelle.
- There are no known contaminants in the water that would affect the outcome of this study.

9.0 TEST SUBSTANCE

A log of receipt and use of the test substance will be maintained. The test substance identification, lot numbers, expiration dates and storage conditions will be provided by the Sponsor.

9.1 Test Substance Identification

The test substance for this study is select C₉-C₁₆ Aromatic Fraction of Jet-A.

Lot number: 97-POSF-3404-AR916

The Sponsor will arrange for the Primary Client (i.e., the USAF) to provide sufficient quantities of test substance to conduct this study. The identity, strength, purity, composition, stability, and methods of synthesis of the bulk test substance are the responsibility of the Sponsor. Test substance (formulated) analysis for concentration verification is the responsibility of Battelle. Samples collected for concentration analyses will be stored frozen until they are analyzed. An archive sample from each batch of the test substance used on study will be collected and maintained by the Primary Client.

9.2 Test Substance Storage

When not in use, the test substance will be stored at a temperature between -5 and 4°C, protected from light and moisture, or as specified by the Sponsor.

9.3 Carrier

The carrier for this study is corn oil. The carrier will be supplied by Battelle. The carrier will be considered to have an expiration date of 30 days after a bulk container is first opened.

9.4 Carrier Storage

When not in use, the carrier will be stored at ambient temperature, or as specified by the Sponsor.

9.5 Test Substance Preparation

Test substance will be formulated as specified by the Primary Client (the USAF). Solutions will be prepared by direct dilution in corn oil, to appropriate concentrations, assuming 100 percent purity. Dosing solutions will be prepared weekly and stored in a controlled area at a temperature between -5 and 4°C and protected from light. All unused test substance will be returned to the Primary Client.

9.6 Carrier Preparation

No formulation of the carrier is necessary.

9.7 Dose Analysis

Dose analysis of the formulated test substance will be conducted by Battelle using a validated analytical method provided by the Primary Client (the USAF). Before initiation of the study, the analytical method will be validated by Battelle personnel, and the appropriate changes will be made to the method (with Sponsor approval) to allow implementation of the method using Battelle analytical equipment and facilities.

Prior to dosing, formulated test substance will be prepared and analyzed for stability over 21 days. Verification of concentration of the low, mid, and high dose formulated batches from Week 1, Week 8, and Week 12 will be conducted. Formulated test substance will be prepared weekly.

9.8 Carrier/Test substance Administration

One of the potential routes of human exposure is oral, therefore this study uses oral administration of the test substance.

The carrier and test substance formulations will be administered via an appropriately sized gavage needle (separate ones used for each dose group). Dosing will be performed at approximately the same time on each scheduled dosing day.

Test substance solutions will be used throughout the study in the concentration intended to provide the required dosage in mg/kg/day when administered at a constant dose volume of 2.5 mL/kg/day for rats and 10 mL/kg/day for mice. The carrier will be administered at 2.5 mL/kg/day for rats and 10 mL/kg/day for mice.

Individual dose volumes will be calculated according to each animal's most recent body weight.

10.0 EXPERIMENTAL DESIGN

10.1 Group Assignment

Rodents will be assigned to dose groups by body weight no sooner than 5 days prior to initiation of dosing using a computer program (Xybion Path/Tox system) which ensures similar group mean body weights and body weight distributions. Rodents will be excluded from the allocation procedure outside $\pm 20\%$ of the mean body weight.

10.2 Identification

Rodents will be individually identified by a temporary number on each cage card during the quarantine period and identified by ear tag or tail tattoo and cage card after randomization. The permanent animal identification numbers and their groups will be as follows:

ANIMAL NUMBER IDENTIFICATION

Group Number	Species	Sex	Core Animals Day 91 Sacrifice
1 (Control)	Rat	F	101-115
2	Rat	F	201-215
3	Rat	F	301-315
4	Rat	F	401-415
5 (Control)	Mouse	M	501-515
6	Mouse	M	601-615
7	Mouse	M	701-715
8	Mouse	M	801-815

11.0 STUDY PROCEDURES

The study will be comprised of 4 groups of 15 rats/group and 4 groups of 15 mice/group. Each animal will receive a gavage dose of carrier or formulated test substance, once per day for 90 days. The following parameters will be evaluated: body weights, clinical observations, food consumption, morbidity/mortality checks, clinical pathology, gross pathology (organ weights and necropsy), and histopathology (performed by the Primary Client, the USAF).

Group Number	Number of Animals	Treatment	Dose Level (mg/kg/day)	Route of Administration	mg/mL
	Female Rats				
1 (control)	15	Carrier	0	Oral Gavage	0
2	15	C9-C16 Aromatic Fraction of Jet-A	20	Oral Gavage	8
3	15	C9-C16 Aromatic Fraction of Jet-A	100	Oral Gavage	40
4	15	C9-C16 Aromatic Fraction of Jet-A	500	Oral Gavage	100

Group Number	Number of Animals	Treatment	Dose Level (mg/kg/day)	Route of Administration	mg/mL
	Male Mice				
5	15	Carrier	0	Oral Gavage	0
6	15	C9-C16 Aromatic Fraction of Jet-A	20	Oral Gavage	2
7	15	C9-C16 Aromatic Fraction of Jet-A	100	Oral Gavage	10
8	15	C9-C16 Aromatic Fraction of Jet-A	500	Oral Gavage	50

Rats will receive the test substance at a dose volume of 2.5 mL/kg/dose (1X/day) and mice will receive the test substance at a dose volume of 10 mL/kg/dose (1X/day). Dose calculations will be based on the individual body weight obtained on Day 1 for each animal, and adjusted weekly for each animal based upon the most recent body weight.

11.1 Body Weight

Individual body weights of all animals received at Battelle will be recorded at the time of group assignment (within 5 days prior to the initiation of dosing). Body weights of study animals will be recorded on Day 1 (prior to administration), weekly thereafter, and the day prior to necropsy. All animals will be weighed on the day of scheduled necropsy. Doses will be calculated based upon the most recent body weights taken.

11.2 Food Consumption

Individual food consumption will be recorded weekly for all animals.

11.3 Clinical Observations

Observations for moribundity and mortality will be made twice daily (in the morning and afternoon, approximately 6 hours apart, 7 days per week) during the prestudy and study

periods. Detailed cage-side clinical observations for evidence of toxic and/or pharmacologic effects will be performed approximately 1-2 hours postdose during the treatment period and once at least 6 hours after dosing (twice daily). All signs of clinical abnormalities will be recorded.

11.4 Clinical Pathology

Following an overnight fast from food, blood samples will be drawn from each animal for hematology, coagulation, and serum chemistry determinations on the day of scheduled necropsy (Day 91). Blood for hematology and serum chemistry will be obtained from each rodent scheduled for euthanasia via the retro-orbital plexus or by cardiac puncture/abdominal aorta (terminal procedure only), if necessary. Blood for determination of coagulation parameters will be collected by cardiac puncture or via the abdominal aorta (terminal procedure only). Blood samples will be collected in tubes both with and without anticoagulant (EDTA), for hematology and serum chemistry analyses, respectively. Tubes containing blood for serum chemistry will be centrifuged and serum separated. Blood collected for coagulation parameters will be collected into tubes containing sodium citrate. Prior to blood collection, the animals will be anesthetized using a mixture of carbon dioxide/oxygen to aid in restraint and help alleviate any momentary pain during the procedure.

Hematology
Erythrocyte count (RBC) - $10^6/\mu\text{L}$
Hemoglobin (HGB) - g/dL
Methemoglobin (MHG) - g/dL
Hematocrit (HCT) - %
Mean Corpuscular Volume (MCV) - fL
Mean Corpuscular Hemoglobin (MCH) - pg
Mean Corpuscular Hemoglobin Concentration (MCHC) - g/dL
Platelet Count (PLT) - $10^3/\mu\text{L}$
Reticulocyte Count (RET) - %
Total Leukocyte Count (WBC) - $10^3/\mu\text{L}$
Differential Leukocyte Count - $10^3/\mu\text{L}$
Prothrombin Time (PT) - sec
Activated Partial Thromboplastin Time (APTT) - sec

Serum Chemistry
Blood Urea Nitrogen (BUN) - mg/dL
Creatinine (CREA) - mg/dL
Serum Aspartate Aminotransferase (AST) - IU/L
Serum Alanine Aminotransferase (ALT) - IU/L
Alkaline Phosphatase (ALP) - IU/L
Lactate Dehydrogenase (LDH) - IU/L
Creatine Kinase (CPK) - IU/L
gamma Glutamyltransferase (gGT) - IU/L
Sorbitol Dehydrogenase (SDH) - IU/L
Serum Glucose (GLU) - mg/dL
Cholesterol (CHOL) - mg/dL
Triglycerides (TRIG) - mg/dL
Sodium (Na) - mEq/L
Calcium (Ca) - mg/dL
Phosphorus (PHOS) - mg/dL
Potassium (K) - mEq/L
Chloride (Cl) - mEq/L
Total Protein (TP) - g/dL
Albumin (ALB) - g/dL
Globulin (GLOB) - g/dL
Albumin/Globulin ratio (AGR)

11.5 Necropsy

All surviving rodents will be necropsied on Day 91. All rodents will be weighed prior to necropsy and have blood collected for clinical pathology determinations. Rodents will be killed humanely by CO₂ asphyxiation.

Each necropsy will include examination of the external surface of the body; all orifices; the cranial, thoracic, abdominal and pelvic cavities and their contents; and collection of tissues listed in this protocol.

Complete necropsies will be performed as soon as possible on all rodents that die during the study (found dead, moribund, or any other condition). If a necropsy cannot be performed immediately after a rodent is found dead, the animal will be refrigerated to minimize tissue autolysis. Animals will be necropsied within approximately 24 hours after discovery of death. A pathologist will be readily available for consultation.

The following tissues along with gross lesions will be preserved in 10 percent neutral buffered formalin solution, except eyes and testes which will be preserved in Bouin's fixative. Lungs will be perfused with 10 percent formalin and the trachea will be ligated after infusion to ensure trapping of fixative in airways and alveoli. Intestines will be cut in cross section.

Tissues to be Collected for Necropsy Evaluation will be as Follows	
Animal Identification	Pancreas
Adrenal Glands	Pituitary Gland
Aorta	Prostate
Brain	Rectum
Cecum	Salivary Glands
Colon	Sciatic Nerve
Duodenum	Seminal Vesicles
Epididymides	Skeletal Muscle (biceps femoris)
Esophagus	Skin (ventral)
Femur/marrow	Spinal Cord (cross section and longitudinal section)
Harderian Glands	Spleen
Ileum	Sternum
Eyes with Optic Nerve	Stomach
Jejunum	Testes
Heart	Thymus
Kidneys	Thyroid Gland (with parathyroids)
Liver (with gallbladder for mouse)	Tongue
Lungs with Bronchi	Trachea
Lymph Nodes (mandibular, mesenteric)	Urinary Bladder
Mammary Glands	Uterus
Nasopharyngeal (3 sections)	Vagina
Ovaries (with oviducts)	Gross Lesions

11.6 Organ Weights

The adrenal glands, heart, lungs, liver, spleen, kidneys, brain, testes, and ovaries will be weighed fresh from all animals euthanized at the termination of the administration period (Day 91). Paired organs will be weighed together. The thyroid and pituitary glands will be weighed following fixation for rats only. Data will be collected manually or on the Xybion Path/Tox System. Organ weight:body weight and organ weight:brain weight values will be calculated.

11.7 Histopathology

All tissues illustrated in the table above will be collected by Battelle and sent in preservative to the USAF where they will be processed for histopathological evaluations from rodents in the high dose and control groups euthanized on Day 91. Tissues from Groups 1, 4, 5, and 8 will be trimmed, embedded in paraffin, sectioned at 4-6 μ m, stained with hematoxylin and eosin and reviewed microscopically by a board-certified veterinary pathologist at Wright-Patterson AFB. Tissues from Groups 2, 3, 6 and 7 will be retained by the Primary Client for possible processing for histopathological evaluations.

12.0 COMPUTER SYSTEM FOR DATA MANAGEMENT

The Xybion® Path/Tox system will be used for randomization (group assignment), and for the capture, storage and summarization of all appropriate animal derived in-life and postmortem animal pathology data.

13.0 STATISTICAL METHODS

All appropriate quantitative in-life, clinical pathology, and postmortem data collected at Battelle will be analyzed statistically. All data will be analyzed for test substance effects by analysis of variance. For data whose variances are considered homogeneous across test groups, as determined by Bartlett's test for homogeneity at the 0.05 level, tests for differences between the control and comparison groups will be made using Dunnett's test. For non-homogeneous data, as determined by Bartlett's test for homogeneity at the 0.05 level, tests for pair-wise differences between the control and each of the comparison groups will be made using Cochran and Cox's modified two-sample t-test. Statistical significance for each comparison will be reported at the 0.05 level.

14.0 REPORTING

A draft report of this study will be submitted to the Sponsor. The Sponsor shall submit comments, if any, on the draft report to the Study Director. Battelle will submit a final report to the Sponsor after receipt of the Sponsor's comments.

15.0 MONITORING VISITS

The Sponsor or Primary Client may visit Battelle at any time to check the progress of the study.

16.0 STUDY CONDUCT, STORAGE OF STUDY MATERIALS, AND RECORDS RETENTION

This protocol will be the controlling document in case of discrepancies between the Protocol and Standard Operating Procedures.

This study will be conducted in compliance with the U.S. Environmental Protection Agency (EPA) TSCA Good Laboratory Practices regulations, 40 CFR Part 792, August 17, 1989. This study will be listed on Battelle's list of regulated studies. All records required to reconstruct the study will be maintained at Battelle. Records to be maintained will include, but are not limited to:

16.1 Personnel Records

- Names, training and qualification records
- Name, address, and function of any outside consultants.

16.2 Protocol

- Approved and dated study protocol
- Protocol amendments
- Documentation of deviations from the protocol or governing SOPs
- Documentation of any unforeseen circumstances that may affect the interpretation of the study results and corrective actions taken.

16.3 Test Substance Records

- Test substance identity records, including manufacturer, quantity, lot number(s) as provided by the Sponsor
- Battelle test substance receipt records (including storage conditions)
- Battelle test substance inventory and usage records
- Dose preparation data (including carrier data, dose material inventory, and storage conditions).

16.4 Animal Records - Pretest

- Animal receipt records, including supplier, species, strain, age, sex, number of animals, receipt date, and conditions at receipt
- Quarantine and acclimatization records
- Pretest health screening records
- Randomization records
- Animal identification records
- Written quarantine release by laboratory animal veterinarian.

16.5 Animal Records - In-Life

- Animal room location
- Detailed dosing records
- Analytical chemistry data
- Body weight data
- Food consumption data
- Clinical observations
- Clinical pathology data

16.6 Feed and Water

- Feed log and analysis report of each lot
- Copy of most recent water analysis report.

16.7 Pathology Results

- Individual animal necropsy records
- Organ weight data
- Microscopic observations (as provided by Primary Client)

16.8 All Relevant Correspondence

16.9 Reports

- Final report

PROTOCOL AMENDMENT

STUDY NUMBER: G003493-B

STUDY TITLE: 90-Day Oral Gavage Toxicity Study of C₉-C₁₆ Aromatic Fraction of Jet-A in Female Sprague-Dawley CD Rats and Male C57BL/6 Mice

PROTOCOL AMENDMENT

NUMBER: 1

EFFECTIVE DATE: 8/3/98

PART TO BE CHANGED/REVISED:

Protocol Section 8.2 Animal Housing Conditions

CHANGE/REVISION:

The mice will be housed one or two per cage during the first few days of acclimation in order to familiarize the animals to the watering system. They will then be separated into individual housing prior to health evaluations and body weight measurement for randomization.

REASON FOR CHANGE:

The mice are pair housed initially to facilitate their adaptation to the automatic watering system.

PART TO BE CHANGED/REVISED:

Protocol section 9.5 Test Substance Preparation

CHANGE/REVISION:

Prepared dosing solutions will be stored in a controlled area at a temperature between -5 and 7°C and protected from light

REASON FOR CHANGE:

The acceptable storage range is expanded slightly due to the actual temperatures that can be maintained in the storage facility. This new range is still considered acceptable to maintain stability.

PART TO BE CHANGED/REVISED:

Protocol section 9.7 Dose analysis

CHANGE/REVISION:

Prior to dosing, formulated test substance will be prepared and analyzed for stability over 20 days.

REASON FOR CHANGE:

Battelle Study Number G003493-B

Page 1 of 3

During the previous range-finding study, the stability of this substance was evaluated in anticipation of this 90 day study. At that time, the stability was evaluated at day 20. This is sufficient to demonstrate the stability for the weekly preparation used on this study.

PART TO BE CHANGED/REVISED:

Protocol Section 11.0 Study Procedures

CHANGE/REVISION:

The concentration for group 4 in the table is 200 mg/mL.

REASON FOR CHANGE:

The concentration was calculated incorrectly.

PART TO BE CHANGED/REVISED:

Protocol Section 11.4 Clinical Pathology

CHANGE/REVISION:

The mice will not be fasted overnight prior to blood collection for hematology and clinical chemistry.

REASON FOR CHANGE:

The mouse has an elevated metabolism and does not tolerate an overnight fast as well as a rat. Thus the requirement for fasting has been removed for animal welfare concerns.

PART TO BE CHANGED/REVISED:

Protocol Section 11.4. Clinical Pathology

CHANGE/REVISION:

Prothrombin Time, Activated Partial Thromboplastin Time and Methemaglobin will not be evaluated for mice.

REASON FOR CHANGE:

The limited volume of blood which can be collected from the mouse restricts the number of analyses which can be performed from these hematology samples.

PART TO BE CHANGED/REVISED:

Protocol Section 11.5 Necropsy

CHANGE/REVISION:

The nasal/head will be placed in neutral buffered formalin at necropsy to allow better fixation of the pituitary (for rats); the nasals will be transferred to Formical-4 after

removal and weighing the fixed pituitary. The nasal/head from mice will be placed directly into Formical-4.

REASON FOR CHANGE:

The Sponsor has requested that the nasal/head region be preserved in Formical-4 in order to decalcify the tissues.

PART TO BE CHANGED/REVISED:

Protocol Section 11.7 Histopathology

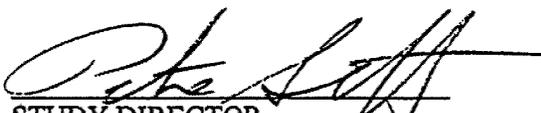
CHANGE/REVISION:

All tissues illustrated in the table above will be collected by Battelle and sent in preservative to the Primary Client where they will be processed for histopathological evaluations from rodents in the high dose and control groups euthanized on Day 91. Tissues from Groups 1, 4, 5, and 8 will be trimmed, embedded in paraffin, sectioned at 4-6 μ m, stained with hematoxylin and eosin and reviewed microscopically by a board-certified veterinary pathologist employed by the Primary Client. Tissues from groups 2, 3, 6 and 7 will be retained by the Primary Client for possible processing for histopathological evaluations depending upon the presence of apparent test article related lesions found in the high dose groups.

REASON FOR CHANGE:

The section has been rewritten to clarify the identity of the Primary Client and to define when tissues of the low and intermediate dose animals may be processed and evaluated.

APPROVED BY:


STUDY DIRECTOR


SPONSOR'S REPRESENTATIVE

8/5/98
DATE

8/6/98
DATE

PROTOCOL AMENDMENT

STUDY NUMBER: G003493-B

STUDY TITLE: 90-Day Oral Gavage Toxicity Study of C₉-C₁₆ Aromatic Fraction of Jet-A in Female Sprague-Dawley CD Rats and Male C57BL/6 Mice

PROTOCOL AMENDMENT
NUMBER: 2

EFFECTIVE DATE: 8/31/98

PART TO BE CHANGED/REVISED:
Protocol Section 11.5 Necropsy

CHANGE/REVISION:

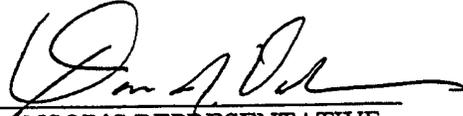
For rats, the pituitary shelf will be cut off at necropsy and placed in formalin prior to weighing. The remaining nasal bones will be placed directly into Formical-4. Mouse nasal bones including the pituitary are to be placed into formalin. Mouse tissue will not be placed into Formical-4. The rat nasal bones will be left in Formical-4 and shipped in Formical 4.

REASON FOR CHANGE:

The Sponsor has clarified the procedures for preservation of the nasal/head region.

APPROVED BY:


STUDY DIRECTOR


SPONSOR'S REPRESENTATIVE

8/31/98
DATE

9/1/98
DATE

Report of Deviation From Technical Protocol

Study Title: 90-Day Oral Gavage Toxicity Study of C₉-C₁₆ Aromatic Fraction of Jet-A in Female Sprague-Dawley CD Rats and Male C57bL/6 Mice

Incident: On August 4, 1998 the PM clinical observation for at least one animal in the high dose group was taken one minute prior to 6 hours post-dose per protocol section 11.3 of the protocol.

Cause: Oversight.

Corrective Action: This deviation report is being prepared to document the incident.

Impact on Study: Minimal.

APPROVED BY:



Peter B. Smith, M.S.
Battelle Study Director

12/3/98

Date

Report of Deviation From Technical Protocol

Study Title: 90-Day Oral Gavage Toxicity Study of C₉-C₁₆ Aromatic Fraction of Jet-A in Female Sprague-Dawley CD Rats and Male C57bL/6 Mice

Incident: On August 15, August 31, September 2, and September 15, 1998 the PM mortality and moribundity check occurred approximately 10, 12, 9, and 9 hours, respectively, after the AM check. Protocol section 11.3 states that they will occur approximately 6 hours apart.

Cause: Oversight.

Corrective Action: This deviation report is being prepared to document the incident.

Impact on Study: Minimal.

APPROVED BY:



Peter B. Smith, M.S.
Battelle Study Director

1/8/99

Date

Report of Deviation From Technical Protocol

Study Title: 90-Day Oral Gavage Toxicity Study of C₉-C₁₆ Aromatic Fraction of Jet-A in Female Sprague-Dawley CD Rats and Male C57BL/6 Mice

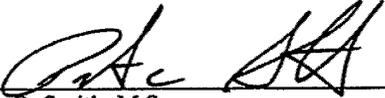
Incident: On September 30, 1998 and October 21, 1998 empty feeder weights were not recorded for animals 811 and 715, respectively.

Cause: Feeders were inadvertently dumped prior to weighing.

Corrective Action: This deviation report is being prepared to document the incident.

Impact on Study: Minimal, as food consumption was recorded for all other weeks.

APPROVED BY:



Peter B. Smith, M.S.
Battelle Study Director

11/8/99
Date

APPENDIX B

Table B-1a.	Individual Abnormal Clinical Observations - Female Rats	B-2
Table B-1b.	Individual Abnormal Clinical Observations - Male Mice.....	B-4
Table B-2.	Individual Animal Body Weights (g).....	B-8
Table B-3.	Individual Animal Food Consumption (g).....	B-12

Table B-1a. Individual Abnormal Clinical Observations - Female Rats

Sex	Group Number	Category	Subcategory	Animal Number	First Day Observed	Last Day Observed	Interval	Total Number of Observations
Female	1	ALOPECIA	FOOT	108	49	91	43	85
Female	1	ALOPECIA	FOOT	109	32	91	60	119
Female	1	ALOPECIA	FOOT	112	32	91	60	119
Female	1	ALOPECIA	LEG	108	70	91	22	43
Female	1	ALOPECIA	LEG	109	37	91	55	109
Female	1	ALOPECIA	LEG	112	73	91	19	37
Female	1	ALOPECIA	LEG	109	66	68	3	6
Female	1	EYES/EARS	EYE DISCHARGE-RED	113	35	35	1	1
Female	1	EYES/EARS	EYE DISCHARGE-RED	101	32	32	1	1
Female	1	RESPIRATORY SYSTEM	NASAL DISCHARGE-RED	212	44	62	19	16
Female	2	ABRASION/LESION	FOOT	212	44	62	19	16
Female	2	ABRASION/LESION	LEG	212	44	62	19	16
Female	2	ALOPECIA	FOOT	206	22	22	1	2
Female	2	ALOPECIA	FOOT	212	32	91	60	119
Female	2	ALOPECIA	FOOT	214	1	50	50	70
Female	2	ALOPECIA	LEG	212	44	91	48	95
Female	2	ALOPECIA	LEG	214	39	50	12	24
Female	2	ALOPECIA	LEG	212	41	43	3	6
Female	2	DISCOLORATION	FOOT	207	38	38	1	1
Female	2	RESPIRATORY SYSTEM	NASAL DISCHARGE-RED	305	40	91	52	103
Female	3	ALOPECIA	BODY VENTRAL	301	6	55	50	99
Female	3	ALOPECIA	FOOT	303	49	50	2	4
Female	3	ALOPECIA	FOOT	305	1	91	91	181
Female	3	ALOPECIA	FOOT	311	7	43	37	73
Female	3	ALOPECIA	FOOT	305	1	91	91	181
Female	3	ALOPECIA	LEG	302	25	25	1	1
Female	3	DIGESTIVE SYSTEM	SALIVATION	303	33	33	1	1
Female	3	DIGESTIVE SYSTEM	SALIVATION	308	9	9	1	1
Female	3	DIGESTIVE SYSTEM	SALIVATION	309	29	58	30	5
Female	3	DIGESTIVE SYSTEM	SALIVATION	314	80	80	1	1
Female	3	DIGESTIVE SYSTEM	SALIVATION	315	22	35	14	2
Female	3	DIGESTIVE SYSTEM	SALIVATION	312	76	86	11	3
Female	3	EYES/EARS	EYE DISCHARGE-RED	405	77	78	2	4
Female	4	ABRASION/LESION	FOOT	401	11	91	81	142
Female	4	ALOPECIA	FOOT	403	51	55	5	10
Female	4	ALOPECIA	FOOT	404	12	91	80	89
Female	4	ALOPECIA	FOOT	405	49	91	43	85
Female	4	ALOPECIA	FOOT	406	80	91	12	22
Female	4	ALOPECIA	FOOT	414	22	91	70	138
Female	4	ALOPECIA	FOOT	415	56	70	15	30
Female	4	ALOPECIA	LEG	405	77	91	15	29

Table B-1a. Individual Abnormal Clinical Observations - Female Rats

Sex	Group Number	Category	Subcategory	Animal Number	First Day Observed	Last Day Observed	Interval	Total Number of Observations
Female	4	ALOPECIA	LEG	406	80	91	12	22
Female	4	DIGESTIVE SYSTEM	SALIVATION	401	4	75	72	28
Female	4	DIGESTIVE SYSTEM	SALIVATION	402	33	34	2	4
Female	4	DIGESTIVE SYSTEM	SALIVATION	403	4	34	31	3
Female	4	DIGESTIVE SYSTEM	SALIVATION	404	11	90	80	89
Female	4	DIGESTIVE SYSTEM	SALIVATION	405	4	75	72	20
Female	4	DIGESTIVE SYSTEM	SALIVATION	406	7	74	68	11
Female	4	DIGESTIVE SYSTEM	SALIVATION	407	3	36	34	10
Female	4	DIGESTIVE SYSTEM	SALIVATION	408	3	90	88	48
Female	4	DIGESTIVE SYSTEM	SALIVATION	409	3	90	88	65
Female	4	DIGESTIVE SYSTEM	SALIVATION	410	5	75	71	9
Female	4	DIGESTIVE SYSTEM	SALIVATION	411	9	87	79	22
Female	4	DIGESTIVE SYSTEM	SALIVATION	412	18	85	68	10
Female	4	DIGESTIVE SYSTEM	SALIVATION	413	26	85	60	11
Female	4	DIGESTIVE SYSTEM	SALIVATION	414	3	90	88	22
Female	4	DIGESTIVE SYSTEM	SALIVATION	415	3	26	24	9
Female	4	DISCOLORATION	FOOT	406	31	34	4	8
Female	4	EYES/EARS	EYE DISCHARGE-CLEAR	401	31	31	1	1
Female	4	EYES/EARS	EYE DISCHARGE-RED	401	29	31	3	4
Female	4	GENERAL APPEARANCE	LETHARGIC	405	10	10	1	1
Female	4	GENERAL APPEARANCE	LETHARGIC	407	3	3	1	1
Female	4	GENERAL APPEARANCE	LETHARGIC	408	3	3	1	1
Female	4	GENERAL APPEARANCE	LETHARGIC	409	3	10	8	2
Female	4	GENERAL APPEARANCE	LETHARGIC	413	3	7	5	2
Female	4	GENERAL APPEARANCE	LETHARGIC	414	12	12	1	1
Female	4	GENERAL APPEARANCE	LETHARGIC	415	3	3	1	1
Female	4	NEURO/MUSCULOSKELETAL	ATAXIC (INCOORDINATION)	407	41	41	1	1
Female	4	RESPIRATORY SYSTEM	LABORED RESPIRATION	407	41	41	1	1
Female	4	RESPIRATORY SYSTEM	NASAL DISCHARGE-RED	401	4	4	1	1
Female	4	RESPIRATORY SYSTEM	NASAL DISCHARGE-RED	404	25	25	1	1
Female	4	RESPIRATORY SYSTEM	NASAL DISCHARGE-RED	407	32	32	1	1
Female	4	RESPIRATORY SYSTEM	NASAL DISCHARGE-RED	410	66	66	1	1
Female	4	RESPIRATORY SYSTEM	NASAL DISCHARGE-RED	415	32	32	1	2
Female	4	RESPIRATORY SYSTEM	NASAL DISCHARGE-RED	406	32	34	3	6
Female	4	SWELLING	FOOT	406	32	34	3	6

Table B-1b. Individual Abnormal Clinical Observations - Male Mice

Sex	Group Number	Category	Subcategory	Animal Number	First Day Observed	Last Day Observed	Interval	Total Number of Observations
Male	5	ALOPECIA	NECK	515	85	91	7	13
Male	5	GENERAL APPEARANCE	HUNCHED POSTURE	501	54	54	1	2
Male	5	GENERAL APPEARANCE	HUNCHED POSTURE	504	67	67	1	1
Male	5	GENERAL APPEARANCE	HUNCHED POSTURE	509	40	69	30	7
Male	5	GENERAL APPEARANCE	HUNCHED POSTURE	513	41	41	1	1
Male	5	GENERAL APPEARANCE	ROUGH COAT	501	3	9	7	8
Male	5	GENERAL APPEARANCE	ROUGH COAT	502	4	65	62	19
Male	5	GENERAL APPEARANCE	ROUGH COAT	503	3	81	79	14
Male	5	GENERAL APPEARANCE	ROUGH COAT	504	2	90	89	60
Male	5	GENERAL APPEARANCE	ROUGH COAT	505	3	88	86	75
Male	5	GENERAL APPEARANCE	ROUGH COAT	506	2	82	81	36
Male	5	GENERAL APPEARANCE	ROUGH COAT	507	2	86	85	68
Male	5	GENERAL APPEARANCE	ROUGH COAT	508	6	89	84	48
Male	5	GENERAL APPEARANCE	ROUGH COAT	509	2	91	90	154
Male	5	GENERAL APPEARANCE	ROUGH COAT	510	5	89	85	62
Male	5	GENERAL APPEARANCE	ROUGH COAT	511	2	85	84	68
Male	5	GENERAL APPEARANCE	ROUGH COAT	512	2	89	88	86
Male	5	GENERAL APPEARANCE	ROUGH COAT	513	2	80	79	59
Male	5	GENERAL APPEARANCE	ROUGH COAT	514	2	90	89	59
Male	5	GENERAL APPEARANCE	ROUGH COAT	515	2	87	86	60
Male	5	GENERAL APPEARANCE	THIN APPEARANCE	508	15	15	1	1
Male	5	GENERAL APPEARANCE	THIN APPEARANCE	509	62	62	1	1
Male	6	ALOPECIA	NECK	608	73	91	19	37
Male	6	GENERAL APPEARANCE	HUNCHED POSTURE	602	39	81	43	9
Male	6	GENERAL APPEARANCE	HUNCHED POSTURE	603	32	67	36	4
Male	6	GENERAL APPEARANCE	HUNCHED POSTURE	605	12	68	57	9
Male	6	GENERAL APPEARANCE	HUNCHED POSTURE	606	18	18	1	1
Male	6	GENERAL APPEARANCE	HUNCHED POSTURE	607	32	47	16	4
Male	6	GENERAL APPEARANCE	HUNCHED POSTURE	608	18	81	64	4
Male	6	GENERAL APPEARANCE	HUNCHED POSTURE	609	39	40	2	3
Male	6	GENERAL APPEARANCE	HUNCHED POSTURE	611	12	72	61	30
Male	6	GENERAL APPEARANCE	HUNCHED POSTURE	612	40	67	28	4
Male	6	GENERAL APPEARANCE	HUNCHED POSTURE	613	12	41	30	10
Male	6	GENERAL APPEARANCE	HUNCHED POSTURE	614	13	46	34	12
Male	6	GENERAL APPEARANCE	HUNCHED POSTURE	615	13	67	55	7
Male	6	GENERAL APPEARANCE	LETHARGIC	603	12	12	1	1
Male	6	GENERAL APPEARANCE	LETHARGIC	608	12	12	1	1
Male	6	GENERAL APPEARANCE	LETHARGIC	612	68	68	1	1
Male	6	GENERAL APPEARANCE	LETHARGIC	613	12	12	1	1
Male	6	GENERAL APPEARANCE	LETHARGIC	614	12	12	1	1

Table B-1b. Individual Abnormal Clinical Observations - Male Mice

Sex	Group Number	Category	Subcategory	Animal Number	First Day Observed	Last Day Observed	Interval	Total Number of Observations
Male	6	GENERAL APPEARANCE	ROUGH COAT	601	2	90	89	135
Male	6	GENERAL APPEARANCE	ROUGH COAT	602	2	90	89	33
Male	6	GENERAL APPEARANCE	ROUGH COAT	603	2	82	81	65
Male	6	GENERAL APPEARANCE	ROUGH COAT	604	5	78	74	76
Male	6	GENERAL APPEARANCE	ROUGH COAT	605	2	75	74	44
Male	6	GENERAL APPEARANCE	ROUGH COAT	606	2	86	85	56
Male	6	GENERAL APPEARANCE	ROUGH COAT	607	2	90	89	78
Male	6	GENERAL APPEARANCE	ROUGH COAT	608	2	89	88	31
Male	6	GENERAL APPEARANCE	ROUGH COAT	609	2	84	83	60
Male	6	GENERAL APPEARANCE	ROUGH COAT	610	2	88	87	73
Male	6	GENERAL APPEARANCE	ROUGH COAT	611	2	90	89	146
Male	6	GENERAL APPEARANCE	ROUGH COAT	612	5	86	82	111
Male	6	GENERAL APPEARANCE	ROUGH COAT	613	2	86	85	112
Male	6	GENERAL APPEARANCE	ROUGH COAT	614	2	85	84	84
Male	6	GENERAL APPEARANCE	ROUGH COAT	615	2	90	89	90
Male	6	GENERAL APPEARANCE	THIN APPEARANCE	611	13	13	1	1
Male	6	GENERAL APPEARANCE	THIN APPEARANCE	613	30	30	1	1
Male	6	GENERAL APPEARANCE	THIN APPEARANCE	614	14	14	1	2
Male	6	GENERAL APPEARANCE	THIN APPEARANCE	615	13	14	2	3
Male	7	DIGESTIVE SYSTEM	FEW FECES	711	20	20	1	2
Male	7	GENERAL APPEARANCE	HUNCHED POSTURE	701	15	82	68	13
Male	7	GENERAL APPEARANCE	HUNCHED POSTURE	702	26	39	14	4
Male	7	GENERAL APPEARANCE	HUNCHED POSTURE	703	32	68	37	6
Male	7	GENERAL APPEARANCE	HUNCHED POSTURE	704	26	67	42	3
Male	7	GENERAL APPEARANCE	HUNCHED POSTURE	705	32	39	8	2
Male	7	GENERAL APPEARANCE	HUNCHED POSTURE	706	18	40	23	5
Male	7	GENERAL APPEARANCE	HUNCHED POSTURE	707	18	83	66	13
Male	7	GENERAL APPEARANCE	HUNCHED POSTURE	708	12	82	71	7
Male	7	GENERAL APPEARANCE	HUNCHED POSTURE	709	26	57	32	10
Male	7	GENERAL APPEARANCE	HUNCHED POSTURE	710	8	68	61	14
Male	7	GENERAL APPEARANCE	HUNCHED POSTURE	711	18	90	73	30
Male	7	GENERAL APPEARANCE	HUNCHED POSTURE	712	33	67	35	3
Male	7	GENERAL APPEARANCE	HUNCHED POSTURE	713	18	41	24	4
Male	7	GENERAL APPEARANCE	HUNCHED POSTURE	714	26	82	57	6
Male	7	GENERAL APPEARANCE	HUNCHED POSTURE	715	32	90	59	11
Male	7	GENERAL APPEARANCE	LETHARGIC	701	18	44	27	3
Male	7	GENERAL APPEARANCE	LETHARGIC	703	12	32	21	5
Male	7	GENERAL APPEARANCE	LETHARGIC	704	32	32	1	1
Male	7	GENERAL APPEARANCE	LETHARGIC	705	12	25	14	2
Male	7	GENERAL APPEARANCE	LETHARGIC	706	18	39	22	2
Male	7	GENERAL APPEARANCE	LETHARGIC	708	12	39	28	4
Male	7	GENERAL APPEARANCE	LETHARGIC	709	26	32	7	3

Table B-1b. Individual Abnormal Clinical Observations - Male Mice

Sex	Group Number	Category	Subcategory	Animal Number	First Day Observed	Last Day Observed	Interval	Total Number of Observations
Male	7	GENERAL APPEARANCE	LETHARGIC	710	18	32	15	4
Male	7	GENERAL APPEARANCE	LETHARGIC	711	40	77	38	8
Male	7	GENERAL APPEARANCE	LETHARGIC	713	12	64	53	6
Male	7	GENERAL APPEARANCE	LETHARGIC	714	18	69	52	5
Male	7	GENERAL APPEARANCE	LETHARGIC	715	32	32	1	1
Male	7	GENERAL APPEARANCE	ROUGH COAT	701	5	88	84	76
Male	7	GENERAL APPEARANCE	ROUGH COAT	702	5	91	87	115
Male	7	GENERAL APPEARANCE	ROUGH COAT	703	2	90	89	71
Male	7	GENERAL APPEARANCE	ROUGH COAT	704	5	89	85	41
Male	7	GENERAL APPEARANCE	ROUGH COAT	705	2	77	76	36
Male	7	GENERAL APPEARANCE	ROUGH COAT	706	2	88	87	115
Male	7	GENERAL APPEARANCE	ROUGH COAT	707	2	90	89	55
Male	7	GENERAL APPEARANCE	ROUGH COAT	708	4	82	79	59
Male	7	GENERAL APPEARANCE	ROUGH COAT	709	2	86	85	73
Male	7	GENERAL APPEARANCE	ROUGH COAT	710	2	88	87	156
Male	7	GENERAL APPEARANCE	ROUGH COAT	711	2	81	80	68
Male	7	GENERAL APPEARANCE	ROUGH COAT	712	2	90	89	134
Male	7	GENERAL APPEARANCE	ROUGH COAT	713	2	90	89	57
Male	7	GENERAL APPEARANCE	ROUGH COAT	714	2	90	89	112
Male	7	GENERAL APPEARANCE	ROUGH COAT	715	2	91	90	118
Male	7	GENERAL APPEARANCE	THIN APPEARANCE	706	84	84	1	1
Male	7	GENERAL APPEARANCE	THIN APPEARANCE	711	19	62	44	6
Male	7	GENERAL APPEARANCE	THIN APPEARANCE	714	49	49	1	1
Male	8	DIGESTIVE SYSTEM	FEW FECES	802	5	5	1	2
Male	8	DIGESTIVE SYSTEM	FEW FECES	811	20	20	1	2
Male	8	DIGESTIVE SYSTEM	FEW FECES	812	20	21	2	3
Male	8	GENERAL APPEARANCE	HUNCHED POSTURE	801	10	64	55	28
Male	8	GENERAL APPEARANCE	HUNCHED POSTURE	802	4	83	80	24
Male	8	GENERAL APPEARANCE	HUNCHED POSTURE	803	7	8	2	4
Male	8	GENERAL APPEARANCE	HUNCHED POSTURE	804	7	82	76	24
Male	8	GENERAL APPEARANCE	HUNCHED POSTURE	805	4	74	71	25
Male	8	GENERAL APPEARANCE	HUNCHED POSTURE	806	11	47	37	14
Male	8	GENERAL APPEARANCE	HUNCHED POSTURE	807	2	91	90	34
Male	8	GENERAL APPEARANCE	HUNCHED POSTURE	808	4	85	82	32
Male	8	GENERAL APPEARANCE	HUNCHED POSTURE	809	8	75	68	14
Male	8	GENERAL APPEARANCE	HUNCHED POSTURE	810	11	89	79	19
Male	8	GENERAL APPEARANCE	HUNCHED POSTURE	811	3	89	87	24
Male	8	GENERAL APPEARANCE	HUNCHED POSTURE	812	8	90	83	23
Male	8	GENERAL APPEARANCE	HUNCHED POSTURE	813	10	90	81	25
Male	8	GENERAL APPEARANCE	HUNCHED POSTURE	814	25	67	43	9
Male	8	GENERAL APPEARANCE	HUNCHED POSTURE	815	11	81	71	6
Male	8	GENERAL APPEARANCE	HYPOTHERMIC	803	8	8	1	2

Table B-1b. Individual Abnormal Clinical Observations - Male Mice

Sex	Group Number	Category	Subcategory	Animal Number	First Day Observed	Last Day Observed	Interval	Total Number of Observations
Male	8	GENERAL APPEARANCE	LETHARGIC	801	10	76	67	24
Male	8	GENERAL APPEARANCE	LETHARGIC	802	4	52	49	21
Male	8	GENERAL APPEARANCE	LETHARGIC	803	4	8	5	5
Male	8	GENERAL APPEARANCE	LETHARGIC	804	7	67	61	30
Male	8	GENERAL APPEARANCE	LETHARGIC	805	3	55	53	18
Male	8	GENERAL APPEARANCE	LETHARGIC	806	5	33	29	12
Male	8	GENERAL APPEARANCE	LETHARGIC	807	1	69	69	43
Male	8	GENERAL APPEARANCE	LETHARGIC	808	4	79	76	44
Male	8	GENERAL APPEARANCE	LETHARGIC	809	8	77	70	22
Male	8	GENERAL APPEARANCE	LETHARGIC	810	4	79	76	58
Male	8	GENERAL APPEARANCE	LETHARGIC	811	3	69	67	39
Male	8	GENERAL APPEARANCE	LETHARGIC	812	4	79	76	52
Male	8	GENERAL APPEARANCE	LETHARGIC	813	11	67	57	26
Male	8	GENERAL APPEARANCE	LETHARGIC	814	25	64	40	7
Male	8	GENERAL APPEARANCE	LETHARGIC	815	4	52	49	16
Male	8	GENERAL APPEARANCE	ROUGH COAT	801	2	90	89	152
Male	8	GENERAL APPEARANCE	ROUGH COAT	802	2	89	88	69
Male	8	GENERAL APPEARANCE	ROUGH COAT	803	2	8	7	12
Male	8	GENERAL APPEARANCE	ROUGH COAT	804	2	90	89	123
Male	8	GENERAL APPEARANCE	ROUGH COAT	805	2	89	88	75
Male	8	GENERAL APPEARANCE	ROUGH COAT	806	2	90	89	92
Male	8	GENERAL APPEARANCE	ROUGH COAT	807	1	90	90	168
Male	8	GENERAL APPEARANCE	ROUGH COAT	808	2	89	88	132
Male	8	GENERAL APPEARANCE	ROUGH COAT	809	2	90	89	136
Male	8	GENERAL APPEARANCE	ROUGH COAT	810	2	91	90	168
Male	8	GENERAL APPEARANCE	ROUGH COAT	811	2	89	88	156
Male	8	GENERAL APPEARANCE	ROUGH COAT	812	2	89	88	149
Male	8	GENERAL APPEARANCE	ROUGH COAT	813	2	91	90	124
Male	8	GENERAL APPEARANCE	ROUGH COAT	814	2	85	84	134
Male	8	GENERAL APPEARANCE	ROUGH COAT	815	2	89	88	103
Male	8	GENERAL APPEARANCE	THIN APPEARANCE	802	8	8	1	1
Male	8	GENERAL APPEARANCE	THIN APPEARANCE	803	8	8	1	1
Male	8	GENERAL APPEARANCE	THIN APPEARANCE	804	10	10	1	1
Male	8	GENERAL APPEARANCE	THIN APPEARANCE	805	55	55	1	2
Male	8	GENERAL APPEARANCE	THIN APPEARANCE	807	5	54	50	6
Male	8	GENERAL APPEARANCE	THIN APPEARANCE	808	35	35	1	1
Male	8	GENERAL APPEARANCE	THIN APPEARANCE	811	20	20	1	2
Male	8	GENERAL APPEARANCE	THIN APPEARANCE	812	20	20	1	2
Male	8	GENERAL APPEARANCE	LABORED RESPIRATION	803	8	8	1	2
Male	8	RESPIRATORY SYSTEM	LABORED RESPIRATION	807	1	1	1	1
Male	8	RESPIRATORY SYSTEM	UROGENITAL REGION-WET	807	53	53	1	2
Male	8	URINARY SYSTEM	UROGENITAL REGION-WET	814	63	64	2	2

Table B-2. Individual Animal Body Weights (g)

Animal	Study Day														
	-4	1	8	15	22	29	36	43	50	57	64	71	78	85	90
Female Rats															
101	143.2	169.0	180.2	204.0	215.6	232.0	248.6	253.1	263.5	253.8	270.5	276.0	275.3	287.9	283.5
102	136.6	151.9	169.6	182.5	183.4	202.8	205.6	215.6	230.4	232.5	233.7	239.5	239.4	242.3	246.4
103	151.3	169.5	202.6	222.2	237.6	250.7	264.5	269.1	277.9	276.7	284.9	295.2	308.7	315.7	316.3
104	137.1	153.2	178.9	199.9	218.5	218.2	237.7	243.5	255.1	246.0	252.2	265.8	262.8	260.1	265.8
105	130.1	149.0	171.9	194.5	210.9	224.1	232.3	236.2	253.5	248.4	262.4	276.8	284.5	284.2	287.3
106	141.3	156.9	179.4	205.6	226.8	239.3	253.4	250.0	260.2	258.7	277.0	277.8	284.7	292.2	289.4
107	145.8	173.5	199.1	233.9	250.8	260.2	282.9	287.0	300.4	294.3	309.0	313.6	321.1	324.4	325.8
108	150.7	168.9	196.1	218.7	233.0	252.4	282.8	281.0	296.2	298.9	303.3	321.3	328.7	332.2	339.1
109	149.0	172.1	188.1	198.3	218.4	233.0	242.5	244.3	256.7	257.6	263.0	274.9	275.4	277.9	278.5
110	158.5	174.9	197.2	232.8	256.2	273.9	277.1	293.2	293.0	291.3	308.2	315.2	324.4	330.6	335.9
111	133.8	156.3	180.2	200.1	214.8	229.5	234.6	247.5	258.6	251.5	263.3	265.8	268.1	271.1	274.5
112	140.0	157.3	187.4	209.4	234.3	233.2	255.4	248.8	266.1	262.5	278.7	284.3	294.3	295.1	300.4
113	144.8	163.7	187.3	203.9	220.7	232.6	245.6	246.6	256.5	248.8	261.3	268.9	276.1	283.0	280.6
114	138.9	158.5	184.5	212.8	224.9	249.2	259.4	269.5	282.2	274.1	286.9	294.6	295.7	308.8	309.4
115	129.5	150.7	183.3	195.0	214.7	230.3	232.8	246.1	256.4	248.8	264.5	259.9	274.9	276.1	276.0
(N)	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
201	149.5	166.9	189.6	216.0	231.6	249.0	246.8	260.9	274.9	278.1	280.0	287.7	289.2	298.9	299.2
202	154.2	171.4	201.5	220.4	245.4	251.7	267.1	275.2	269.2	274.1	281.8	296.4	301.0	311.2	315.1
203	130.5	152.8	173.3	206.9	220.2	228.2	249.4	254.6	272.1	278.4	282.4	280.5	291.0	293.2	292.8
204	137.5	161.1	181.4	205.6	218.9	225.2	240.5	245.9	249.9	259.6	261.9	277.8	286.7	277.9	281.2
205	138.0	156.0	180.6	197.1	224.8	240.7	249.3	252.1	268.2	255.8	277.9	284.2	294.7	303.2	334.0
206	134.7	148.3	172.8	190.1	203.5	214.4	222.6	234.3	230.4	231.0	238.4	257.7	263.7	266.4	261.5
207	143.6	166.1	182.9	210.6	229.3	243.6	259.2	257.6	272.6	278.4	287.6	289.0	286.2	296.0	295.9
208	152.1	179.2	186.1	223.5	260.1	271.4	269.8	285.5	298.9	289.4	295.1	308.5	316.3	320.7	320.3
209	148.1	165.3	191.6	221.8	239.0	247.9	264.7	274.8	280.6	276.1	294.9	311.6	313.8	325.1	319.1
210	132.7	152.4	173.1	195.7	212.3	224.1	227.9	236.0	254.1	247.6	251.4	266.0	266.3	268.9	266.2
211	141.4	163.0	184.8	200.6	220.6	247.6	258.4	263.6	283.0	281.6	308.9	305.9	313.5	313.6	318.7
212	145.7	162.1	177.7	204.5	228.1	238.4	245.5	255.3	265.3	260.6	275.5	275.6	284.6	295.2	295.9
213	140.1	160.5	178.2	197.0	224.1	224.1	244.3	255.7	263.6	254.5	262.8	269.1	281.7	274.2	275.2
214	143.8	157.0	174.7	201.3	214.3	220.7	236.2	227.5	253.3	248.0	254.4	269.6	280.3	283.8	277.6
215	129.6	143.7	165.9	189.8	208.7	219.7	238.3	245.6	249.9	248.6	255.9	270.1	280.8	280.8	281.8
(N)	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15

Table B-2. Individual Animal Body Weights (g)

Animal	Study Day														
	-4	1	8	15	22	29	36	43	50	57	64	71	78	85	90
	Female Rats														
301	142.0	161.0	180.1	197.6	213.6	221.7	233.9	248.8	248.7	259.1	262.3	270.2	271.8	277.2	276.2
302	145.8	168.1	186.3	217.8	234.7	255.6	270.9	266.2	273.2	273.6	278.0	283.0	286.8	288.2	283.4
303	144.3	165.3	189.9	213.7	228.9	238.2	252.9	259.8	266.1	263.6	265.2	281.1	288.4	288.6	291.9
304	132.7	146.9	161.5	186.8	209.0	217.2	224.4	235.8	253.1	243.0	257.9	264.8	265.9	272.8	269.6
305	132.2	151.8	172.4	190.8	209.7	220.3	229.6	235.3	237.1	239.4	251.2	249.5	255.7	260.6	256.1
306	139.9	157.5	186.7	214.0	229.5	261.7	265.8	281.6	292.3	288.3	296.7	311.2	327.1	320.2	313.1
307	153.4	176.7	201.9	223.1	243.9	258.6	268.0	279.8	295.7	300.3	312.5	328.6	341.6	349.2	352.3
308	137.6	155.0	189.3	218.3	231.7	233.5	260.1	262.3	274.4	277.3	276.4	288.9	291.7	295.0	293.3
309	129.4	146.9	175.6	194.6	220.6	233.5	243.3	255.1	260.7	255.8	272.1	278.3	289.2	292.6	292.8
310	147.2	166.2	188.6	212.6	225.4	229.6	243.7	250.0	247.8	252.4	271.1	266.8	278.5	282.9	269.3
311	138.5	151.0	173.0	193.4	205.3	219.0	229.0	239.7	246.5	237.4	249.2	266.4	267.5	275.0	274.2
312	134.0	154.8	175.3	204.4	226.8	245.4	255.1	270.3	278.7	265.1	286.0	297.0	298.4	316.2	305.3
313	150.3	168.5	181.3	205.0	227.5	253.9	261.9	271.7	284.3	275.7	306.8	307.6	316.1	330.1	314.7
314	152.5	175.1	199.9	231.7	242.7	265.0	297.6	289.3	303.6	297.7	305.8	319.5	320.4	344.8	345.2
315	141.4	164.1	187.2	216.9	239.5	249.6	266.8	281.5	299.0	295.1	304.6	319.4	325.5	335.9	330.1
(N)	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
401	140.9	161.4	172.3	195.2	212.0	225.6	232.7	239.9	244.7	244.7	252.9	261.2	263.0	264.9	261.7
402	136.9	148.3	174.1	198.1	213.3	228.5	238.2	246.5	253.3	251.7	262.7	273.6	275.6	275.3	279.2
403	147.0	158.1	182.6	208.4	219.5	233.9	221.7	251.9	255.6	251.0	268.5	267.9	278.0	286.3	277.0
404	133.2	151.8	171.5	207.6	226.6	240.1	244.6	262.3	270.9	264.9	281.9	284.7	284.0	286.8	287.0
405	145.7	165.2	187.8	204.8	222.6	244.3	259.4	268.2	274.1	282.9	303.7	315.1	313.1	328.3	322.8
406	153.1	172.9	193.7	214.1	240.8	256.1	266.2	271.7	286.6	281.1	300.7	310.9	312.8	320.7	310.7
407	143.3	162.0	182.2	199.0	222.0	236.1	244.6	dead							
408	150.1	160.9	186.1	214.1	225.0	240.5	255.4	262.6	274.4	267.9	285.2	293.3	298.4	308.0	305.7
409	144.9	158.6	177.9	197.5	211.6	226.6	236.1	250.0	258.3	254.3	266.6	275.0	277.9	287.1	280.1
410	136.2	152.5	168.0	193.4	212.7	227.6	240.2	252.3	253.9	262.4	267.0	282.8	280.5	284.4	275.1
411	130.1	144.4	170.6	187.6	199.6	219.1	230.3	242.7	238.2	238.2	253.7	261.7	273.1	283.1	282.2
412	130.4	140.5	152.7	164.9	181.5	189.0	199.8	207.2	210.5	209.0	220.4	226.5	235.1	237.7	236.7
413	141.9	154.4	179.1	198.1	217.7	226.3	243.3	240.2	249.1	248.2	267.2	273.8	272.2	279.1	276.1
414	139.2	157.8	170.0	189.3	202.1	218.1	222.9	233.4	243.6	239.8	248.2	253.5	256.9	260.4	258.0
415	154.4	175.4	196.6	225.0	243.5	253.8	279.1	287.0	297.9	303.5	328.4	337.3	352.6	358.9	350.0
(N)	15	15	15	15	15	15	15	14	14	14	14	14	14	14	14

Table B-2. Individual Animal Body Weights (g)

Animal	Study Day														
	-5	1	8	15	22	29	36	43	50	57	64	71	78	85	90
	Male Mice														
501	22.1	23.0	23.0	23.5	24.6	25.1	25.1	26.0	26.6	26.3	26.0	26.3	26.3	27.2	26.3
502	23.3	24.1	24.7	25.4	25.7	26.3	26.2	26.6	26.0	26.0	26.9	26.9	26.5	27.5	27.8
503	22.8	23.5	24.1	24.5	25.2	25.6	25.9	26.4	26.9	27.8	27.5	28.5	28.4	28.5	28.8
504	23.7	25.1	25.3	26.1	26.2	27.2	28.0	28.3	29.0	28.5	28.4	28.8	28.5	28.7	29.2
505	23.6	25.1	25.4	26.7	27.1	28.2	28.5	29.1	29.5	30.7	29.7	30.5	30.7	31.3	31.2
506	22.2	23.3	23.3	24.0	24.6	25.0	25.4	25.3	26.3	26.2	26.6	26.1	27.0	27.7	26.8
507	23.5	24.6	24.9	25.6	26.7	26.9	26.7	27.1	27.8	27.1	28.8	28.4	29.0	28.4	29.3
508	22.7	23.4	24.0	20.1	23.8	24.8	25.9	26.1	26.5	26.5	26.2	26.5	26.0	27.2	26.5
509	23.2	24.6	25.9	26.1	26.7	27.1	27.7	28.1	28.3	28.3	29.0	28.3	28.5	28.6	28.3
510	22.8	24.5	24.9	25.7	25.6	26.9	27.1	27.2	27.5	28.0	27.9	27.9	28.3	29.0	28.7
511	22.9	23.7	24.3	24.8	25.8	26.3	27.3	27.2	28.1	28.8	28.7	29.4	28.9	29.4	29.8
512	24.2	24.9	25.5	25.4	26.3	27.1	27.4	27.9	28.2	28.0	28.2	28.6	28.4	29.3	29.2
513	23.8	25.5	25.0	25.4	25.7	26.1	26.7	26.9	27.9	28.0	27.3	27.7	28.6	28.9	29.2
514	22.3	23.6	24.1	24.3	24.9	25.8	26.2	26.4	26.7	26.4	26.4	26.8	26.9	27.9	27.9
515	23.2	25.2	25.2	25.8	27.0	27.5	27.3	28.6	28.7	28.7	28.5	28.5	28.6	28.8	28.3
(N)	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
601	23.2	25.0	26.5	26.6	27.3	27.9	28.8	29.0	29.3	30.1	30.2	29.8	31.0	30.6	30.8
602	22.0	22.7	22.5	22.9	23.1	24.5	25.2	25.4	26.4	26.1	26.3	26.2	26.4	27.5	27.4
603	23.6	24.4	25.2	25.7	25.7	26.7	26.9	27.4	28.1	28.6	28.4	28.8	29.7	29.5	29.3
604	23.4	23.4	23.7	24.0	25.0	25.5	26.1	26.1	26.6	27.6	27.2	27.6	27.6	28.2	28.5
605	22.1	23.1	23.4	23.3	23.3	24.2	25.2	25.8	25.6	25.6	24.9	25.0	25.2	25.5	25.4
606	22.5	23.6	24.8	25.1	25.6	25.6	26.0	26.8	27.2	27.8	28.0	27.5	28.3	27.8	27.9
607	22.8	23.6	24.9	24.8	25.3	26.0	27.0	27.1	27.0	27.6	28.0	28.0	28.3	28.3	28.7
608	22.7	23.4	23.4	23.7	24.5	25.2	26.1	26.7	27.2	27.0	27.6	27.4	27.1	27.5	28.2
609	23.6	24.7	25.1	25.1	25.7	26.5	26.7	27.8	28.2	28.6	28.5	28.6	29.1	28.6	29.2
610	23.0	23.5	23.5	25.3	25.6	25.8	26.2	27.2	28.1	28.3	28.7	28.8	29.6	29.9	29.5
611	22.3	24.0	23.9	24.1	23.2	24.6	24.9	25.9	25.8	26.7	26.6	26.7	27.4	27.0	27.7
612	23.9	25.8	27.2	27.3	27.7	28.6	29.2	29.7	31.2	31.0	31.1	31.4	32.1	33.0	33.2
613	23.0	25.4	25.6	26.3	27.1	20.6	27.4	27.3	27.5	27.3	27.5	27.0	27.2	27.1	27.9
614	23.9	24.7	24.9	23.8	24.4	25.1	26.0	26.2	27.5	27.2	27.6	27.9	27.8	28.1	28.5
615	23.5	23.8	24.2	23.9	25.1	26.3	26.4	26.1	27.8	28.3	28.7	28.7	29.3	29.3	28.3
(N)	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15

Table B-2. Individual Animal Body Weights (g)

Animal	Study Day														
	-5	1	8	15	22	29	36	43	50	57	64	71	78	85	90
	Male Mice														
701	22.5	22.6	22.3	23.2	23.8	24.0	25.2	24.9	25.8	25.7	25.3	25.9	26.1	26.3	26.3
702	23.5	24.4	23.6	24.9	25.6	26.3	27.2	27.3	27.7	28.2	28.4	28.8	29.5	29.9	30.8
703	23.6	24.7	25.0	25.3	25.9	26.2	26.6	26.4	27.3	26.9	27.5	27.7	28.2	28.8	28.4
704	22.8	24.3	24.0	24.4	25.5	25.1	25.3	26.0	26.8	27.2	26.9	27.2	27.3	27.9	28.4
705	22.0	22.7	23.0	23.1	24.2	24.6	25.2	25.4	25.5	25.8	26.1	26.6	26.4	26.8	27.6
706	23.1	23.8	24.5	25.2	25.9	26.4	27.1	27.5	27.7	27.7	27.3	27.7	28.3	25.9	29.3
707	23.7	24.1	24.7	24.8	25.3	26.2	26.3	27.3	27.4	27.8	27.3	27.9	28.2	28.5	28.4
708	22.7	23.9	24.2	24.9	25.2	26.0	26.7	27.4	27.8	28.6	28.2	29.1	29.6	30.0	30.1
709	23.4	25.7	27.1	27.6	27.9	28.6	29.0	29.0	29.2	29.6	29.9	30.9	31.1	30.2	30.8
710	23.8	24.7	22.0	23.8	24.3	24.6	25.1	25.4	26.1	26.6	26.3	26.5	27.2	27.5	27.4
711	22.1	22.0	22.5	23.1	24.2	24.4	24.9	25.1	25.6	25.8	25.9	26.5	26.9	27.4	27.3
712	24.1	24.1	24.2	24.4	25.4	26.2	26.3	26.8	27.2	27.1	27.3	27.7	28.3	28.8	28.3
713	22.3	23.4	23.8	24.2	24.1	25.3	25.5	25.9	25.8	26.5	26.0	26.3	27.1	27.3	27.1
714	23.0	23.4	23.8	24.1	24.4	25.7	26.0	26.7	27.0	26.9	26.5	27.0	26.9	27.0	27.9
715	23.2	23.6	23.5	23.3	23.9	24.8	25.3	25.5	26.5	26.5	27.0	27.3	28.0	28.4	28.9
(N)	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
801	22.9	25.1	25.7	26.3	26.5	27.0	27.4	27.3	28.3	27.7	28.0	27.5	27.7	27.9	29.0
802	23.5	24.5	20.8	24.9	25.8	26.3	27.0	27.6	28.1	28.1	28.2	26.0	29.2	28.7	30.1
803	22.4	23.5	19.9	dead											
804	22.0	23.6	23.0	23.9	24.5	25.2	25.7	25.3	25.6	25.6	25.3	26.1	25.7	26.5	26.2
805	23.6	24.4	24.2	24.6	25.5	25.8	26.2	26.6	27.7	26.8	26.4	26.9	26.8	27.0	27.7
806	22.7	24.4	25.0	25.6	26.1	26.9	27.5	28.6	29.3	29.2	28.4	28.7	30.0	30.4	29.8
807	22.9	24.2	23.9	24.0	24.6	25.0	25.3	25.9	26.5	26.4	25.7	26.3	26.6	26.9	27.6
808	23.8	24.5	24.5	25.7	25.7	26.2	24.1	25.7	27.1	26.7	26.5	27.1	27.2	27.7	27.9
809	23.7	23.9	24.1	25.2	25.3	26.0	27.0	27.2	27.9	28.0	28.4	28.7	28.5	29.0	29.0
810	22.2	23.4	25.0	25.3	25.4	26.6	27.4	27.3	28.1	28.1	28.5	28.5	29.0	28.8	29.9
811	23.9	24.7	25.0	26.3	26.4	27.1	27.5	27.7	29.0	28.3	28.7	28.8	30.2	29.8	30.8
812	23.1	24.3	24.4	25.3	26.4	26.2	25.7	26.2	27.4	27.3	27.1	28.1	28.1	27.5	28.6
813	23.2	23.3	23.5	23.8	24.1	25.0	25.7	25.8	26.9	26.6	26.5	27.2	27.1	28.0	29.2
814	23.4	24.1	24.0	24.2	25.7	25.9	26.7	27.2	28.1	28.1	27.8	28.4	27.9	28.3	29.9
815	22.4	22.5	22.9	23.9	24.5	24.7	25.5	25.8	25.8	26.5	25.4	26.0	25.8	26.4	27.6
(N)	15	15	15	15	15	15	14	14	14	14	14	14	14	14	14

Table B-3. Individual Animal Food Consumption (g)

Animal	Study Day														
	8	15	22	29	36	43	50	57	64	71	78	85	90		
Female Rats															
101	14.30	14.80	14.47	14.64	15.73	15.90	12.5	11.2	13.3	14.3	13.7	16.0	14.96		
102	14.89	14.94	12.76	13.20	13.50	12.86	13.5	13.0	13.6	13.5	13.4	14.4	15.06		
103	16.84	16.44	15.50	15.47	15.63	14.51	13.5	12.2	13.0	14.7	16.5	15.2	16.02		
104	15.33	15.80	15.67	13.86	15.17	13.79	13.5	13.2	14.2	14.8	13.5	14.1	14.82		
105	13.61	15.30	14.99	14.50	14.04	14.16	15.5	12.2	14.2	16.6	16.4	16.3	15.10		
106	15.53	21.83	17.06	17.20	15.83	14.79	13.1	12.8	spilled	spilled	spilled	15.7	16.12		
107	17.27	18.71	17.67	16.47	18.36	17.36	16.5	15.1	16.7	17.0	16.1	17.1	17.02		
108	18.06	18.06	17.81	17.31	19.89	17.77	spilled	17.7	16.7	18.6	17.7	16.6	18.64		
109	14.17	14.94	15.04	14.03	14.19	14.51	13.7	11.9	14.1	13.9	13.0	13.6	14.84		
110	15.66	17.84	18.31	17.59	17.23	17.64	13.8	12.8	16.3	16.3	16.7	17.4	17.54		
111	15.80	16.50	15.91	14.56	15.17	15.31	13.7	12.3	13.6	13.4	14.2	13.5	14.78		
112	16.27	17.29	17.83	15.99	17.69	14.66	14.8	13.1	16.4	15.6	16.2	15.7	15.54		
113	14.57	14.47	14.57	14.06	13.96	14.47	13.8	10.6	13.8	14.5	14.3	14.5	15.60		
114	15.59	16.33	15.47	16.29	16.29	15.44	14.7	12.7	13.6	14.1	13.7	15.1	15.54		
115	14.59	14.51	13.80	15.39	14.04	14.86	14.5	13.2	14.2	12.8	13.8	13.8	14.28		
(N)	15	15	15	15	15	15	14	15	14	14	14	15	15		
201	18.17	18.51	18.29	17.81	17.40	16.97	15.9	16.0	14.5	16.5	16.2	17.4	17.36		
202	16.73	20.86	18.77	17.84	spilled	spilled	16.2	15.0	spilled	17.8	18.1	18.0	17.78		
203	14.83	16.54	spilled	15.54	15.86	16.00	16.2	17.2	14.5	14.7	15.5	15.8	16.56		
204	16.80	17.60	17.11	15.31	16.79	16.09	14.6	15.7	16.3	17.8	17.4	15.8	15.72		
205	14.57	14.67	16.26	16.07	15.24	15.34	15.0	10.5	14.4	14.1	15.8	16.7	14.76		
206	14.20	14.19	14.79	15.66	15.03	16.09	13.2	13.6	14.9	spilled	15.6	15.6	15.48		
207	14.54	15.20	15.79	15.33	16.21	14.61	14.5	14.3	14.2	14.9	12.5	15.4	14.94		
208	14.03	16.89	19.87	17.94	15.20	16.56	15.1	13.5	15.1	16.9	16.0	16.6	17.58		
209	16.91	18.19	18.56	17.99 *	17.79	16.77	16.3	15.0	spilled	20.1	19.8	20.3	18.44		
210	15.89	17.19	18.40	16.83	17.87	20.13	24.6	13.7	14.3	16.4	15.8	16.2	16.20		
211	14.90	15.80	16.61	17.67	16.09	16.84	17.9	16.4	spilled	14.7	spilled	17.3	16.96		
212	14.31	spilled	spilled	15.07	spilled	spilled	spilled	14.6	spilled	spilled	16.7	16.7	17.08		
213	16.37	19.50	spilled	spilled	spilled	spilled	spilled	12.9	spilled	18.9	spilled	13.0	16.84		
214	15.07	16.21	15.67	15.13	16.14	15.23	15.1	13.4	15.0	17.3	17.4	17.3	16.44		
215	13.16	15.89	16.99	16.33	16.77	15.64	13.5	13.6	14.8	15.4	15.4	16.0	16.44		
(N)	15	14	12	14	12	12	13	15	10	13	13	15	15		

Table B-3. Individual Animal Food Consumption (g)

Animal	Study Day														
	8	15	22	29	36	43	50	57	64	71	78	85	90		
	Female Rats														
301	15.51	16.00	15.26	spilled	spilled	20.81	14.0	15.7	13.1	15.6	15.3	14.8	14.88		
302	15.09	16.61	16.31	16.17	17.53	14.29	14.1	13.5	13.6	14.9	14.6	15.0	14.20		
303	15.86	16.26	15.73	15.24	15.24	14.50	14.0	13.0	12.9	15.6	15.1	15.0	15.26		
304	13.80	15.54	17.96	13.77	15.19	14.57	15.5	12.8	13.7	14.3	14.8	14.8	14.16		
305	14.91	14.99	15.04	14.59	13.94	14.89	12.5	12.9	13.1	13.9	14.3	14.2	13.26		
306	16.57	18.74	18.70	25.33	18.19	17.43	17.5	15.3	15.6	17.9	19.8	16.3	14.92		
307	17.80	18.70	19.17	17.01	18.49	17.69	17.7	18.2	20.4	22.3	22.6	22.2	24.60		
308	14.90	17.60	15.97	spilled	16.97	15.87	16.4	14.7	15.2	16.8	15.8	16.2	15.90		
309	15.37	15.77	17.51	15.69	15.34	16.03	13.8	12.2	13.5	15.3	15.0	14.3	15.08		
310	14.49	15.26	spilled	12.64	15.57	13.69	12.3	12.7	13.7	14.2	15.1	14.4	12.98		
311	15.50	14.81	14.30	14.57	14.03	14.83	13.6	12.4	13.5	15.6	15.1	16.2	14.70		
312	14.90	17.59	16.89	17.97	20.99	18.49	15.4	12.5	15.2	16.6	16.4	18.0	17.18		
313	16.46	spilled	21.49	28.40	spilled	spilled	spilled	16.0	spilled	spilled	spilled	21.4	17.92		
314	16.60	20.61	16.36	20.40	21.90	19.64	16.7	15.2	15.7	18.7	16.5	20.6	23.04		
315	15.04	16.63	18.10	16.91	17.11	17.64	16.9	15.8	14.8	16.2	17.8	17.0	16.12		
(N)	15	14	14	13	13	14	14	15	14	14	14	15	15		
401	12.67	15.01	15.50	15.13	14.57	14.17	14.4	13.3	15.1	15.0	14.9	15.4	15.04		
402	14.16	16.34	16.69	17.34	17.37	19.97	15.5	15.5	16.5	16.9	17.0	17.2	21.38		
403	13.30	16.30	15.24	16.39	15.44	16.04	14.5	13.2	15.4	15.6	16.3	15.9	16.22		
404	14.69	17.80	17.74	16.14	17.44	18.53	15.4	14.6	17.5	17.7	16.2	18.1	18.18		
405	15.81	16.11	17.67	18.66	18.57	17.90	17.8	18.0	spilled	18.6	17.7	18.9	18.34		
406	15.63	16.33	18.69	19.60	17.61	16.33	17.2	17.0	18.2	18.2	17.7	19.1	18.04		
407	14.91	16.83	17.56	16.53	16.57	18.22	dead	dead	dead	dead	dead	dead	dead		
408	16.13	17.04	17.63	17.51	17.41	18.66	19.0	16.5	19.4	18.7	20.1	20.4	22.42		
409	14.69	15.90	16.29	16.91	17.30	16.91	16.2	15.4	17.5	17.3	16.8	17.4	17.32		
410	13.40	16.60	16.81	16.86	17.24	17.00	16.1	16.3	16.2	17.5	17.5	16.9	16.70		
411	14.70	16.29	16.76	18.33	16.51	16.63	15.1	13.6	16.3	17.5	18.4	18.3	17.86		
412	12.46	13.06	13.89	12.89	13.70	13.31	13.0	12.0	13.3	13.6	15.1	14.6	14.50		
413	18.09	16.70	17.51	16.77	spilled	spilled	spilled	15.1	spilled	spilled	16.1	16.7	18.62		
414	12.21	14.10	14.41	14.73	14.27	14.34	15.0	12.9	13.8	13.1	13.9	14.7	14.98		
415	15.71	spilled	18.76	19.33	21.01	19.41	19.4	19.2	20.3	20.6	22.9	22.4	21.52		
(N)	15	14	15	15	14	14	13	14	12	13	14	14	14		

Table B-3. Individual Animal Food Consumption (g)

Animal	Study Day														
	8	15	22	29	36	43	50	57	64	71	78	85	90		
	Male Nfice														
501	3.41	3.41	3.57	3.53	3.29	4.29	4.9	3.1	3.4	3.6	3.5	3.5	3.80		
502	4.00	4.17	4.39	3.56	3.20	4.17	2.9	3.2	3.7	3.7	3.4	3.4	4.18		
503	3.13	3.67	3.34	3.30	3.19	3.26	3.2	3.1	3.2	3.6	3.0	3.4	3.66		
504	3.89	4.87	3.34	3.57	3.43	3.74	3.5	3.3	3.5	4.6	3.3	3.5	3.66		
505	3.63	3.76	3.61	3.74	3.51	3.74	3.4	3.7	3.4	3.8	3.6	3.7	3.84		
506	3.41	3.39	3.26	2.84	3.17	3.09	3.0	3.0	3.2	3.4	3.3	3.4	3.54		
507	3.07	3.21	3.46	3.20	2.86	3.17	3.1	2.9	3.6	3.4	3.2	3.3	4.04		
508	3.73	3.27	4.39	3.53	3.73	3.20	3.2	3.3	3.2	3.6	3.3	3.6	3.50		
509	4.80	5.10	3.84	4.10	4.09	4.29	3.7	3.9	4.4	4.1	4.1	4.2	4.40		
510	3.39	3.69	3.49	3.69	3.17	3.14	3.3	3.1	3.2	3.5	3.6	3.6	3.78		
511	3.33	3.60	3.73	3.79	3.70	3.31	3.3	3.6	3.4	3.7	3.5	3.4	4.10		
512	3.46	3.09	3.36	3.23	3.06	3.30	2.8	3.0	3.3	3.4	3.3	3.4	3.54		
513	3.41	3.54	3.49	3.46	3.30	3.43	3.2	3.3	3.4	3.4	3.7	3.6	3.58		
514	3.51	3.50	3.67	3.74	3.11	3.40	3.1	2.9	3.4	3.5	3.3	3.6	3.36		
515	3.93	3.99	4.13	3.53	3.56	3.90	3.5	3.3	3.7	4.5	3.5	4.1	4.18		
(N)	15	15	15	15	15	15	15	15	15	15	15	15	15		
601	3.70	4.23	3.81	4.01	3.86	3.97	3.7	3.8	4.0	4.1	4.1	3.6	4.12		
602	3.49	3.24	2.93	3.29	3.24	3.33	3.3	2.9	3.1	3.4	3.3	3.6	3.58		
603	4.17	4.09	3.54	3.56	3.64	3.63	3.4	3.5	3.5	3.8	3.7	3.7	3.82		
604	3.41	3.39	3.23	3.29	3.23	3.13	3.0	3.2	3.2	3.4	3.3	3.7	3.38		
605	4.07	4.00	2.90	3.27	3.30	3.39	3.1	3.0	3.1	3.3	3.1	3.3	3.46		
606	3.81	3.71	3.53	3.47	3.50	3.73	3.0	3.1	3.4	3.6	3.7	3.3	3.50		
607	3.80	3.43	3.19	3.36	3.30	3.30	3.1	3.2	3.5	3.5	3.6	3.5	3.76		
608	3.36	3.36	3.59	3.41	3.40	3.46	3.3	3.2	3.4	3.5	3.3	3.4	3.52		
609	3.29	3.29	3.34	3.29	3.23	3.21	3.2	3.2	3.1	3.4	3.5	3.3	3.78		
610	3.46	4.67	3.00	3.51	3.50	3.73	3.4	3.4	3.4	3.7	3.6	3.6	3.64		
611	3.54	3.43	3.33	3.34	2.94	3.51	3.3	3.3	3.2	3.5	3.4	3.5	3.84		
612	4.30	3.96	3.41	3.50	3.67	3.50	3.8	3.5	3.5	3.7	3.7	3.8	4.24		
613	4.01	4.61	4.21	2.86	4.59	3.84	3.3	3.6	3.7	3.6	3.7	3.7	3.90		
614	3.86	3.27	4.29	2.66	3.20	3.17	3.2	3.0	3.4	3.6	3.4	3.7	3.84		
615	3.99	2.97	5.37	3.84	3.49	3.44	3.8	3.7	3.9	4.1	4.0	4.0	3.68		
(N)	15	15	15	15	15	15	15	15	15	15	15	15	15		

Table B-3. Individual Animal Food Consumption (g)

Animal	Study Day														
	8	15	22	29	36	43	50	57	64	71	78	85	90		
	Male Mice														
701	3.09	3.20	3.30	3.24	3.13	3.03	3.3	3.0	3.0	3.5	3.2	3.3	3.44		
702	3.31	3.66	3.17	3.73	3.27	3.44	3.1	3.3	3.4	3.1	3.6	3.5	3.94		
703	3.43	4.00	3.40	3.47	3.14	3.27	3.2	3.0	3.5	3.3	3.4	3.4	3.54		
704	3.59	3.46	3.74	3.30	3.19	3.44	3.1	3.0	3.2	3.4	3.4	3.5	3.74		
705	3.50	3.29	2.99	3.14	3.10	3.36	3.1	3.1	3.2	3.3	3.3	3.4	3.54		
706	4.19	3.37	3.24	3.29	3.33	3.24	3.0	3.1	2.9	3.4	3.4	2.5	5.14		
707	4.61	4.87	4.80	4.91	3.14	3.87	3.3	3.4	3.5	3.8	3.5	3.9	3.96		
708	3.61	3.60	3.29	3.49	3.39	3.34	3.2	3.5	3.4	3.8	3.4	3.9	3.66		
709	6.30	6.36	5.10	7.46	9.26	6.29	4.0	4.2	5.7	5.4	5.1	3.7	4.42		
710	3.33	4.71	4.29	3.54	3.33	3.77	3.6	3.5	3.8	4.1	3.7	4.1	4.28		
711	3.67	2.93	2.89	3.37	2.97	3.01	3.0	2.9	2.9	3.2	3.1	3.3	3.56		
712	4.11	3.53	3.49	3.96	3.80	3.54	3.3	3.1	3.7	3.5	3.4	3.9	3.74		
713	3.87	3.84	3.20	7.57	2.86	3.71	3.0	3.1	3.2	3.6	3.5	3.6	3.80		
714	3.64	3.16	3.41	3.41	3.24	3.40	2.4	3.3	3.0	3.1	3.2	3.3	3.78		
715	3.93	2.84	2.99	3.16	3.23	3.31	3.2	3.1	3.3	3.6	NT	3.7	3.66		
(N)	15	15	15	15	15	15	15	15	15	15	14	15	15		
801	3.60	3.61	3.23	3.23	2.91	3.30	3.2	3.1	3.5	3.5	3.6	3.6	3.70		
802	3.70	4.17	3.54	3.56	3.43	3.49	3.6	3.4	3.6	2.9	4.0	3.8	4.08		
803	2.51	5.47	3.73	3.41	3.49	3.31	3.2	3.1	3.2	3.6	dead	dead	dead		
804	3.71	4.44	4.06	3.70	3.33	3.47	3.3	2.6	3.3	3.5	3.3	3.5	3.36		
805	3.61	4.90	3.59	3.97	3.67	7.80	5.0	4.5	3.5	4.1	4.0	4.5	3.90		
806	3.93	3.76	3.36	3.54	2.80	3.24	3.1	2.8	2.9	3.3	3.3	3.3	3.86		
807	3.37	3.80	3.77	3.21	2.00	3.39	3.2	2.8	3.2	3.2	3.0	3.2	3.22		
808	3.56	4.36	3.01	3.30	3.06	3.06	3.1	2.9	3.0	3.4	3.2	3.4	3.34		
809	4.76	2.97	3.37	3.41	3.00	3.06	3.1	2.9	3.1	3.2	3.2	3.4	3.44		
810	3.51	3.66	3.06	4.16	2.80	3.41	3.5	NT	3.1	3.4	3.6	3.6	3.74		
811	3.40	3.79	2.63	3.40	2.97	3.03	3.1	2.9	2.8	3.4	3.1	2.9	3.52		
812	3.69	2.59	2.99	3.27	3.04	3.00	3.1	2.8	3.4	3.3	3.1	3.6	4.50		
813	4.23	3.34	3.46	3.14	4.29	2.89	3.3	3.0	3.3	3.4	3.3	3.5	3.68		
814	3.57	3.31	3.23	3.07	2.91	3.00	3.0	2.7	2.8	3.1	2.9	3.5	3.66		
(N)	15	14	14	14	14	14	14	13	14	14	14	14	14		

NT = Not taken

APPENDIX C

Table C-1.	Individual Animal Hematology Parameters, Day 91	C-2
Table C-2.	Individual Animal Coagulation Parameters for Female Rats, Day 91	C-10
Table C-3.	Individual Animal Serum Chemistry Parameters, Day 91	C-12

Table C-1. Individual Animal Hematology Parameters, Day 91

Animal	Neutrophils (10 ³ /μL)	Lymphocytes (10 ³ /μL)	Monocytes (10 ³ /μL)	Eosinophils (10 ³ /μL)	Basophils (10 ³ /μL)	White Blood Cells (10 ³ /μL)	Red Blood Cells (10 ⁶ /μL)
Female Rats							
101	1.02	7.16	0.01	0.10	0	8.3	9.46
102	1.70	6.95	0.11	0.10	0	8.9	8.16
103	0.96	9.88	0.01	0.07	0	10.9	8.65
104	1.02	9.02	0.13	0.22	0.01	10.4	8.65
105	1.09	11.00	0.04	0.26	0	12.4	9.38
106	1.14	10.50	0.03	0.24	0	11.9	8.79
107	0.65	7.80	0.16	0.08	0	8.7	8.08
108	1.09	8.06	0.04	0.24	0	9.4	8.12
109	1.38	3.36	0.07	0.09	0	4.9	8.51
110	1.36	10.40	0.07	0.16	0	12	7.38
111	0.79	7.06	0.02	0.18	0	8	8.48
112	0.64	9.51	0.11	0.08	0.03	10.4	8.65
113	0.77	6.55	0.06	0.11	0	7.5	8.65
114	1.31	7.96	0.03	0.12	0.01	9.4	8.38
115	1.35	10.90	0.02	0.20	0.01	12.5	8.65
201	1.02	7.02	0.05	0.14	0	8.2	9.09
202	0.61	6.74	0.11	0.09	0	7.6	8.27
203	0.33	6.18	0.04	0.10	0	6.7	8.65
204	1.13	10.30	0.06	0.10	0	11.6	8.98
205	0.74	10.00	0.11	0.12	0.01	11	8.06
206	0.80	9.63	0.07	0.09	0.01	10.6	8.8
207	1.31	12.80	0.26	0.16	0	14.5	8.91
208	0.87	7.32	0.02	0.19	0	8.4	8.59
209	0.79	7.72	0.15	0.11	0	8.8	7.85
210	1.19	10.90	0.02	0.15	0	12.3	8.65
211	1.55	8.06	0.02	0.14	0	9.8	8.41
212	1.27	12.10	0.09	0.10	0.01	13.6	8.3
213	0.46	9.38	0.10	0.16	0.01	10.1	8.37
214	0.78	11.90	0.03	0.16	0	12.9	8.82
215	0.76	9.98	0.74	0.12	0.02	11.6	8.18

Table C-1. Individual Animal Hematology Parameters, Day 91

Animal	Neutrophils (10 ³ /μL)	Lymphocytes (10 ³ /μL)	Monocytes (10 ³ /μL)	Eosinophils (10 ³ /μL)	Basophils (10 ³ /μL)	White Blood Cells (10 ⁶ /μL)	Red Blood Cells (10 ⁶ /μL)
Female Rats							
301	0.53	8.16	0.02	0.13	0	8.8	7.73
302	1.40	6.08	0.01	0.10	0	7.6	7.61
304	0.67	11.80	0.08	0.14	0.01	12.7	8.36
305	1.12	11.00	0.02	0.10	0	12.2	8.34
306	1.40	9.76	0.13	0.17	0	11.5	8.26
307	0.89	6.51	0.19	0.07	0.01	7.7	7.58
308	0.65	11.90	0.22	0.15	0	12.9	8
309	0.85	10.80	0.06	0.14	0.01	11.8	8.27
310	0.58	12.50	0.05	0.13	0	13.2	8.91
311	6.33	7.30	1.27	0.11	0.06	15.1	8.61
312	1.27	15.30	0.07	0.23	0.01	16.9	8.5
313	0.69	6.79	0.69	0.03	0.02	8.2	7.85
314	1.08	10.40	0.04	0.12	0	11.7	8.34
315	0.90	9.91	0.13	0.13	0.02	11.1	8.69
401	1.35	11.30	0.12	0.12	0.01	12.9	7.89
402	0.84	6.25	0.05	0.06	0.01	7.2	8.4
403	1.22	10.10	0.05	0.11	0.02	11.5	6.87
404	0.83	9.59	0.25	0.12	0.02	10.8	8.03
406	0.70	18.50	0.21	0.26	0.03	19.7	7.7
408	0.89	10.20	0.15	0.09	0	11.3	7.53
409	0.61	12.00	0.15	0.13	0	12.9	7.69
410	1.52	8.33	0.07	0.12	0	10	7.57
411	0.74	10.20	0.21	0.11	0.01	11.3	8.11
412	1.38	12.40	0.03	0.14	0.01	14	7.59
413	1.07	5.23	0.21	0.10	0	6.6	8.15
414	1.21	14.70	0.15	0.20	0.01	16.2	7.95
415	1.62	10.20	0.05	0.22	0	12.1	7.09

Table C-1. Individual Animal Hematology Parameters, Day 91

Animal	Hemoglobin (g/dL)	Hematocrit (%)	Mean Corpuscular Volume (fL)	Mean Corpuscular Hemoglobin (pg)	Mean Corpuscular Hemoglobin Concentration (g/dL)	Platelets (10 ³ /μL)	Reticulocytes (%)
Female Rats							
101	16.8	52.5	55.5	17.8	32.0	958	0.6
102	15.9	47.6	58.4	19.5	33.5	1060	0.4
103	16	49.3	57	18.5	32.4	859	0.7
104	16.6	49.6	57.3	19.1	33.4	1083	0.5
105	16.4	50.2	53.5	17.5	32.8	795	0.4
106	15.2	47.4	54	17.3	32.1	1202	0.8
107	15.2	46.6	57.7	18.8	32.6	1012	1.0
108	15.6	46.7	57.5	19.2	33.3	1106	0.1
109	15.6	48.1	56.5	18.4	32.5	1011	0.3
110	13.9	42.3	57.3	18.8	32.9	872	0.1
111	15.8	48.1	56.8	18.7	32.9	1119	0.4
112	17	51.1	59.1	19.6	33.2	1210	0.5
113	16.3	50	57.8	18.9	32.7	830	0.9
114	15.9	47.9	57.2	19	33.2	1170	0.9
115	16.5	49.5	57.2	19.1	33.4	1082	0.4
201	17.3	52.1	57.4	19.1	33.2	934	0.7
202	16.3	49.4	59.8	19.7	32.9	943	0.2
203	15.8	47.9	55.3	18.3	33.1	746	0.4
204	15.1	48.7	54.3	16.8	31.0	701	0.8
205	15.2	45.4	56.3	18.8	33.4	1075	0.2
206	17.1	51.8	58.8	19.5	33.1	1158	0.5
207	16.3	49	54.9	18.3	33.3	1198	0.8
208	15.8	49.1	57.2	18.5	32.3	956	0.7
209	14.8	45.5	58	18.9	32.5	537	0.4
210	15.1	46.6	53.9	17.5	32.5	1092	0.5
211	15.5	47	55.9	18.4	32.9	1230	0.1
212	15.3	46.4	55.9	18.5	33.0	1049	0.4
213	15	45.4	54.2	18	33.1	1371	0.4
214	16.3	49	55.6	18.5	33.3	1216	0.3
215	16.1	48.3	59	19.7	33.4	987	0.1

Table C-1. Individual Animal Hematology Parameters, Day 91

Animal	Hemoglobin (g/dL)	Hematocrit (%)	Mean Corpuscular Volume (fL)	Mean Corpuscular Hemoglobin (pg)	Mean Corpuscular Hemoglobin Concentration (g/dL)	Platelets (10 ³ /μL)	Reticulocytes (%)
Female Rats							
301	14.4	44.4	57.5	18.7	32.5	900	0.3
302	13.3	40.5	53.3	17.5	32.8	1001	0.1
304	15.4	46.4	55.5	18.5	33.3	1042	0.3
305	14.5	44.7	53.6	17.4	32.4	1111	0.2
306	15	45.9	55.6	18.2	32.8	682	0.2
307	14.2	43.5	57.4	18.7	32.5	895	0.6
308	14.6	44.1	55.2	18.3	33.2	1093	0.3
309	15.1	45.7	55.2	18.3	33.0	973	0.3
310	16.6	50	56.1	18.6	33.2	1165	0.8
311	15.2	46.7	54.3	17.6	32.4	1269	0.3
312	15.2	46.4	54.7	17.9	32.8	768	0.1
313	15	45.6	58.1	19.1	32.9	1111	0.4
314	15.2	46	55.2	18.2	33.0	940	0.8
315	16.1	50.6	58.3	18.6	31.9	1236	0.5
401	15.5	47.3	60	19.6	32.7	973	0.5
402	14.8	46.5	55.3	17.6	31.9	1085	0.4
403	13.4	41.2	60	19.5	32.6	1056	1.6
404	15.1	46.2	57.5	18.8	32.6	954	0.3
406	14.4	44.9	58.3	18.7	32.2	1142	0.8
408	14	42.6	56.6	18.6	33.0	1126	0.6
409	14.3	44.4	57.6	18.6	32.2	794	0.5
410	14	43.8	57.8	18.5	32.0	1097	0.7
411	14.5	44.5	54.9	17.9	32.7	861	0.8
412	13.9	43.4	57.2	18.3	32.0	879	0.6
413	14.7	46.4	57	18	31.6	900	0.7
414	15.3	46.7	58.8	19.3	32.8	1133	0.3
415	13.4	41.4	58.5	18.9	32.3	905	0.7

Table C-1. Individual Animal Hematology Parameters, Day 91

Animal	Neutrophils (10 ³ /μL)	Lymphocytes (10 ³ /μL)	Monocytes (10 ³ /μL)	Eosinophils (10 ³ /μL)	Basophils (10 ³ /μL)	White Blood Cells (10 ³ /μL)	Red Blood Cells (10 ⁶ /μL)
Male Mice							
501	0.85	8.38	0.25	0.02	0.01	9.5	10.1
502	0.83	10.70	0.11	0.03	0.01	11.7	10
503	0.33	5.39	0.06	0.00	0.01	5.8	9.74
504	0.80	7.34	0.02	0.00	0	8.2	9.25
505	0.72	8.47	0.26	0.01	0.01	9.5	9.72
506	0.96	8.82	0.05	0.01	0.01	9.9	9.62
507	0.73	7.99	0.21	0.02	0.01	9	10.9
508	0.81	8.09	0.06	0.00	0	9	9.69
509	0.65	3.13	0.19	0.01	0	4	9.78
510	0.55	5.25	0.20	0.01	0	6	9.43
512	0.92	5.63	0.10	0.01	0	6.7	9.57
513	2.29	8.84	0.31	0.02	0.01	11.5	9.34
514	0.78	6.87	0.37	0.00	0	8	9.25
515	2.34	6.33	0.18	0.02	0	8.9	9.54
601	0.92	7.06	0.13	0.00	0	8.1	9.11
602	1.35	12.50	0.20	0.01	0.01	14	10.7
603	1.26	13.70	0.23	0.02	0.02	15.2	10.5
605	0.87	8.23	0.25	0.03	0	9.4	9.81
606	0.83	6.05	0.11	0.02	0	7	9
607	1.16	9.14	0.19	0.01	0	10.5	9.74
608	1.04	6.88	0.44	0.01	0	8.4	9.46
609	1.03	6.80	0.12	0.01	0	8	10.6
610	1.36	7.13	0.04	0.01	0	8.5	9.93
611	1.10	8.42	0.07	0.01	0	9.6	10.6
612	1.02	11.90	0.20	0.01	0	13.1	9.22
613	NT	NT	NT	NT	NT	NT	NT
614	1.18	11.00	0.07	0.00	0.03	12.3	9.71
615	0.65	9.31	0.08	0.07	0	10.1	9.87

Table C-1. Individual Animal Hematology Parameters, Day 91

Animal	Neutrophils (10 ³ /μL)	Lymphocytes (10 ³ /μL)	Monocytes (10 ³ /μL)	Eosinophils (10 ³ /μL)	Basophils (10 ³ /μL)	White Blood Cells (10 ⁶ /μL)	Red Blood Cells (10 ⁶ /μL)
Male Mice							
702	0.86	9.78	0.25	0.02	0	10.9	10.3
703	0.98	5.61	0.14	0.02	0.01	6.8	8.63
704	0.89	11.10	0.25	0.02	0.01	12.3	9.9
705	0.96	7.32	0.25	0.03	0	8.6	10.5
706	0.91	8.00	0.47	0.03	0	9.4	9.46
707	0.85	9.25	0.19	0.03	0.01	10.3	10.2
708	1.01	8.89	0.08	0.01	0	10	NT
709	1.14	6.67	0.05	0.00	0	7.9	9.59
711	0.19	4.54	0.12	0.08	0	4.9	8.81
712	0.65	6.14	0.04	0.02	0	6.9	9.42
713	0.69	7.87	0.08	0.01	0.01	8.7	10.3
714	0.88	6.74	0.08	0.02	0	7.7	9.83
715	0.84	9.34	0.06	0.01	0.01	10.2	10
801	0.52	4.89	0.16	0.02	0	5.6	9.22
805	0.90	9.44	0.27	0.01	0.01	10.6	9.9
806	0.46	5.83	0.08	0.11	0	6.5	9.97
807	0.86	6.42	0.22	0.01	0	7.5	9.28
808	0.85	6.88	0.13	0.03	0	7.9	9.03
809	0.58	4.78	0.07	0.01	0	5.4	9.05
810	1.46	5.38	0.03	0.01	0	6.9	9.31
811	0.54	6.10	0.08	0.05	0	6.8	9.65
812	0.44	4.90	0.07	0.01	0	5.4	9.25
813	0.66	6.48	0.03	0.01	0	7.2	9.3
814	0.83	8.02	0.25	0.00	0.01	9.1	8.94
815	0.50	4.50	0.04	0.01	0	5.1	10.1

Table C-1. Individual Animal Hematology Parameters, Day 91

Animal	Hemoglobin (g/dL)	Hematocrit (%)	Mean Corpuscular Volume (fL)	Mean Corpuscular Hemoglobin (pg)	Mean Corpuscular Hemoglobin Concentration (g/dL)	Platelets (10 ³ /μL)	Reticulocytes (%)
Male Mice							
501	14.4	45	44.5	14.3	32.1	1112	0.8
502	14.4	43.6	43.6	14.4	33.1	1154	0.7
503	14	43.6	44.8	14.3	32.0	1504	0.4
504	13.5	41.5	44.9	14.6	32.5	837	0.9
505	14.1	43.1	44.3	14.5	32.6	1039	0.6
506	14	42.7	44.4	14.6	32.9	1136	0.9
507	15.5	47.4	43.6	14.2	32.6	557	1.2
508	13.7	43	44.4	14.1	31.9	1203	0.6
509	14.2	43.6	44.5	14.6	32.7	1108	0.9
510	13.8	41.6	44.1	14.6	33.1	1236	0.4
512	13.5	42.1	44	14.1	32.0	900	0.9
513	13.6	41.4	44.3	14.6	33.0	1310	0.8
514	13.3	40.4	43.7	14.4	33.0	1237	0.9
515	13.5	41.3	43.3	14.2	32.8	1389	1.1
601	13.7	41.8	45.9	15	32.8	899	1.7
602	15.4	46.1	43.1	14.4	33.4	479	0.5
603	15.4	46.6	44.4	14.6	33.0	826	0.6
605	14.2	43.5	44.3	14.5	32.6	940	0.9
606	13.2	40.1	44.6	14.7	32.9	1041	1.0
607	14.1	43.2	44.3	14.4	32.6	1144	1.3
608	13.6	40.5	42.8	14.4	33.7	871	0.6
609	15.6	41.7	39.4	14.7	37.4	617	0.7
610	14.5	44.2	44.5	14.6	32.9	1021	1.1
611	15.2	47.1	44.4	14.3	32.1	292	0.4
612	13.5	41.2	44.7	14.6	32.8	1303	0.3
613	NT	NT	NT	NT	NT	NT	0.5
614	14	43.3	44.6	14.5	32.4	1037	0.2
615	14.1	43.4	44	14.3	32.5	1055	1.0

Table C-1. Individual Animal Hematology Parameters, Day 91

Animal	Hemoglobin (g/dL)	Hematocrit (%)	Mean Corpuscular Volume (fL)	Mean Corpuscular Hemoglobin (pg)	Mean Corpuscular Hemoglobin Concentration (g/dL)	Platelets (10 ³ /µL)	Reticulocytes (%)
Male Mice							
702	14.7	45.6	44.3	14.2	32.1	254	0.8
703	12.6	38.5	44.6	14.6	32.7	1339	0.8
704	14.5	44.2	44.6	14.6	32.8	716	0.8
705	15.1	46.8	44.5	14.3	32.2	272	1.6
706	13.8	41.6	44	14.6	33.1	607	1.1
707	14.7	44.7	44	14.5	32.9	937	0.3
708	13.8	NT	NT	NT	NT	NT	0.4
709	14.1	43	44.9	14.7	32.8	1169	**
711	12.5	39	44.2	14.1	32.0	74	0.3
712	14	42.5	45.2	14.9	33.0	1478	1.8
713	14.7	45	43.9	14.3	32.6	1081	1.1
714	14.2	43.4	44.2	14.5	32.8	1441	1.6
715	14.5	44.6	44.6	14.5	32.5	951	0.6
801	13.9	41.8	45.4	15.1	33.3	1171	0.8
805	14.8	44.7	45.1	14.9	33.1	829	1.1
806	15	44.8	44.9	15	33.4	888	0.5
807	13.7	41.9	45.1	14.7	32.6	822	0.7
808	13.2	39.7	44	14.6	33.2	945	0.7
809	13.4	41.2	45.5	14.8	32.6	1239	0.7
810	14	41.9	45	15.1	33.5	1342	1.0
811	14	43.2	44.8	14.5	32.3	736	0.9
812	13.9	42.3	45.7	15	32.9	1224	1.0
813	13.8	42.4	45.6	14.8	32.5	968	1.1
814	13.4	40.5	45.3	14.9	33.0	1066	1.4
815	14.7	44.7	44.4	14.6	32.9	578	1.0

Table C-2. Individual Animal Coagulation Parameters for Female Rats, Day 91

Animal	Prothrombin Time (seconds)	Activated Partial Thromboplastin Time (seconds)
101	10.9	13.1
102	10.8	16.0
103	11.3	15.1
104	11.7	14.3
106	11.2	13.2
107	11.4	13.9
108	11.2	14.0
109	11.4	14.6
110	11.7	16.2
111	10.8	15.0
112	11.1	14.9
113	11.3	13.7
114	11.7	13.1
115	11.8	16.7
201	12.0	16.0
202	11.8	12.7
203	12.0	10.4
204	10.8	15.7
205	10.9	13.7
206	11.3	13.1
207	11.1	11.9
208	11.0	13.0
209	11.9	11.5
210	10.7	12.3
211	11.0	12.5
212	11.5	14.6
213	11.4	13.6
214	11.2	13.1
215	11.5	12.4

Table C-2. Individual Animal Coagulation Parameters for Female Rats, Day 91

Animal	Prothrombin Time (seconds)	Activated Partial Thromboplastin Time (seconds)
301	11.1	13.9
302	10.6	13.4
304	11.0	13.2
305	11.4	12.6
306	11.1	10.4
307	10.7	13.7
308	11.3	14.8
309	11.2	13.5
310	10.8	14.5
311	11.6	13.3
312	11.1	8.8
313	11.0	13.5
314	11.4	12.4
315	11.1	12.6
401	11.0	12.7
402	10.9	12.6
403	11.0	9.6
404	11.1	12.3
405	11.1	12.3
406	11.4	13.1
408	11.0	14.6
409	11.5	12.7
410	11.0	13.5
411	11.7	11.9
412	11.1	11.6
413	11.5	14.0
414	11.3	12.3
415	10.9	14.0

Table C-3. Individual Animal Serum Chemistry Parameters, Day 91

Animal	Sorbitol Dehydrogenase (μ/L)	Alkaline Phosphatase (μ/L)	Aspartate Amino-transferase (μ/L)	Alanine Amino-transferase (μ/L)	Gamma Glutamyl Transferase (μ/L)	Total Protein (g/dL)	Albumin (g/dL)	Glucose (mg/dL)	Blood Urea Nitrogen (mg/dL)	Creatinine (mg/dL)	Calcium (mg/dL)
Female Rats											
101	24	55	87	34	0	7.9	5.5	119	15	0.7	12.1
102	19	56	68	38	0	9.1	6	103	17	0.7	12.1
103	25	110	94	33	0	7.8	5.2	117	13	0.7	11.4
104	25	49	83	24	1	7.2	5	109	23	0.8	11.4
105	22	39	77	36	1	8.3	5.7	113	14	0.6	12
106	25	84	88	55	0	8.1	5.3	127	17	0.7	11.9
107	16	40	63	33	0	7.3	5.2	91	15	0.5	11.3
108	17	38	71	26	0	7.4	5.2	105	16	0.6	11.3
109	18	49	64	29	0	8.4	6	110	12	0.7	11.5
110	14	46	54	37	1	8.7	6.2	127	16	0.6	11.9
111	21	43	81	30	0	8.9	6.1	115	14	0.6	11.9
112	38	77	121	65	0	8.6	5.8	103	14	0.7	12.2
113	28	54	90	39	0	7.6	5.2	132	15	0.7	11.6
114	24	60	99	39	0	7.8	5.5	122	14	0.6	11.8
115	18	60	70	39	0	8.6	5.8	107	13	0.6	12.1
201	18	38	75	32	0	8.6	5.7	115	15	0.6	12
202	25	74	101	40	0	7.7	5.7	102	13	0.6	11.5
203	17	49	79	31	2	7.1	4.9	126	12	0.6	11.3
204	20	42	77	42	1	8	5.8	107	13	0.6	12.1
205	19	54	61	42	0	8.8	6.1	115	17	0.6	12.7
206	19	98	88	39	0	7.6	5.3	102	12	0.6	11.2
207	21	44	86	38	0	7.5	5.1	113	21	0.7	12.1
208	16	36	91	25	1	7.4	4.7	116	15	0.6	11.5
209	9	39	114	32	0	7.9	6.1	122	13	0.5	11.9
210	71	32	215	104	1	8.4	6.2	123	12	0.5	12.1
211	16	49	60	22	0	7.4	5	115	15	0.6	11.5
212	20	61	73	29	0	7.8	5.2	115	13	0.7	11.8
213	12	41	57	31	0	7.1	5.3	122	14	0.5	11.5
214	17	73	71	32	1	7.4	5.4	112	11	0.6	11.8
215	22	53	93	38	0	7.3	4.8	115	13	0.5	11.4

NT = Not taken

Table C-3. Individual Animal Serum Chemistry Parameters, Day 91

Animal	Sorbitol Dehydrogenase (μ/L)	Alkaline Phosphatase (μ/L)	Aspartate Amino-transferase (μ/L)	Alanine Amino-transferase (μ/L)	Gamma Glutamyl Transferase (μ/L)	Total Protein (g/dL)	Albumin (g/dL)	Glucose (mg/dL)	Blood Urea Nitrogen (mg/dL)	Creatinine (mg/dL)	Calcium (mg/dL)
Female Rats											
301	13	35	53	28	0	7.4	5.4	103	13	0.5	11.7
302	16	21	81	32	0	8.4	6.1	112	11	0.5	11.8
303	5	63	212	43	0	7.8	5.2	115	12	0.6	11.7
304	13	43	67	28	1	7.5	5.3	122	11	0.5	11.5
305	123	36	256	152	1	8.4	5.9	119	13	0.5	12
306	13	46	101	29	1	7	4.9	121	12	0.6	11.8
307	10	45	179	45	0	8.8	6.3	125	18	0.6	12.4
308	12	33	99	25	0	7.5	5.4	114	12	0.5	12.1
309	19	47	58	31	0	8.6	6	131	13	0.7	12.5
310	52	48	106	73	0	9.3	6.8	119	14	0.6	13
311	21	44	76	28	0	7.4	5.1	114	12	0.7	11.9
312	18	45	79	35	0	7.1	5.1	145	13	0.6	11.8
313	23	28	74	26	0	8.5	6.3	115	16	0.6	12.4
314	16	56	62	25	1	6.8	4.5	119	9	0.5	10.9
315	23	37	67	29	0	8.8	6.2	125	16	0.7	12.5
401	27	47	73	38	0	8.8	6.3	114	14	0.8	12.5
402	20	72	73	48	0	8.1	5.8	138	14	0.6	12.2
403	8	54	215	37	0	7.9	5.6	123	11	0.6	11.4
404	23	54	83	33	1	7.9	5.7	108	15	0.7	11.7
405	20	42	72	41	0	7.5	5.3	110	15	0.5	11.4
406	15	49	59	58	0	7.1	4.8	114	14	0.5	11.5
408	21	31	77	47	0	8.4	5.9	124	15	0.7	12.2
409	13	55	65	39	0	6.7	4.8	113	13	0.5	10.8
410	19	36	67	37	1	8.1	5.7	123	13	0.6	12.2
411	19	50	72	31	0	7.6	5.5	119	14	0.6	12.1
412	14	38	63	34	0	8.3	6.3	117	14	0.6	11.9
413	16	29	78	36	0	8.6	6.3	115	16	0.6	11.8
414	15	53	66	30	2	7.4	5.4	110	13	0.6	12
415	11	35	56	34	0	8	5.7	125	13	0.6	11.7

NT = Not taken

Table C-3. Individual Animal Serum Chemistry Parameters, Day 91

Animal	Sorbitol Dehydrogenase (μ/L)	Alkaline Phosphatase (μ/L)	Aspartate Amino-transferase (μ/L)	Alanine Amino-transferase (μ/L)	Gamma Glutamyl Transferase (μ/L)	Total Protein (g/dL)	Albumin (g/dL)	Glucose (mg/dL)	Blood Urea Nitrogen (mg/dL)	Creatinine (mg/dL)	Calcium (mg/dL)
Male Mice											
501	45	80	113	26	0	5.6	4	162	20	0.3	10
502	45	90	49	21	0	5.5	4	168	23	NT	9.6
503	53	84	57	26	0	5.9	4	184	25	0.3	9.7
504	48	95	56	17	2	5.7	3.7	170	19	0.3	9.5
505	49	82	71	24	1	5.5	3.8	186	24	0.3	9.4
506	42	90	48	24	0	5.6	3.9	148	28	0.3	9.8
507	55	104	166	32	NT	NT	NT	NT	NT	NT	NT
508	43	93	48	41	0	5.6	3.9	187	21	0.3	9.6
509	44	81	61	21	NT	NT	NT	NT	NT	NT	NT
510	45	96	51	21	1	5.6	3.8	178	22	0.3	9.3
511	65	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
512	50	80	67	18	1	5.7	4	171	32	0.3	9.8
513	42	64	75	25	1	5.6	3.7	155	24	0.3	10
514	46	95	58	25	0	5.7	3.9	160	25	0.3	10
515	38	70	63	22	3	5.5	3.3	158	22	0.2	9.6
601	169	91	161	69	0	5.5	3.7	166	19	0.3	9.8
602	45	85	65	25	NT	NT	NT	NT	NT	NT	NT
603	54	89	88	26	0	6.2	4.1	176	22	0.3	10
604	52	85	85	25	0	5.7	4.1	NT	NT	NT	NT
605	46	96	114	26	0	5.4	NT	190	NT	NT	9.6
606	46	92	50	18	0	5.6	3.8	169	27	0.3	9.5
607	49	106	53	20	0	5.8	4	164	23	0.4	9.8
608	48	80	65	24	1	5.7	4	153	26	0.3	10.2
609	49	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
610	40	69	49	22	2	5.6	3.8	192	23	0.3	10
611	51	92	66	26	1	5.8	NT	188	NT	NT	9.6
612	52	82	75	24	0	5.5	3.7	158	30	0.3	9.7
613	49	95	189	35	NT	NT	NT	NT	NT	NT	NT
614	47	95	60	24	1	5.5	3.8	178	21	0.3	9.8
615	47	91	92	23	0	5.8	3.9	176	21	0.3	10

NT = Not taken

Table C-3. Individual Animal Serum Chemistry Parameters, Day 91

Animal	Sorbitol Dehydrogenase (μ/L)	Alkaline Phosphatase (μ/L)	Aspartate Amino-transferase (μ/L)	Alanine Amino-transferase (μ/L)	Gamma Glutamyl Transferase (μ/L)	Total Protein (g/dL)	Albumin (g/dL)	Glucose (mg/dL)	Blood Urea Nitrogen (mg/dL)	Creatinine (mg/dL)	Calcium (mg/dL)
Male Mice											
701	40	93	170	27	0	5.3	NT	161	NT	NT	NT
702	49	90	109	26	2	5.9	4	170	25	0.3	9.9
703	42	91	54	21	0	5.3	3.8	188	23	0.3	9.5
704	52	82	78	20	1	5.8	NT	NT	NT	NT	NT
705	49	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
706	NT	72	99	20	0	4.9	NT	178	25	0.3	9.2
707	52	99	170	32	0	5.8	4.1	164	25	0.3	9.6
708	49	70	64	22	0	5.4	3.9	209	20	0.3	9.7
709	47	85	43	21	0	5.7	4	170	23	0.3	9.8
710	69	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
712	49	81	65	22	0	5.4	3.8	170	23	0.3	9.7
713	49	92	67	23	NT	NT	NT	NT	NT	NT	NT
714	54	88	52	25	0	5.9	NT	180	24	NT	9.7
715	51	79	55	26	0	5.6	3.8	191	19	0.3	9.9
801	45	97	66	22	0	5.4	NT	164	22	0.3	9.6
804	41	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
805	41	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
806	50	102	51	NT	NT	NT	NT	NT	NT	NT	9.4
807	48	85	107	35	0	5.5	NT	194	NT	NT	9.5
808	39	83	41	19	0	5.5	3.8	174	19	0.3	9.8
809	45	87	70	22	0	5.8	3.9	186	19	0.3	9.8
810	42	64	46	21	0	5.6	3.7	193	23	0.4	9.8
811	45	80	57	22	0	5.7	4	187	21	0.2	8.7
812	47	80	57	16	0	5.5	3.9	164	22	0.3	9.5
813	44	86	47	18	0	5.6	4	178	22	0.4	9.8
814	45	85	102	23	0	5.4	3.8	164	21	0.3	9.8
815	45	89	71	23	0	5.8	NT	186	24	NT	9.8

NT = Not taken

Table C-3. Individual Animal Serum Chemistry Parameters, Day 91

Animal	Phosphorus (mg/dL)	Creatine Kinase (μ/L)	Lactate Dehydrogenase (μ/L)	Triglycerides (mg/dL)	Cholesterol (mg/dL)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Globulin (g/dL)	AG Ratio	Methemoglobin (g/dL)
101	7.5	208	93	36	67	155	7.3	103	2.4	2.29	0.4
102	8.0	104	80	46	65	152	7.3	102	3.1	1.94	0.3
103	7.6	261	124	53	51	153	6.4	104	2.6	2	0.3
104	8.4	188	308	32	76	153	7.9	104	2.2	2.27	0.3
105	9.1	219	178	43	82	152	8.6	105	2.6	2.19	0.3
106	7.7	163	114	46	72	150	7.6	105	2.8	1.89	0.3
107	6.7	179	94	45	80	149	6	100	2.1	2.48	0.2
108	6.6	212	347	88	61	147	6.6	104	2.2	2.36	0.2
109	5.3	108	74	60	87	152	6.9	106	2.4	2.5	0.2
110	7.0	72	53	95	96	147	6.7	101	2.5	2.48	0.3
111	7.8	286	265	47	62	156	7.7	108	2.8	2.18	0.3
112	9.5	264	169	31	71	156	7.4	107	2.8	2.07	0.3
113	6.6	388	135	31	52	156	7.1	106	2.4	2.17	0.3
114	6.7	138	81	60	60	154	7.4	106	2.3	2.39	0.3
115	8.1	108	72	95	95	154	7.1	102	2.8	2.07	0.3
201	9.0	204	242	35	81	154	8.1	107	2.9	1.97	0.3
202	8.0	220	114	49	57	151	7.3	104	2	2.85	0.2
203	8.1	232	224	45	50	147	6.8	102	2.2	2.23	0.2
204	7.5	167	91	84	108	151	6.8	103	2.2	2.64	0.2
205	8.5	165	102	74	92	149	6.9	103	2.7	2.26	0.2
206	8.3	109	80	33	82	153	6.9	105	2.3	2.3	0.3
207	9.1	242	113	68	66	153	7.4	104	2.4	2.13	0.3
208	8.3	220	94	41	89	151	6.5	103	2.7	1.74	0.3
209	6.5	512	197	45	70	146	5.8	101	1.8	3.39	0.3
210	7.8	293	244	25	106	148	6.1	101	2.2	2.82	0.3
211	7.3	92	78	42	55	149	7	101	2.4	2.08	0.3
212	9.2	138	82	28	80	150	7.2	101	2.6	2	0.3
213	8.2	105	65	23	75	149	6.9	101	1.8	2.94	0.2
214	8.7	146	80	37	56	152	7.2	106	2	2.7	0.3
215	8.2	271	210	27	47	149	7	104	2.5	1.92	0.2
301	8.0	84	82	31	61	146	6.2	102	2	2.7	0.2
302	6.8	290	200	31	111	144	6.8	101	2.3	2.65	0.2
303	7.8	1571	433	40	61	150	7.3	104	2.6	2	NT
304	7.8	149	102	29	64	145	6.6	103	2.2	2.41	0.3
305	7.9	157	142	46	95	147	6.1	102	2.5	2.36	0.2

NT = Not taken

Table C-3. Individual Animal Serum Chemistry Parameters, Day 91

Animal	Phosphorus (mg/dL)	Creatine Kinase (μ/L)	Lactate Dehydrogenase (μ/L)	Triglycerides (mg/dL)	Cholesterol (mg/dL)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Globulin (g/dL)	AG Ratio	Methemoglobin (g/dL)
Female Rats											
306	9.0	302	125	33	70	149	7.4	105	2.1	2.33	0.3
307	8.0	986	514	67	123	150	6.6	103	2.5	2.52	0.3
308	8.9	406	176	31	72	153	5.9	107	2.1	2.57	0.3
309	8.1	95	70	82	86	152	7.3	104	2.6	2.31	0.2
310	8.3	114	55	39	134	154	6.3	105	2.5	2.72	0.3
311	7.2	105	84	38	48	151	7.2	105	2.3	2.22	0.3
312	8.2	243	175	29	71	148	7	105	2	2.55	0.2
313	8.9	219	113	59	90	151	6.9	103	2.2	2.86	0.3
314	7.1	79	71	21	57	147	6.1	101	2.3	1.96	0.2
315	7.8	131	92	67	76	153	7.3	105	2.6	2.38	0.3
401	8.4	124	85	43	94	152	7.9	104	2.5	2.52	0.3
402	7.7	157	95	30	88	150	7.2	105	2.3	2.52	0.3
403	6.7	473	803	33	72	147	6.3	103	2.3	2.43	0.2
404	7.4	146	90	34	88	153	7.5	107	2.2	2.59	0.2
405	7.9	171	92	71	77	143	5.8	102	2.2	2.41	NT
406	7.7	96	72	35	91	147	6.6	102	2.3	2.09	0.3
408	8.0	198	190	31	100	151	7.3	105	2.5	2.36	NT
409	7.2	120	60	33	69	148	5.7	103	1.9	2.53	0.3
410	7.9	136	74	30	76	147	7.4	102	2.4	2.38	0.2
411	9.1	143	79	25	60	151	7.6	104	2.1	2.62	0.3
412	8.4	137	72	40	99	151	6.3	103	2	3.15	0.3
413	7.7	259	357	23	92	152	7.1	107	2.3	2.74	0.2
414	7.3	102	55	45	85	149	6.7	103	2	2.7	0.3
415	7.6	124	69	61	102	147	5.7	101	2.3	2.48	0.3

NT = Not taken

Table C-3. Individual Animal Serum Chemistry Parameters, Day 91

Animal	Phosphorus (mg/dL)	Creatine Kinase (μ/L)	Lactate Dehydrogenase (μ/L)	Triglycerides (mg/dL)	Cholesterol (mg/dL)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Globulin (g/dL)	AG Ratio
501	0.5	460	237	55	91	152	9.3	109	1.6	2.5
502	NT	101	153	80	87	149	8.4	109	1.5	2.67
503	6.5	130	156	70	108	152	8.9	109	1.9	2.11
504	6.4	67	116	44	84	153	8.2	109	2	1.85
505	7.9	192	186	53	111	152	8.7	107	1.7	2.24
506	7.1	115	154	94	88	155	8.6	111	1.7	2.29
507	NT	NT	NT	NT	NT	150	8.7	106	NT	NT
508	88	88	135	71	91	153	8.5	110	1.7	2.29
509	NT	NT	NT	NT	NT	153	8.3	110	NT	NT
510	6.9	124	134	66	111	153	8.8	107	1.8	2.11
511	NT	NT	NT	NT	NT	148	8.2	110	NT	NT
512	7.3	171	161	75	107	154	9.4	110	1.7	2.35
513	6.8	247	180	73	126	153	8.6	110	1.9	1.95
514	6.8	119	162	60	111	153	8.8	108	1.8	2.17
515	7.7	131	179	88	100	152	8.4	107	2.2	1.5
601	6.6	82	176	52	67	154	8.1	108	1.8	2.06
602	NT	NT	NT	NT	NT	149	8.5	111	NT	NT
603	8.6	275	182	52	109	154	9.7	110	2.1	1.95
604	NT	356	221	NT	NT	152	8.7	109	1.6	2.56
605	NT	588	275	70	NT	151	8.3	109	NT	NT
606	6.7	104	143	97	105	152	8.6	108	1.8	2.11
607	7.6	84	147	98	115	154	9.4	110	1.8	2.22
608	7.1	189	153	72	98	155	8.5	109	1.7	2.35
609	NT	NT	NT	NT	NT	151	8.9	109	NT	NT
610	7.7	68	136	79	125	153	8.4	107	1.8	2.11
611	NT	185	176	55	NT	153	8.3	107	NT	NT
612	8.0	237	190	121	122	151	8.7	109	1.8	2.06
613	NT	NT	NT	NT	NT	151	9	110	NT	NT
614	7.6	146	155	63	101	152	9.3	108	1.7	2.24
615	7.6	300	229	42	104	152	8.7	107	1.9	2.05
701	NT	749	302	NT	NT	152	8.6	108	NT	NT
702	8.2	451	220	135	134	154	9	110	1.9	2.11
703	7.3	132	115	79	109	154	8.2	109	1.5	2.53
704	NT	207	171	NT	NT	153	8.7	109	NT	NT
705	NT	NT	NT	NT	NT	151	9.3	110	NT	NT
706	8.1	363	248	NT	NT	149	8.9	109	NT	NT
707	6.9	730	333	87	124	154	8.5	110	1.7	2.41

NT = Not taken

Table C-3. Individual Animal Serum Chemistry Parameters, Day 91

Animal	Phosphorus (mg/dL)	Creatine Kinase (μ/L)	Lactate Dehydrogenase (μ/L)	Triglycerides (mg/dL)	Cholesterol (mg/dL)	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)	Globulin (g/dL)	AG Ratio
Female Rats										
708	7.7	194	172	72	114	151	8.4	106	1.5	2.6
709	6.6	47	125	78	106	153	8.6	110	1.7	2.35
710	NT	NT	NT	NT	NT	148	8.6	110	NT	NT
712	7.6	174	148	66	113	153	8.2	110	1.6	2.38
713	NT	NT	NT	NT	NT	151	9.3	109	NT	NT
714	NT	108	171	79	112	151	8.9	105	NT	NT
715	7.7	120	156	49	111	152	9	108	1.8	2.11
801	6.9	232	162	68	118	151	8.6	107	NT	NT
804	NT	NT	NT	NT	NT	149	9.4	112	NT	NT
805	NT	NT	NT	NT	NT	148	9.2	110	NT	NT
806	NT	NT	NT	NT	NT	154	8.7	109	NT	NT
807	NT	443	271	42	NT	154	7.3	110	NT	NT
808	6.4	78	93	46	116	154	7.3	108	1.7	2.24
809	7.1	225	149	65	144	152	8.7	106	1.9	2.05
810	6.9	79	154	43	116	153	8.6	108	1.9	1.95
811	7.1	140	134	76	139	152	8.7	108	1.7	2.35
812	6.3	130	148	54	122	155	8.6	113	1.6	2.44
813	7.2	83	112	41	125	154	9.1	111	1.6	2.5
814	7.3	404	199	69	119	155	8.5	111	1.6	2.38
815	NT	180	160	76	125	155	8.1	110	NT	NT

NT = Not taken

APPENDIX D

Table D-1.	Individual Animal Organ Weights (g)	D-2
Table D-2.	Individual Animal Organ-to-Body Weight Ratios	D-6
Table D-3.	Individual Animal Organ-to-Brain Weight Ratios	D-10

Table D-1. Individual Animal Organ Weights (g)

Animal	Brain	Heart	Kidney	Liver	Lung	Ovary	Spleen	Adrenal Gland	Thyroid Gland	Pituitary Gland	
	Female Rats										
101	1.843	0.977	1.859	7.427	1.472	0.148	0.473	0.067	0.023	0.019	
102	1.896	0.977	1.706	7.332	1.509	0.112	0.538	0.081	0.039	0.020	
103	2.042	1.162	1.994	8.679	1.510	0.121	0.700	0.058	0.023	0.022	
104	1.981	0.856	1.965	7.803	1.185	0.084	0.485	0.063	0.019	0.017	
105	1.693	0.875	1.856	7.630	1.335	0.142	0.490	0.055	0.025	0.019	
106	1.937	0.951	1.867	8.352	1.331	0.118	0.609	0.063	0.034	0.023	
107	1.888	1.217	2.475	10.552	1.754	0.153	0.705	0.061	0.025	0.021	
108	2.080	0.986	1.924	9.068	1.452	0.110	0.455	0.078	0.024	0.024	
109	1.836	1.073	1.806	8.097	1.520	0.118	0.547	0.071	0.020	0.020	
110	1.960	1.066	2.192	11.203	1.639	0.099	0.562	0.063	0.017	0.027	
111	1.878	1.108	1.951	8.678	1.418	0.111	0.435	0.060	0.018	0.021	
112	1.880	1.067	1.850	7.472	1.687	0.124	0.515	0.058	0.020	0.017	
113	1.928	1.216	1.836	8.516	1.633	0.157	0.473	0.084	0.018	0.016	
114	1.930	1.062	1.880	7.260	1.461	0.134	0.496	0.063	0.024	0.015	
115	2.006	1.090	1.871	8.515	1.547	0.145	0.573	0.042	0.020	0.019	
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	
201	1.881	1.016	1.793	8.090	1.300	0.133	0.500	0.051	0.029	0.013	
202	1.958	1.036	1.892	9.192	1.450	0.150	0.563	0.079	0.022	0.021	
203	2.019	1.007	2.001	7.553	1.388	0.183	0.503	0.066	0.018	0.021	
204	1.858	1.096	1.851	8.218	1.365	0.084	0.455	0.054	0.014	0.027	
205	1.705	1.051	1.830	8.860	1.828	0.130	0.493	0.068	0.017	0.026	
206	1.865	0.957	1.961	7.533	1.601	0.123	0.525	0.078	0.020	0.019	
207	1.871	0.969	1.911	8.009	1.363	0.138	0.513	0.055	0.020	0.017	
208	1.845	1.079	1.892	7.885	1.667	0.118	0.490	0.067	0.020	0.022	
209	1.918	1.161	2.219	9.222	1.327	0.089	0.582	0.076	0.022	0.032	
210	1.895	1.015	2.070	8.838	1.641	0.122	0.443	0.076	0.022	0.030	
211	1.925	0.940	1.884	9.032	1.446	0.102	0.515	0.070	0.035	0.026	
212	1.776	1.049	1.831	8.399	1.635	0.119	0.492	0.059	0.029	0.025	
213	1.870	0.941	1.954	7.500	1.373	0.116	0.447	0.059	0.033	0.023	
214	1.913	0.974	1.804	7.137	1.348	0.113	0.449	0.065	0.020	0.015	
215	1.897	0.913	1.607	7.118	1.063	0.105	0.442	0.052	0.023	0.027	
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	

Table D-1. Individual Animal Organ Weights (g)

Animal	Brain	Heart	Kidney	Liver	Lung	Ovary	Spleen	Adrenal Gland	Thyroid Gland	Pituitary Gland	
	Female Rats										
301	1.937	1.012	1.809	8.405	1.543	0.161	0.470	0.062	0.025	0.015	
302	1.634	0.974	2.183	8.328	1.478	0.102	0.483	0.059	0.021	0.028	
303	1.923	0.953	1.909	7.461	1.301	0.088	0.384	0.060	0.019	0.017	
304	1.829	0.865	1.779	7.513	1.525	0.112	0.494	0.067	0.014	0.018	
305	1.751	0.890	1.770	9.343	1.170	0.085	0.451	0.052	0.027	0.023	
306	1.798	0.924	1.814	7.344	1.361	0.111	0.423	0.064	0.030	0.023	
307	1.966	1.338	2.506	11.919	1.705	0.098	0.571	0.084	0.032	0.033	
308	1.903	1.036	2.187	8.800	1.448	0.134	0.691	0.055	0.026	0.021	
309	1.836	1.008	1.788	8.340	1.409	0.112	0.467	0.059	0.019	0.018	
310	1.772	1.090	2.000	8.810	1.457	0.092	0.440	0.064	0.015	0.024	
311	1.808	0.985	1.865	7.912	1.221	0.136	0.516	0.073	0.021	0.023	
312	1.936	0.908	1.827	8.155	1.286	0.140	0.573	0.084	0.017	0.018	
313	1.817	1.272	2.210	10.398	1.273	0.118	0.556	0.074	0.025	0.029	
314	1.871	1.148	2.140	9.809	1.744	0.129	0.544	0.069	0.035	0.021	
315	1.949	1.094	2.021	9.505	1.330	0.153	0.479	0.072	0.031	0.030	
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	
401	1.832	0.864	1.893	10.130	1.143	0.107	0.454	0.060	0.024	0.015	
402	1.924	1.076	2.249	11.899	1.563	0.149	0.531	0.070	0.025	0.017	
403	1.864	0.992	1.997	11.047	1.213	0.169	0.553	0.088	0.025	0.020	
404	1.724	1.054	1.947	11.419	1.580	0.136	0.478	0.053	0.019	0.020	
405	1.817	1.053	2.034	10.933	1.455	0.112	0.424	0.055	0.016	0.035	
406	1.815	1.066	2.193	11.960	1.495	0.141	0.676	0.068	0.019	0.022	
408	1.898	1.271	2.376	12.682	1.768	0.097	0.553	0.077	0.024	0.028	
409	1.940	1.057	2.200	10.856	1.473	0.119	0.693	0.050	0.019	0.019	
410	1.952	0.924	2.002	10.637	1.419	0.127	0.413	0.068	0.021	0.013	
411	1.904	1.004	1.927	9.804	1.291	0.138	0.407	0.063	0.026	0.020	
412	1.705	0.905	1.805	10.611	1.447	0.078	0.362	0.066	0.024	0.019	
413	1.728	1.162	2.065	10.523	1.535	0.151	0.466	0.057	0.025	0.016	
414	1.842	0.838	1.720	9.432	1.423	0.150	0.488	0.062	0.024	0.024	
415	1.954	1.292	2.581	14.392	1.482	0.080	0.544	0.067	0.030	0.033	
(N)	(14)	(14)	(14)	(14)	(14)	(14)	(14)	(14)	(14)	(14)	

Table D-1. Individual Animal Organ Weights (g)

Animal	Brain	Heart	Kidney	Liver	Lung	Testis	Spleen	Adrenal Gland
	Male Mice							
501	0.450	0.144	0.377	1.360	0.217	0.204	0.061	0.006
502	0.427	0.151	0.394	1.439	0.224	0.202	0.061	0.003
503	0.448	0.155	0.388	1.534	0.192	0.163	0.084	0.009
504	0.450	0.188	0.462	1.246	0.167	0.189	0.084	0.009
505	0.426	0.169	0.429	1.602	0.213	0.185	0.061	0.012
506	0.462	0.145	0.381	1.516	0.219	0.180	0.061	0.007
507	0.474	0.178	0.404	1.518	0.187	0.213	0.073	0.006
508	0.403	0.147	0.365	1.414	0.211	0.185	0.059	0.013
509	0.443	0.174	0.442	1.544	0.169	0.126	0.061	0.006
510	0.451	0.167	0.394	1.546	0.182	0.168	0.073	0.009
511	0.435	0.153	0.442	1.686	0.180	0.215	0.079	0.005
512	0.428	0.145	0.413	1.461	0.218	0.204	0.076	0.007
513	0.410	0.158	0.399	1.542	0.276	0.205	0.083	0.014
514	0.415	0.148	0.379	1.391	0.179	0.173	0.080	0.012
515	0.436	0.146	0.384	1.451	0.185	0.150	0.098	0.010
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)
601	0.471	0.184	0.515	1.172	0.199	0.132	0.114	0.007
602	0.441	0.145	0.365	1.386	0.206	0.207	0.079	0.012
603	0.416	0.161	0.399	1.435	0.232	0.185	0.072	0.011
604	0.426	0.151	0.382	1.403	0.202	0.201	0.069	0.010
605	0.383	0.133	0.372	1.363	0.165	0.190	0.065	0.012
606	0.443	0.153	0.354	1.455	0.162	0.181	0.081	0.006
607	0.427	0.153	0.422	1.491	0.167	0.140	0.084	0.012
608	0.433	0.160	0.403	1.504	0.205	0.211	0.063	0.005
609	0.426	0.145	0.411	1.546	0.211	0.204	0.073	0.017
610	0.439	0.158	0.394	1.593	0.185	0.194	0.076	0.009
611	0.405	0.149	0.420	1.553	0.159	0.176	0.078	0.010
612	0.440	0.191	0.437	1.811	0.178	0.193	0.088	0.005
613	0.420	0.157	0.386	1.527	0.170	0.128	0.071	0.008
614	0.429	0.147	0.390	1.346	0.221	0.180	0.072	0.002
615	0.451	0.186	0.379	1.476	0.204	0.149	0.069	0.010
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)

Table D-1. Individual Animal Organ Weights (g)

Animal	Brain	Heart	Kidney	Liver	Lung	Testis	Spleen	Adrenal Gland
	Male Mice							
701	0.412	0.150	0.392	1.449	0.230	0.173	0.067	0.014
702	0.428	0.168	0.424	1.767	0.173	0.136	0.078	0.009
703	0.407	0.151	0.370	1.461	0.208	0.188	0.076	0.004
704	0.410	0.156	0.374	1.456	0.197	0.202	0.065	0.013
705	0.427	0.147	0.349	1.394	0.148	0.204	0.061	0.007
706	0.466	0.167	0.378	1.332	0.190	0.167	0.064	0.009
707	0.404	0.160	0.368	1.468	0.184	0.188	0.067	0.004
708	0.446	0.147	0.384	1.616	0.161	0.171	0.067	0.006
709	0.414	0.158	0.446	1.697	0.202	0.204	0.076	0.021
710	0.392	0.184	0.398	1.801	0.594	0.147	0.157	0.008
711	0.437	0.170	0.361	1.345	0.200	0.164	0.068	0.010
712	0.441	0.155	0.408	1.404	0.171	0.193	0.072*	0.005
713	0.432	0.138	0.406	1.440	0.204	0.196	0.070	0.007
714	0.422	0.143	0.386	1.391	0.180	0.193	0.064	0.008
715	0.406	0.149	0.421	1.371	0.224	0.194	0.064	0.005
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)
801	0.449	0.182	0.459	1.833	0.230	0.225	0.084	0.013
802	0.442	0.155	0.412	1.644	0.259	0.194	0.067	0.008
804	0.401	0.120	0.364	1.341	0.195	0.163	0.068	0.012
805	0.425	0.151	0.383	1.690	0.154	0.187	0.091	0.004
806	0.435	0.148	0.411	1.669	0.300	0.124	0.070	0.005
807	0.419	0.145	0.361	1.397	0.215	0.117	0.079	0.005
808	0.427	0.137	0.392	1.442	0.197	0.181	0.065	0.006
809	0.449	0.150	0.373	1.581	0.181	0.197	0.072	0.005
810	0.458	0.161	0.408	1.605	0.203	0.191	0.088	0.007
811	0.466	0.160	0.420	1.595	0.192	0.199	0.070	0.011
812	0.416	0.152	0.360	1.454	0.190	0.208	0.059	0.006
813	0.436	0.150	0.412	1.448	0.161	0.190	0.066	0.005
814	0.419	0.149	0.400	1.533	0.205	0.182	0.069	0.005
815	0.418	0.132	0.346	1.374	0.162	0.184	0.067	0.008
(N)	(14)	(14)	(14)	(14)	(14)	(14)	(14)	(14)

Table D-2. Individual Animal Organ-to-Body Weight Ratios

Animal	Brain	Heart	Kidney	Liver	Lung	Ovary	Spleen	Adrenal Gland	Thyroid Gland	Pituitary Gland
Female Rats										
101	0.671	0.356	0.677	2.704	0.536	0.054	0.172	0.025	0.009	0.007
102	0.814	0.419	0.732	3.147	0.648	0.048	0.231	0.035	0.017	0.009
103	0.679	0.386	0.663	2.884	0.502	0.040	0.233	0.019	0.008	0.007
104	0.788	0.340	0.781	3.101	0.471	0.033	0.193	0.025	0.007	0.007
105	0.619	0.320	0.679	2.790	0.488	0.052	0.179	0.020	0.009	0.007
106	0.694	0.341	0.669	2.991	0.477	0.042	0.218	0.023	0.012	0.008
107	0.602	0.388	0.789	3.363	0.559	0.049	0.225	0.020	0.008	0.007
108	0.645	0.306	0.597	2.814	0.451	0.034	0.141	0.024	0.007	0.007
109	0.699	0.409	0.688	3.084	0.579	0.045	0.208	0.027	0.008	0.008
110	0.612	0.333	0.685	3.500	0.512	0.031	0.176	0.020	0.005	0.008
111	0.724	0.427	0.752	3.347	0.547	0.043	0.168	0.023	0.007	0.008
112	0.671	0.381	0.660	2.666	0.602	0.044	0.184	0.021	0.007	0.006
113	0.724	0.457	0.690	3.199	0.614	0.059	0.178	0.032	0.007	0.006
114	0.655	0.360	0.638	2.463	0.496	0.045	0.168	0.021	0.008	0.005
115	0.749	0.407	0.699	3.182	0.578	0.054	0.214	0.016	0.008	0.007
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)
201	0.668	0.361	0.637	2.873	0.462	0.047	0.177	0.018	0.010	0.004
202	0.663	0.351	0.640	3.111	0.491	0.051	0.191	0.027	0.007	0.007
203	0.723	0.361	0.717	2.634	0.497	0.065	0.180	0.024	0.006	0.007
204	0.689	0.406	0.686	3.047	0.506	0.031	0.169	0.020	0.005	0.010
205	0.594	0.366	0.638	3.087	0.637	0.045	0.172	0.024	0.006	0.009
206	0.763	0.391	0.802	3.082	0.655	0.050	0.215	0.032	0.008	0.008
207	0.666	0.345	0.680	2.851	0.485	0.049	0.183	0.020	0.007	0.006
208	0.604	0.353	0.620	2.584	0.546	0.039	0.160	0.022	0.007	0.007
209	0.635	0.384	0.735	3.054	0.439	0.030	0.193	0.025	0.007	0.010
210	0.733	0.393	0.801	3.420	0.635	0.047	0.172	0.029	0.008	0.011
211	0.637	0.311	0.623	2.987	0.478	0.034	0.170	0.023	0.012	0.009
212	0.632	0.373	0.651	2.988	0.582	0.042	0.175	0.021	0.010	0.009
213	0.708	0.356	0.739	2.839	0.520	0.044	0.169	0.022	0.012	0.009
214	0.725	0.369	0.684	2.704	0.511	0.043	0.170	0.025	0.007	0.006
215	0.714	0.344	0.605	2.679	0.400	0.039	0.167	0.020	0.009	0.010
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)

Table D-2. Individual Animal Organ-to-Body Weight Ratios

Animal	Brain	Heart	Kidney	Liver	Lung	Ovary	Spleen	Adrenal Gland	Thyroid Gland	Pituitary Gland
	Female Rats									
301	0.736	0.385	0.687	3.193	0.586	0.061	0.179	0.024	0.010	0.006
302	0.593	0.354	0.792	3.023	0.537	0.037	0.175	0.022	0.008	0.010
303	0.687	0.341	0.683	2.667	0.465	0.031	0.137	0.021	0.007	0.006
304	0.709	0.336	0.690	2.914	0.592	0.044	0.192	0.026	0.005	0.007
305	0.705	0.358	0.713	3.761	0.471	0.034	0.181	0.021	0.011	0.009
306	0.592	0.304	0.597	2.416	0.448	0.036	0.139	0.021	0.010	0.008
307	0.585	0.398	0.746	3.546	0.507	0.029	0.170	0.025	0.009	0.010
308	0.682	0.371	0.784	3.155	0.519	0.048	0.248	0.020	0.009	0.008
309	0.651	0.358	0.634	2.959	0.500	0.040	0.166	0.021	0.007	0.006
310	0.682	0.420	0.769	3.390	0.561	0.035	0.169	0.025	0.006	0.009
311	0.691	0.376	0.713	3.024	0.467	0.052	0.197	0.028	0.008	0.009
312	0.639	0.300	0.604	2.694	0.425	0.046	0.189	0.028	0.006	0.006
313	0.600	0.420	0.730	3.433	0.420	0.039	0.183	0.024	0.008	0.010
314	0.563	0.346	0.645	2.954	0.525	0.039	0.164	0.021	0.010	0.006
315	0.616	0.346	0.638	3.001	0.420	0.048	0.151	0.023	0.010	0.009
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)
401	0.724	0.342	0.749	4.007	0.452	0.042	0.180	0.024	0.010	0.006
402	0.702	0.393	0.821	4.343	0.570	0.054	0.194	0.025	0.009	0.006
403	0.704	0.374	0.754	4.172	0.458	0.064	0.209	0.033	0.009	0.008
404	0.616	0.377	0.696	4.081	0.565	0.049	0.171	0.019	0.007	0.007
405	0.584	0.339	0.654	3.514	0.468	0.036	0.136	0.018	0.005	0.011
406	0.600	0.352	0.725	3.951	0.494	0.047	0.223	0.023	0.006	0.007
408	0.650	0.435	0.813	4.340	0.605	0.033	0.189	0.026	0.008	0.010
409	0.717	0.390	0.813	4.009	0.544	0.044	0.256	0.018	0.007	0.007
410	0.734	0.348	0.753	4.000	0.534	0.048	0.155	0.026	0.008	0.005
411	0.710	0.374	0.718	3.654	0.481	0.051	0.152	0.023	0.010	0.007
412	0.753	0.400	0.798	4.689	0.640	0.034	0.160	0.029	0.010	0.008
413	0.663	0.446	0.792	4.037	0.589	0.058	0.179	0.022	0.010	0.006
414	0.745	0.339	0.696	3.814	0.576	0.061	0.197	0.025	0.010	0.010
415	0.572	0.378	0.756	4.216	0.434	0.023	0.159	0.020	0.009	0.010
(N)	(14)	(14)	(14)	(14)	(14)	(14)	(14)	(14)	(14)	(14)

Table D-2. Individual Animal Organ-to-Body Weight Ratios

Animal	Brain	Heart	Kidney	Liver	Lung	Testis	Spleen	Adrenal Gland
	Male Mice							
501	1.698	0.544	1.421	5.132	0.819	0.768	0.231	0.021
502	1.504	0.533	1.386	5.068	0.788	0.712	0.215	0.011
503	1.562	0.540	1.351	5.343	0.668	0.569	0.293	0.031
504	1.529	0.638	1.571	4.238	0.569	0.644	0.286	0.030
505	1.366	0.542	1.375	5.134	0.682	0.592	0.194	0.038
506	1.681	0.528	1.386	5.512	0.795	0.654	0.222	0.024
507	1.611	0.607	1.373	5.162	0.637	0.724	0.249	0.019
508	1.477	0.538	1.338	5.179	0.772	0.677	0.217	0.046
509	1.566	0.615	1.561	5.455	0.599	0.445	0.215	0.022
510	1.576	0.583	1.377	5.407	0.635	0.587	0.256	0.030
511	1.437	0.504	1.459	5.565	0.594	0.710	0.260	0.018
512	1.563	0.528	1.508	5.332	0.795	0.746	0.277	0.024
513	1.408	0.544	1.371	5.299	0.947	0.703	0.284	0.047
514	1.504	0.537	1.374	5.038	0.648	0.626	0.291	0.044
515	1.547	0.517	1.362	5.144	0.656	0.531	0.348	0.037
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)
601	1.553	0.606	1.699	3.866	0.657	0.435	0.375	0.021
602	1.632	0.537	1.351	5.132	0.764	0.766	0.291	0.044
603	1.416	0.548	1.355	4.881	0.790	0.628	0.243	0.038
604	1.495	0.528	1.339	4.924	0.708	0.705	0.244	0.036
605	1.498	0.521	1.451	5.324	0.643	0.742	0.252	0.045
606	1.615	0.559	1.291	5.309	0.591	0.659	0.297	0.022
607	1.487	0.534	1.469	5.194	0.582	0.488	0.291	0.043
608	1.552	0.573	1.443	5.391	0.735	0.756	0.224	0.016
609	1.449	0.493	1.399	5.257	0.717	0.692	0.247	0.057
610	1.454	0.525	1.304	5.276	0.612	0.643	0.253	0.030
611	1.455	0.535	1.510	5.586	0.571	0.633	0.280	0.036
612	1.313	0.570	1.303	5.407	0.532	0.576	0.263	0.014
613	1.523	0.567	1.398	5.533	0.616	0.463	0.258	0.030
614	1.522	0.522	1.384	4.772	0.782	0.637	0.254	0.008
615	1.582	0.651	1.331	5.179	0.714	0.524	0.244	0.033
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)

Table D-2. Individual Animal Organ-to-Body Weight Ratios

Animal	Brain	Heart	Kidney	Liver	Lung	Testis	Spleen	Adrenal Gland
				Male Mice				
701	1.538	0.559	1.463	5.406	0.859	0.645	0.250	0.052
702	1.399	0.548	1.384	5.774	0.566	0.445	0.253	0.029
703	1.435	0.533	1.303	5.146	0.732	0.661	0.266	0.013
704	1.457	0.554	1.329	5.183	0.702	0.719	0.231	0.048
705	1.551	0.536	1.270	5.068	0.537	0.740	0.222	0.026
706	1.617	0.578	1.311	4.625	0.660	0.581	0.222	0.030
707	1.428	0.566	1.300	5.187	0.649	0.664	0.236	0.016
708	1.497	0.493	1.289	5.424	0.539	0.575	0.223	0.021
709	1.336	0.509	1.439	5.473	0.653	0.657	0.244	0.069
710	1.410	0.661	1.432	6.479	2.137	0.527	0.564	0.029
711	1.596	0.619	1.318	4.909	0.730	0.599	0.247	0.038
712	1.542	0.541	1.427	4.909	0.598	0.674	0.250	0.017
713	1.583	0.505	1.486	5.276	0.748	0.719	0.256	0.025
714	1.513	0.514	1.384	4.987	0.645	0.692	0.230	0.028
715	1.420	0.521	1.471	4.794	0.784	0.678	0.224	0.017
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)
801	1.587	0.641	1.621	6.478	0.812	0.793	0.297	0.047
802	1.493	0.522	1.392	5.553	0.874	0.656	0.225	0.026
804	1.543	0.460	1.399	5.159	0.749	0.625	0.262	0.044
805	1.540	0.546	1.386	6.124	0.556	0.677	0.331	0.016
806	1.441	0.489	1.362	5.525	0.994	0.412	0.231	0.015
807	1.657	0.571	1.428	5.523	0.849	0.460	0.311	0.019
808	1.535	0.492	1.411	5.187	0.707	0.649	0.232	0.021
809	1.512	0.503	1.257	5.323	0.609	0.662	0.241	0.016
810	1.574	0.554	1.400	5.514	0.698	0.656	0.303	0.024
811	1.506	0.517	1.359	5.161	0.623	0.642	0.225	0.036
812	1.505	0.550	1.303	5.269	0.689	0.755	0.215	0.023
813	1.548	0.530	1.460	5.133	0.572	0.675	0.235	0.018
814	1.448	0.516	1.383	5.303	0.711	0.628	0.239	0.017
815	1.526	0.481	1.261	5.014	0.590	0.671	0.246	0.030
(N)	(14)	(14)	(14)	(14)	(14)	(14)	(14)	(14)

Table D-3. Individual Animal Organ-to-Brain Weight Ratios

Animal	Heart	Kidney	Liver	Lung	Ovary	Spleen	Adrenal Gland	Thyroid Gland	Pituitary Gland
Female Rat									
101	53.01	100.86	402.87	79.86	8.02	25.65	3.66	1.27	1.05
102	51.52	89.94	386.63	79.59	5.90	28.36	4.26	2.06	1.08
103	56.92	97.62	424.99	73.94	5.92	34.28	2.82	1.13	1.08
104	43.22	99.15	393.80	59.80	4.23	24.49	3.17	0.95	0.84
105	51.65	109.62	450.60	78.83	8.37	28.95	3.26	1.47	1.09
106	49.08	96.39	431.15	68.72	6.09	31.45	3.26	1.78	1.17
107	64.46	131.13	558.97	92.89	8.09	37.33	3.25	1.32	1.13
108	47.42	92.50	436.07	69.84	5.27	21.88	3.76	1.15	1.15
109	58.44	98.37	440.99	82.76	6.43	29.79	3.86	1.08	1.08
110	54.41	111.87	571.73	83.63	5.04	28.70	3.19	0.86	1.38
111	58.99	103.90	462.17	75.49	5.92	23.14	3.19	0.98	1.12
112	56.76	98.43	397.55	89.75	6.60	27.39	3.10	1.05	0.93
113	63.10	95.24	441.79	84.74	8.13	24.52	4.37	0.91	0.81
114	55.03	97.39	376.15	75.68	6.93	25.71	3.25	1.25	0.75
115	54.34	93.29	424.56	77.12	7.25	28.55	2.08	1.01	0.93
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)
201	54.00	95.28	430.00	69.08	7.05	26.56	2.70	1.52	0.66
202	52.92	96.64	469.52	74.05	7.68	28.77	4.01	1.11	1.08
203	49.87	99.10	364.15	68.74	9.04	24.90	3.28	0.87	1.02
204	58.99	99.63	442.42	73.46	4.51	24.49	2.90	0.76	1.48
205	61.67	107.34	519.76	107.23	7.60	28.91	4.01	1.02	1.50
206	51.29	105.15	403.86	85.83	6.58	28.15	4.20	1.05	0.99
207	51.78	102.10	427.95	72.81	7.36	27.42	2.93	1.06	0.90
208	58.48	102.55	427.50	90.37	6.40	26.54	3.62	1.08	1.21
209	60.51	115.68	480.74	69.18	4.66	30.33	3.94	1.16	1.65
210	53.56	109.24	466.36	86.59	6.45	23.39	4.02	1.14	1.57
211	48.84	97.85	469.09	75.08	5.32	26.76	3.64	1.82	1.35
212	59.08	103.11	473.02	92.09	6.70	27.69	3.32	1.62	1.41
213	50.33	104.46	401.07	73.44	6.22	23.92	3.13	1.75	1.25
214	50.94	94.31	373.13	70.47	5.92	23.49	3.38	1.03	0.80
215	48.11	84.71	375.20	56.01	5.53	23.32	2.76	1.22	1.42
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)

Table D-3. Individual Animal Organ-to-Brain Weight Ratios

Animal	Heart	Kidney	Liver	Lung	Ovary	Spleen	Adrenal Gland	Thyroid Gland	Pituitary Gland
	Female Rat								
301	52.24	93.40	433.84	79.65	8.29	24.27	3.22	1.30	0.80
302	59.61	133.58	509.63	90.46	6.25	29.58	3.64	1.29	1.69
303	49.56	99.30	388.00	67.66	4.58	19.97	3.10	0.97	0.88
304	47.31	97.27	410.77	83.37	6.14	26.99	3.66	0.76	0.99
305	50.84	101.10	533.68	66.83	4.84	25.73	2.98	1.55	1.30
306	51.38	100.85	408.39	75.67	6.15	23.55	3.57	1.66	1.27
307	68.06	127.47	606.23	86.72	4.96	29.05	4.26	1.61	1.66
308	54.44	114.95	462.50	76.11	7.02	36.31	2.89	1.38	1.11
309	54.89	97.38	454.17	76.75	6.09	25.43	3.22	1.04	0.99
310	61.53	112.86	497.15	82.21	5.16	24.81	3.61	0.83	1.37
311	54.46	103.13	437.50	67.53	7.51	28.51	4.02	1.16	1.28
312	46.89	94.41	421.36	66.44	7.24	29.61	4.34	0.89	0.95
313	70.00	121.65	572.35	70.07	6.49	30.58	4.05	1.38	1.59
314	61.37	114.39	524.37	93.22	6.92	29.08	3.71	1.86	1.11
315	56.13	103.67	487.60	68.23	7.83	24.56	3.68	1.59	1.53
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)
401	47.16	103.37	553.12	62.38	5.85	24.81	3.28	1.32	0.79
402	55.91	116.90	618.44	81.22	7.75	27.60	3.61	1.27	0.88
403	53.21	107.17	592.75	65.06	9.07	29.67	4.72	1.32	1.10
404	61.13	112.94	662.41	91.67	7.90	27.71	3.09	1.09	1.15
405	57.97	111.98	601.84	80.08	6.14	23.36	3.03	0.89	1.92
406	58.72	120.85	659.06	82.39	7.79	37.24	3.76	1.06	1.20
408	66.96	125.16	668.19	93.17	5.13	29.12	4.08	1.29	1.49
409	54.46	113.41	559.51	75.91	6.15	35.71	2.55	0.95	0.96
410	47.34	102.55	544.80	72.69	6.50	21.14	3.49	1.09	0.67
411	52.76	101.23	514.98	67.84	7.25	21.36	3.29	1.37	1.02
412	53.05	105.88	622.33	84.89	4.55	21.25	3.85	1.38	1.11
413	67.22	119.47	608.95	88.83	8.71	26.98	3.29	1.46	0.94
414	45.48	93.39	512.02	77.27	8.14	26.51	3.36	1.33	1.28
415	66.10	132.05	736.49	75.84	4.08	27.84	3.44	1.54	1.69
(N)	(14)	(14)	(14)	(14)	(14)	(14)	(14)	(14)	(14)

Table D-3. Individual Animal Organ-to-Brain Weight Ratios

Animal	Heart	Kidney	Liver	Male Mice					Spleen	Adrenal Gland
				Lung	Testis	Spleen	Adrenal Gland	Adrenal Gland		
501	32.03	83.69	302.27	48.23	45.23	13.58	1.25	1.25		
502	35.46	92.18	337.05	52.39	47.35	14.29	0.73	0.73		
503	34.55	86.46	342.07	42.74	36.43	18.74	2.01	2.01		
504	41.74	102.78	277.22	37.20	42.14	18.69	1.98	1.98		
505	39.64	100.66	375.75	49.94	43.30	14.22	2.79	2.79		
506	31.43	82.44	327.90	47.26	38.91	13.22	1.45	1.45		
507	37.68	85.24	320.53	39.54	44.94	15.44	1.18	1.18		
508	36.44	90.60	350.73	52.27	45.82	14.69	3.13	3.13		
509	39.28	99.66	348.35	38.22	28.41	13.72	1.42	1.42		
510	36.96	87.36	343.04	40.26	37.25	16.26	1.89	1.89		
511	35.05	101.56	387.30	41.36	49.40	18.12	1.24	1.24		
512	33.82	96.47	341.22	50.84	47.71	17.70	1.54	1.54		
513	38.60	97.37	376.26	67.23	49.95	20.16	3.32	3.32		
514	35.71	91.40	335.08	43.11	41.64	19.37	2.94	2.94		
515	33.42	88.01	332.46	42.40	34.33	22.49	2.36	2.36		
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)		
601	38.99	109.41	248.94	42.31	27.99	24.16	1.38	1.38		
602	32.89	82.77	314.48	46.82	46.94	17.82	2.72	2.72		
603	38.72	95.72	344.68	55.80	44.37	17.18	2.69	2.69		
604	35.34	89.56	329.24	47.33	47.11	16.28	2.39	2.39		
605	34.79	96.90	355.48	42.93	49.56	16.85	3.00	3.00		
606	34.61	79.91	328.69	36.60	40.83	18.37	1.38	1.38		
607	35.92	98.76	349.27	39.15	32.83	19.56	2.86	2.86		
608	36.93	92.98	347.37	47.37	48.71	14.46	1.06	1.06		
609	34.03	96.50	362.73	49.47	47.76	17.04	3.92	3.92		
610	36.07	89.66	362.88	42.11	44.23	17.38	2.10	2.10		
611	36.75	103.76	383.84	39.20	43.52	19.25	2.50	2.50		
612	43.42	99.25	411.78	40.53	43.85	20.01	1.09	1.09		
613	37.26	91.82	363.31	40.47	30.41	16.94	2.00	2.00		
614	34.27	90.89	313.44	51.39	41.81	16.70	0.51	0.51		
615	41.17	84.14	327.40	45.14	33.10	15.40	2.11	2.11		
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)	(15)		

Table D-3. Individual Animal Organ-to-Brain Weight Ratios

Animal	Heart	Kidney	Liver	Lung	Testis	Spleen	Adrenal Gland
	Male Mice						
701	36.38	95.15	351.57	55.86	41.93	16.26	3.40
702	39.19	98.90	412.63	40.47	31.78	18.10	2.08
703	37.16	90.82	358.71	51.01	46.10	18.53	0.91
704	38.05	91.21	355.63	48.18	49.35	15.85	3.27
705	34.54	81.90	326.80	34.65	47.71	14.30	1.69
706	35.78	81.10	286.10	40.85	35.95	13.72	1.87
707	39.67	91.04	363.25	45.43	46.52	16.51	1.09
708	32.92	86.14	362.40	36.03	38.43	14.93	1.39
709	38.11	107.73	409.71	48.85	49.17	18.28	5.14
710	46.88	101.53	459.35	151.52	37.39	39.99	2.09
711	38.82	82.62	307.66	45.75	37.56	15.49	2.36
712	35.07	92.50	318.27	38.74	43.73	16.23	1.11
713	31.89	93.89	333.35	47.26	45.43	16.18	1.57
714	33.94	91.45	329.54	42.63	45.76	15.21	1.85
715	36.72	103.57	337.60	55.23	47.77	15.81	1.21
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)
801	40.41	102.12	408.10	51.18	49.98	18.70	2.96
802	34.96	93.24	371.90	58.55	43.96	15.05	1.72
804	29.83	90.66	334.26	48.54	40.52	16.97	2.87
805	35.48	90.02	397.67	36.12	43.98	21.48	1.01
806	33.94	94.51	383.41	69.00	28.56	16.04	1.06
807	34.46	86.19	333.27	51.25	27.78	18.79	1.15
808	32.03	91.89	337.84	46.06	42.29	15.14	1.34
809	33.28	83.10	351.94	40.27	43.77	15.92	1.05
810	35.20	88.99	350.45	44.38	41.71	19.28	1.53
811	34.35	90.20	342.56	41.33	42.64	14.93	2.36
812	36.53	86.52	349.99	45.80	50.16	14.30	1.54
813	34.26	94.36	331.71	36.96	43.61	15.17	1.19
814	35.62	95.51	366.13	49.07	43.38	16.51	1.19
815	31.52	82.64	328.58	38.68	43.96	16.10	1.99
(N)	(15)	(15)	(15)	(15)	(15)	(15)	(15)

APPENDIX E

Analytical Chemistry Report..... E-2



**REPORT ON DOSE ANALYSIS OF
C₉-C₁₆ AROMATIC FRACTION OF JET-A IN CORN OIL**

G003493B

January 11, 1999

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EXECUTIVE SUMMARY

A method for the analysis of C₉-C₁₆ aromatic fraction of Jet A in corn oil, was developed, validated and then used to analyze samples in support of Battelle study # G003493B "90-Day Oral Gavage Toxicity Study of C₉-C₁₆ Aromatic Fraction of Jet-A in Female Sprague-Dawley CD Rats and Male C57BL/6 Mice". Multiple peaks were present in the samples. Based on the validation data reported in Battelle Study # G003493A, three peaks (B, E and F) were used for calculation of the dose analysis results. There appeared to be a small amount of carryover for peak B in the blank; however, all standards and drifts were within acceptance criteria. All batches were found to be within all acceptance criteria.

A stability study was conducted under Battelle Study # G003493A in support of the current study. The peaks designated B-F were selected for monitoring during the stability evaluation. The overall data indicated that the doses were stable for 20 days but showed a slight decreasing trend. The data for individual components suggested that the doses were consistently stable for 7 days, but responses for Components B and E were between 89 – 92 % of the day 0 value on day 20. This data was reported with the previous study but is presented again in this report.

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ATTACHMENT B – ANALYTICAL METHOD

Analytical Method: Dose Analysis of C₉-C₁₆ Aromatic Fraction of Jet-A in Corn OilB-2

1 INTRODUCTION

This report presents a description of an analytical method for the analysis of C₉-C₁₆ aromatic fraction of Jet A (Jet-A) in corn oil, the results of the dose analyses, and the results of the stability study conducted under Battelle Study # G003493B. This work was performed at Battelle, 505 King Avenue, Columbus, OH 43201 in support of Battelle Study # G003493B "90-Day Oral Gavage Toxicity Study of C₉-C₁₆ Aromatic Fraction of Jet-A in Female Sprague-Dawley CD Rats and Male C57BL/6 Mice".

2 TEST SUBSTANCE AND SAMPLES

The doses were formulated with the test substance (C₉-C₁₆ aromatic fraction of Jet-A (Jet-A)) received from BDM Petroleum Technologies on April 21, 1998 and on August 6, 1998. Doses were submitted by the dose formulation staff of Bioanalytical Chemistry and Dose Formulation and were analyzed in support of a "90-Day Oral Gavage Toxicity Study of C₉-C₁₆ Aromatic Fraction of Jet-A in Female Sprague-Dawley CD Rats and Male C57BL/6 Mice". A sample of the test substance (lot # 97POSF 3404-AR916) was used as a reference standard and was stored refrigerated.

3 DOSE ANALYSIS

3.1 Methods

A gas chromatographic (GC) method for the analysis of Jet-A test substance in corn oil was validated under Battelle Study # G003493A. A copy of the dose analysis method used for this study is included as Attachment B.

Solvent Stock A was prepared at a target concentration of 20 mg/mL Jet-A by diluting approximately 200 mg of accurately weighed Jet-A to 10 mL with hexane. Stock B was prepared at a target concentration of 15 mg/mL in the same manner using approximately 150 mg of accurately weighed test substance.

Carrier standards VS1-VS3 with nominal concentrations of approximately 2000, 1500, and 1000 µg/mL, respectively, were made by combining 1 mL of corn oil with the appropriate volumes of Stocks A or B and diluting to 10 mL with hexane. Carrier standards VS4-VS6 were prepared at nominal concentrations of approximately 600, 300 and 150 µg/mL, respectively, by combination of appropriate volumes of VS1 and VS2 with 1 mL of Carrier and dilution to 10 mL with hexane. These standards had slightly more corn oil than the other standards and samples, but it had no effect on the calibration curve, and was therefore deemed acceptable. Single standards were prepared at all concentrations. Corn oil diluted 1:10 with hexane was used as the carrier blank.

Doses were prepared by diluting 0.5 mL of the 2, 8 and 10 mg/mL formulation to 5 mL with hexane. The 40 and 50 mg/mL doses mixed on 7/30/98 were diluted 0.5 to 5 with hexane, mixed and further diluted by combining 1 mL of diluted dose with 0.9 mL corn oil and diluting to 10 mL with hexane. Similarly, the 40 and 50 mg/mL doses mixed on all other dates were diluted 0.5 to 5 with hexane, mixed and further diluted by combining 2 mL of Battelle Study No. G003493B

diluted dose with 0.8 mL corn oil and diluting to 10 mL with hexane. The high dose (200 mg/mL) samples mixed on 7/30/98 were diluted by taking a 0.5 mL aliquot of the dose and diluting it to 25 mL with hexane. A 1 mL aliquot of this diluted dose was subsequently combined with 0.98 mL of corn oil and diluted to 10 mL with hexane. The remaining high dose samples were diluted by taking a 0.5 mL aliquot of the dose and diluting it to 10 mL with hexane. A 1 mL aliquot of this diluted dose was subsequently combined with 0.95 mL of corn oil and diluted to 10 mL with hexane. These dilutions resulted in a consistent percent of corn oil carrier in all processed standards and dose formulations.

Single samples were analyzed by GC with flame ionization detection. The system is described in Table 1. An unweighted linear regression equation was calculated correlating the concentration (x) and chromatographic responses (y) of Jet-A calibration standards. This regression equation, the chromatographic responses, and dilution factors of the diluted doses were used to calculate the concentration of Jet-A in the formulation. The symbol A/B is a measure of the agreement of the replicates and is determined by dividing the one analysis result (A) by its replicate (B). Values of 0.9 to 1.1 are normally considered acceptable.

An aliquot of each carrier standard, solvent standard and blank were transferred to autoinjector vials and analyzed with the GC conditions shown in Table 1.

TABLE 1 - GC System

Analytical Column	Restex Rtx-1 15 m X 0.53 mm, 0.25 μ m film thickness
Temperature Gradient	37 °C for 10 min., increase at 2 °C/min to 80 °C, increase to 25° C/min to 330 °C, hold 10 min.
Helium Carrier Flow Rate	~ 5 mL/min
Injection Volume	2 μ L
Detector Type	Flame Ionization
Detector Temperature	300 °C
Injector temperature	250 °C
Injection Mode	Splitless
Run Time	45 minutes

During validation, multiple peaks were monitored for possible construction of calibration curves. Components B, E and F were selected as the most suitable based on peak shape, sensitivity, linear response, and reproducibility. Calibration curves were generated for components B,E and F individually. The data for the combined components were evaluated with respect to meeting standard acceptance criteria (percent relative error (%RE) \leq 10%).

3.2 Results

The results of the dose analysis are reported in Table 2-4.

TABLE 3 - DOSE ANALYSIS RESULTS, ANALYSIS 2

Mix Date	Batch No	Target Conc. (mg/mL)	Comp. B Conc. (mg/mL)	Comp. E Conc. (mg/mL)	Comp. F Conc. (mg/mL)	Average Conc. (mg/mL)	Grand Average Conc. (mg/mL)	A/B	% Relative Error
9/17/98	10-JET-6	2	1.944	2.139	1.651	1.911	1.945	0.97	-2.7
	10-JET-6	2	1.974	2.265	1.698	1.979			
	10-JET-2	8	8.333	8.250	7.932	8.172	8.020	1.04	0.2
	10-JET-2	8	8.090	7.919	7.593	7.867			
	10-JET-7	10	10.40	10.33	9.780	10.17	10.26	0.98	2.6
	10-JET-7	10	10.48	10.58	10.00	10.35			
	10-JET-5	40	40.87	40.61	38.50	39.99	40.35	0.98	0.9
	10-JET-5	40	41.78	41.39	38.94	40.70			
	10-JET-8	50	51.05	50.95	47.92	49.97	49.81	1.01	-0.4
	10-JET-8	50	51.20	50.05	47.70	49.65			
	10-JET-4	200	199.3	196.5	186.6	194.1	195.8	0.98	-2.1
	10-JET-4	200	202.6	201.6	188.3	197.5			

TABLE 3 - DOSE ANALYSIS RESULTS, ANALYSIS 2

Mix Date	Batch No	Target Conc. (mg/mL)	Comp. B Conc. (mg/mL)	Comp. E Conc. (mg/mL)	Comp. F Conc. (mg/mL)	Average Conc. (mg/mL)	Grand Average Conc. (mg/mL)	A/B	% Relative Error
9/17/98	10-JET-6	2	1.944	2.139	1.651	1.911	1.945	0.97	-2.7
	10-JET-6	2	1.974	2.265	1.698	1.979			
	10-JET-2	8	8.333	8.250	7.932	8.172	8.020	1.04	0.2
	10-JET-2	8	8.090	7.919	7.593	7.867			
	10-JET-7	10	10.40	10.33	9.780	10.17	10.26	0.98	2.6
	10-JET-7	10	10.48	10.58	10.00	10.35			
	10-JET-3	40	40.87	40.61	38.50	39.99	40.35	0.98	0.9
	10-JET-3	40	41.78	41.39	38.94	40.70			
	10-JET-8	50	51.05	50.95	47.92	49.97	49.81	1.01	-0.4
	10-JET-8	50	51.20	50.05	47.70	49.65			
	10-JET-4	200	199.3	196.5	186.6	194.1	195.8	0.98	-2.1
	10-JET-4	200	202.6	201.6	188.3	197.5			

TABLE 4 - DOSE ANALYSIS RESULTS, ANALYSIS 3

Mix Date	Batch No	Target Conc. (mg/mL)	Comp. B Conc. (mg/mL)	Comp. E Conc. (mg/mL)	Comp. F Conc. (mg/mL)	Average Conc. (mg/mL)	Grand Average Conc. (mg/mL)	A/B	% Relative Error
10/15/98	14-JET-6	2	1.938	1.880	1.980	1.933	1.956	0.98	-2.2
	14-JET-6	2	1.965	1.976	1.994	1.978			
	14-JET-2	8	8.024	7.981	7.964	7.990	7.974	1.00	-0.3
	14-JET-2	8	8.001	7.955	7.921	7.959			
	14-JET-7	10	9.840	9.820	9.748	9.803	9.813	1.00	-1.9
	14-JET-7	10	9.874	9.762	9.836	9.824			
	14-JET-3	40	39.48	39.28	39.17	39.31	39.39	1.00	-1.5
	14-JET-3	40	39.53	39.66	39.22	39.47			
	14-JET-8	50	48.34	48.17	47.96	48.16	48.67	0.98	-2.7
	14-JET-8	50	49.31	49.21	49.01	49.18			
	14-JET-4	200	195.7	193.1	195.5	194.8	195.7	0.99	-2.1
	14-JET-4	200	197.3	196.7	196.1	196.7			

3.3 Conclusions

All calibration standards and drifts were within standard acceptance criteria (calibration standard concentrations $\leq 10\%$ RE and RSD except at the LOQ where 15% is acceptable). The average concentrations and relative errors for all doses were within acceptable limits for relative errors (dose concentrations $\leq 10\%$ RE).

4 STABILITY EVALUATION

4.1 Methods

A simulated dose was prepared by weighing 0.40929 g of Jet-A, dissolving it in corn oil and diluting to a final volume of 200 mL with corn oil. The formulation was mixed vigorously and stirred 1 hour using a magnetic mixer with a stir bar prior to use. Aliquots of ~15-mL were dispensed into 9 15-mL amber jars for use in the stability study. One bottle was sampled in triplicate to serve as the originally determined (Day 0) value for the stability study during the validation period. The remaining bottles were stored at either room temperature (~25 °C), refrigerated (~5 °C), or frozen (~-20 °C) to assess stability after 7 and 20 days of storage.

Stability samples were analyzed simultaneously with the method performance evaluation reported in G003493A. The standard preparation is described below. Stock A was prepared at a target concentration of 20 mg/mL Jet-A by dissolving approximately 500 mg of accurately weighed Jet-A in hexane and diluting to 25 mL with hexane. Stock B was prepared at a target concentration of 15 mg/mL in the same manner using approximately 375 mg of accurately weighed test substance.

Carrier standards VS1-VS3 with nominal concentrations of approximately 2000, 1500, and 1000 µg/mL, respectively, were made by combining 1 mL of corn oil with the appropriate volumes of Stocks A or B and diluting to 10 mL with hexane. Carrier standards VS4-VS6 with nominal concentrations of approximately 600, 300 and 150 µg/mL, respectively, were prepared by dilution of appropriate volumes of VS1 and VS2 with 1 mL of Carrier and diluted to 10 mL with hexane. These standards had slightly more corn oil than the other standards and samples, but it seemed to have no effect on the calibration curve, and was therefore deemed acceptable. Carrier standards were prepared in triplicate at the high and low concentrations; single standards were prepared at all other concentrations. Corn oil diluted 1:10 with hexane was used as the carrier blank and was analyzed in triplicate.

Solvent standards SS1-SS3 with nominal concentrations of approximately 2000, 1500, and 1000 µg/mL, respectively, were made by diluting appropriate volumes of Stocks A or B to 10 mL with hexane. Solvent standards SS4-SS6 were prepared by dilution of appropriate volumes of SS1 and SS2 to 10 mL with hexane to produce standards with nominal concentrations of approximately 600, 300 and 150 µg/mL respectively. Solvent standards were prepared in triplicate at the high and low concentrations; single standards were prepared at all other concentrations. Hexane was used as the solvent blank and was analyzed a single time.

4.2 Results

The stability of Jet-A in corn oil stored at room temperature, refrigerated and frozen is demonstrated on Figures 2-7.

4.3 Conclusions

The day zero analysis data indicated some drift occurring between drift standards 2 and 3. The average drift for these two points (drift standards 2 and 3) were determined for each component and the day 0 stability samples were adjusted to account for this.

The overall stability data (based on the sum of the results from the individual components) showed that the Jet-A in corn oil was stable for 20 days with average values within $\pm 5\%$ of the initially determined Day 0 value. The data for Components B and E and average data showed a slight downward trend with time, while the data for Components C, D and F exhibited no specific trends. There was no significant difference between storage temperatures for individual components. The majority of the variability in the stability data is probably due to the complex chromatographic pattern, which makes obtaining consistent chromatographic profiles and integration of individual components difficult. Components B, E and F were selected for monitoring in a dose analysis method.

The data indicate that method is suitable for the analysis of the test substance in corn oil, and that the doses could be stored up to 20 days prior to analysis at room temperature, under refrigeration, or frozen.

5 ACKNOWLEDGEMENTS

The analytical work was performed by Mr. Kevin Carrico, Mr. Scott Chaffins, Mrs. Deloria Jacobs, Mr. Dave Koebel, Mrs. Sandra Runyon and the report written by Dr. Denise L. Walters.

ATTACHMENT A - FIGURES

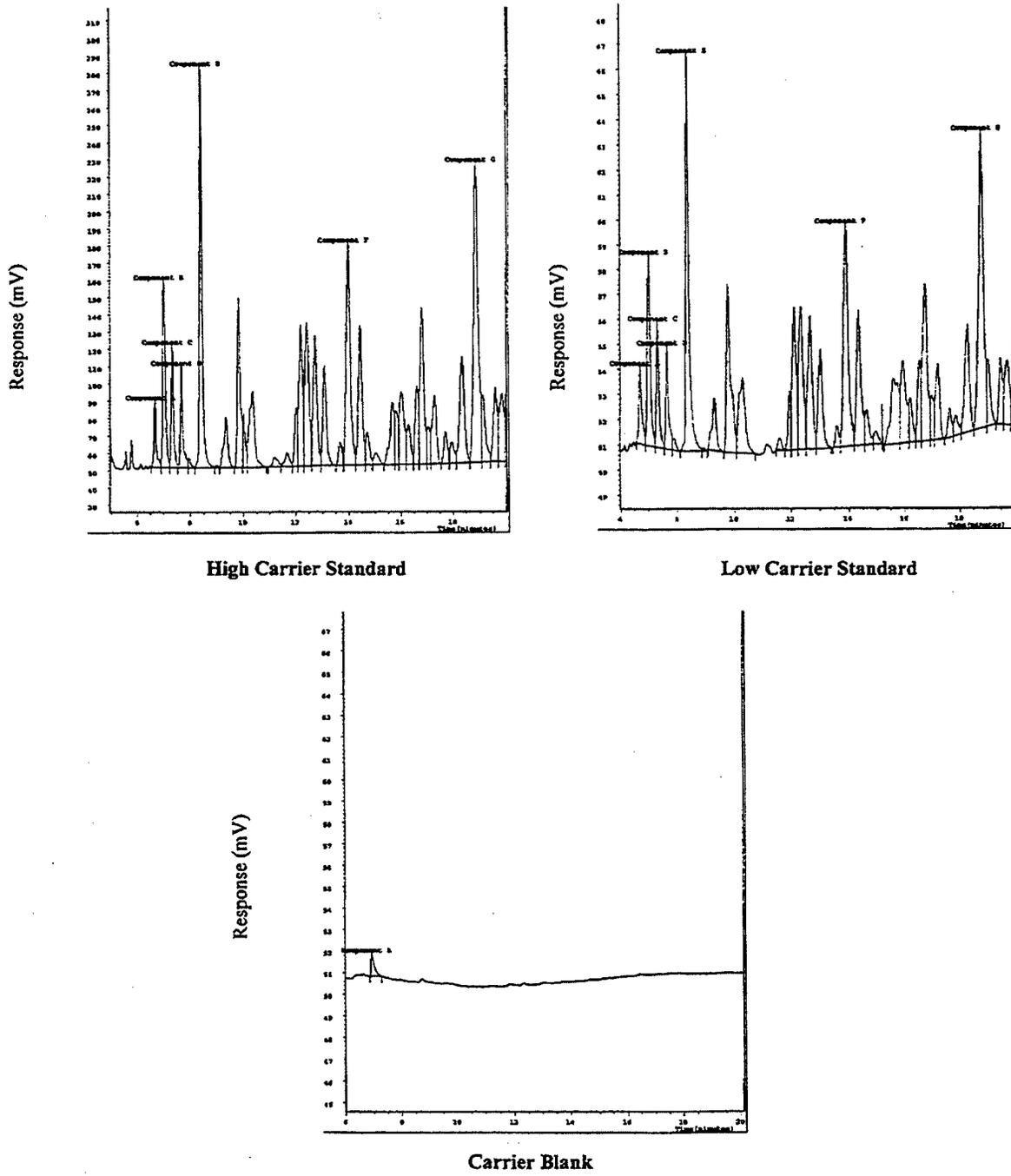


Figure 1. Representative Chromatograms of the High and Low Carrier Standards, and Carrier Blank

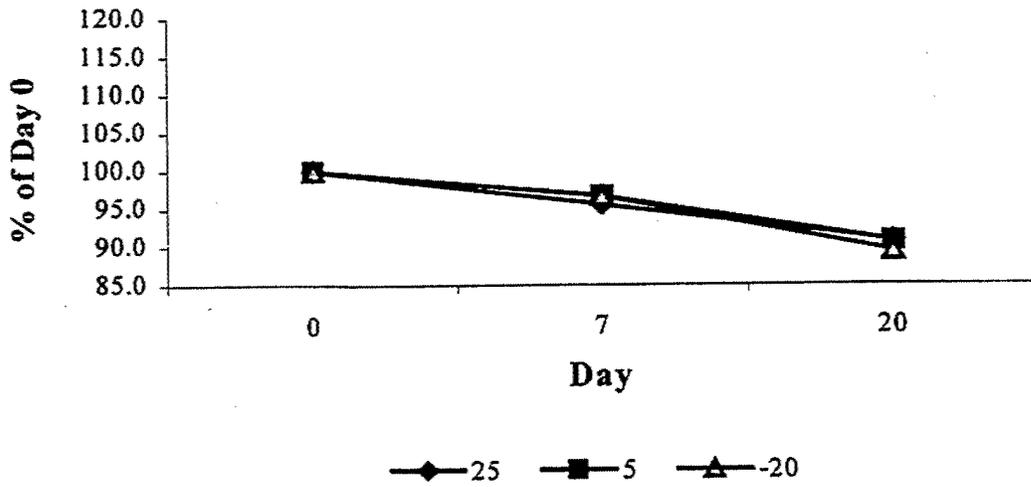


Figure 2. Stability of Jet-A in Corn Oil 204.6 µg/mL at 25, 5 ° and -20 °C, Component B

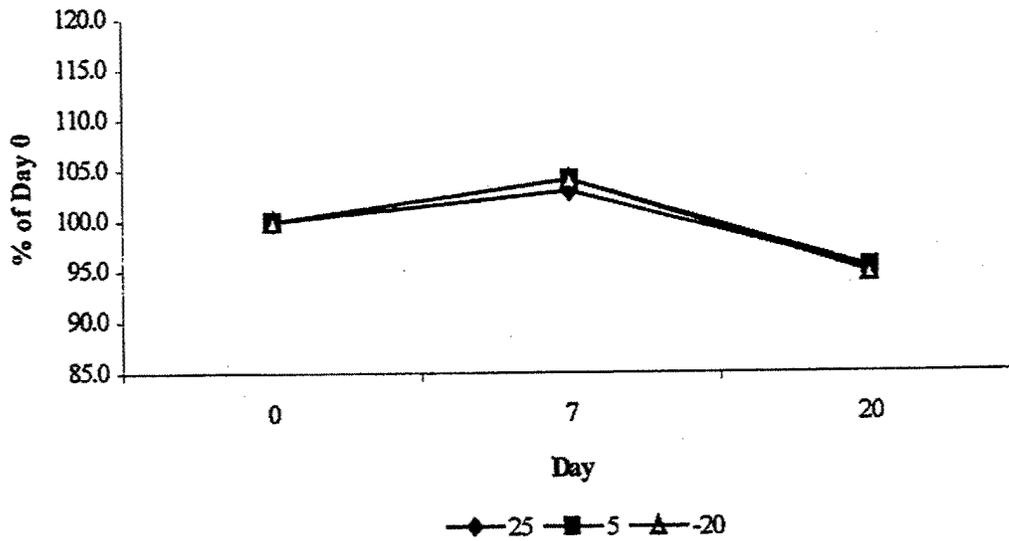


Figure 3. Stability of Jet-A in Corn Oil 204.6 µg/mL at 25, 5 ° and -20 °C, Component C

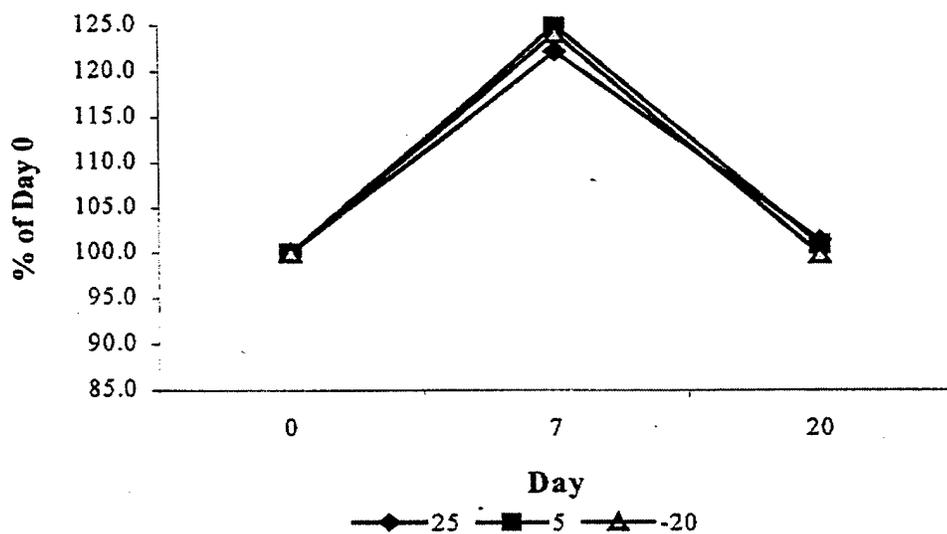


Figure 4. Stability of Jet-A in Corn Oil 204.6 µg/mL 25, 5° and -20 °C, Component D

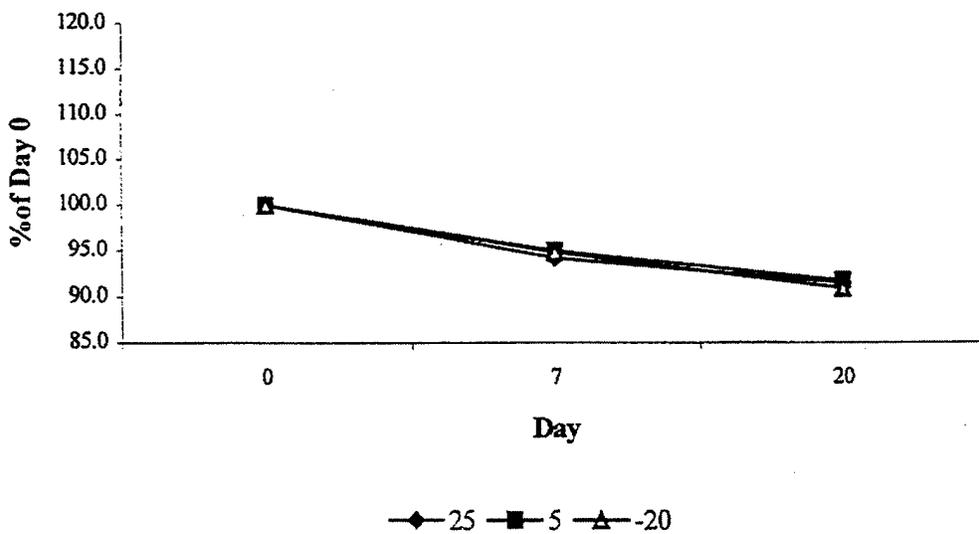


Figure 5. Stability of Jet-A in Corn Oil 204.6 µg/mL at 25, 5° and -20 °C, Component E

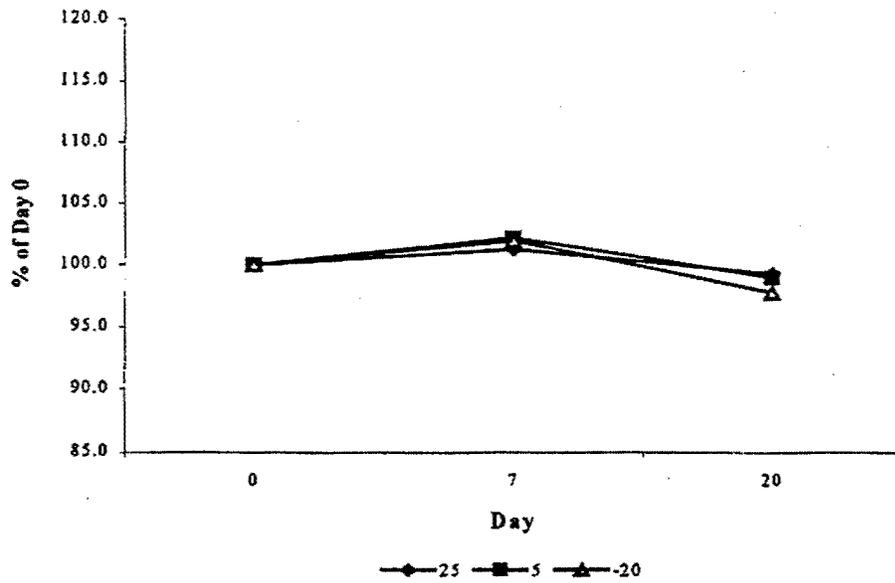


Figure 6. Stability of Jet-A in Corn Oil 204.6 µg/mL at 25, 5° and -20 °C, Component F

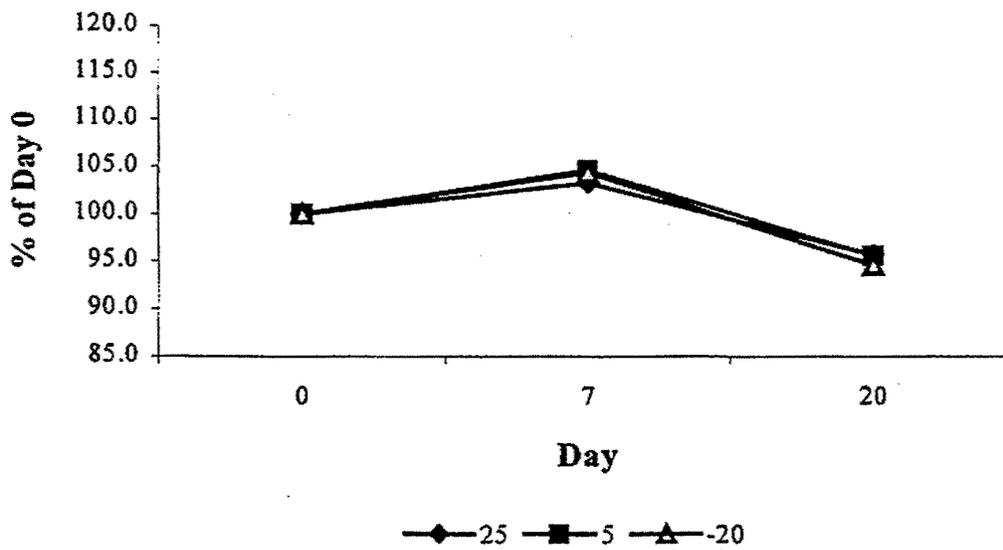


Figure 7. Stability of Jet-A in Corn Oil 204.6 µg/mL at 25, 5° and -20 °C, Average B-F

ATTACHMENT B - ANALYTICAL METHOD

**DOSE ANALYSIS OF C₉-C₁₆ AROMATIC FRACTION OF JET-A IN
CORN OIL
VERSION 1.1**

Study Number: _____

Date: _____

Analyst(s): _____

I. Summary

The Jet Fuel (C₉-C₁₆ aromatic fraction of Jet-A) concentration of doses is determined by GC. Standards are prepared using two independently prepared stock solutions of Jet Fuel in hexane. Standards are diluted with hexane and vehicle and samples are diluted with hexane. Dose concentrations are calculated using the responses of Components B, E and F in the doses, and a regression line constructed from the concentrations and peak responses of Components B, E, and F in the standards.

II. Purpose

To determine the concentration of jet fuel in doses prepared in corn oil.

III. Samples

Pre-Administration _____ Mix Date: _____
Post-Administration _____ Mix Date: _____

See Chain of Custody form, included with this work, for additional sample information.

IV. Materials

See Table 1 for all required chemicals, reagents, vehicles and solvents. Use Table 1 for documentation. Check the labels carefully to ensure that they are not expired and the proper purity/grade. Verify that the lot of the analytical standard is the same as the test substance.

V. General Instructions

- Calibrate all required balances according to the SOP on balance usage.
- Make equivalent dilutions when the volume needed varies from the volume stated in the method.
- Label all standard and reagent solutions as specified in the appropriate SOP. If you intend to reuse a solution for future tasks, be sure the label includes the Task No. for which the solution was initially prepared.
- Sign on the final page of this document to signify that you have followed the method as written, all materials and reagents are current, and all equipment has been properly calibrated. If you deviate from or modify the method, document the change and obtain the approval of the unit manager, study director, or task leader as soon as possible.

**DOSE ANALYSIS OF C₉-C₁₆ AROMATIC FRACTION OF JET-A IN
CORN OIL
VERSION 1.1**

Study Number: _____

Date: _____

Analyst(s): _____

- Initial and date all data entries on the page on which they were made. If only one person enters all data on a page on a single day, then the documentation may be made in a single location on that page by that person. If multiple staff make entries, all must be initialed and dated by the person making the entry.
- The method is written in general chronological order. However, it is not essential that all sections be performed sequentially. The analyst may determine the order for conducting the task in the most efficient manner, unless the order for certain activities is specified.

Table 1-Materials

Chemical	Use	Supplier	Grade or Purity	Lot No
Jet Fuel	Analytical Standard	NA	NA	
Hexane	Extraction			
Corn Oil	Vehicle			

VI. Equipment

See Table 2 for all required major pieces of equipment. Use the table to document the actual piece (e.g., make, model) of equipment. Check calibration of all equipment requiring calibration (e.g., balances) to ensure it is current.

Table 2-Equipment

Equipment	Use	Model No.	X or SN
Analytical Balance	Weigh TA		
Weight Set	Calibrate Balance		
Volumetric Flasks, Class A	Make Volumetric Dilutions	NA	NA
Positive Displacement Pipets	Pipet Doses		
Volumetric Pipets	Pipet Stocks, Vehicle Standards, Diluted Doses		
Refrigerator	Storage of Reference Standard		

**DOSE ANALYSIS OF C₉-C₁₆ AROMATIC FRACTION OF JET-A IN
CORN OIL
VERSION 1.1**

Study Number: _____

Date: _____

Analyst(s): _____

VII. Procedure**A. Preparation of Stocks and Working Standards****1. Solvent Stock Standards**

Weigh the amounts of the jet fuel analytical standard shown in Table 3 into 10-mL volumetric flasks. Dilute to volume with hexane and mix well.

Table 3-Preparation of Stock Standards

Standard	Nominal Conc (mg/mL)	Target Weight (mg)	Actual Weight (mg)*
Stock A	20	200 ± 10	
Stock B	15	150 ± 10	

*Weighed to at least the nearest 0.1 mg.

2. Vehicle Standards

Prepare the vehicle standards from stocks A and B as shown in Table 4. Measure the appropriate amount of the stocks into individual volumetric flasks. Add the appropriate amount of vehicle. Dilute to volume with hexane and mix well.

Table 4- Preparation of Working Vehicle Standards

Standard	Concentration (µg/mL)	Stock Source	Volume of Stock (mL)	Volume of Vehicle (mL)	Final Vol (mL)
VS1	2000	A	1	1	10
VS2	1500	B	1	1	10
VS3	1000	A	0.5	1	10
VS4	600	VS1	3	0.7	10
VS5	300	VS2	2	0.8	10
VS6	150	VS2	1	0.9	10

**DOSE ANALYSIS OF C₉-C₁₆ AROMATIC FRACTION OF JET-A IN
CORN OIL
VERSION 1.1**

Study Number: _____

Date: _____

Analyst(s): _____

B. Preparation of Blank

Prepare a single blank. Pipet 1 mL of vehicle into a 10-mL volumetric flask. Dilute to volume with hexane. Seal and mix thoroughly.

C. Preparation of Doses

Prepare the doses in duplicate following Table 5. Dilute to volume with hexane. Seal and mix thoroughly.

Table 5 – Preparation of Doses

Dose conc. (mg/mL)	Batch No.	Volume of Dose (mL)	Total Volume (mL)	Volume of Dil Dose (mL)	Volume Blk Corn Oil (mL)	Total volume (mL)	Final Conc. (µg/mL)
0		0.5	5	NA	NA	NA	0
2		0.5	5	NA	NA	NA	200
8		0.5	5	NA	NA	NA	800
10		0.5	5	NA	NA	NA	1000
40		0.5	5	2	0.8	10	800
50		0.5	5	2	0.8	10	1000
200		0.5	10	1	0.95	10	1000

D. Analysis of Standards and Blanks

- Use the GC system conditions specified in Table 6. The conditions, which are designated, may be modified by the analyst to produce acceptable chromatography. Make single injections of all standards, blanks and samples.

**DOSE ANALYSIS OF C₉-C₁₆ AROMATIC FRACTION OF JET-A IN
CORN OIL
VERSION 1.1**

Study Number: _____
Date: _____
Analyst(s): _____

Table 6 – Chromatographic System

GC System No:	_____
Controller:	Make _____ Model _____ SN/X _____
Autosampler:	Make _____ Model _____ SN/X _____
A/D Converter	Fisons Chrom Server _____
Column	Restek Rtx-1 15m x 0.53mm x 0.25µm SN _____ Equivalent if used: _____
Column Temperature	37 °C hold 10 min., increase at 2 °C/min. to 80 °C, increase to 330 °C at 25°C/min., post temperature of 330 °C hold 10 min.
Hydrogen Flow	~30 mL/min (_____ mL/min)
Carrier Flow Rate*	~5 mL/min (_____ mL/min) helium
Injection Volume*	2 µL (_____ µL)
Detector Type	FID
Detector Temperature	300 °C
Injector Temperature	250 °C
Run Time*	45 min (_____ min)
Retention Times	

*Parameters which may be modified by the analyst

- Use both the system integrator (if available) and an automated chromatography data software (CDS) system to collect the electronic output. The automated integration software system should serve as the primary data collection system and the system integrator as the back up.

Integration software used: _____ Version _____.

- Set up the CDS to acquire the data. If a CDS is being used that will perform all calculations, enter all required information to allow for the calculations.
- Use any midlevel vehicle standard for the system suitability and drift.

Vehicle standard used: _____

**DOSE ANALYSIS OF C₉-C₁₆ AROMATIC FRACTION OF JET-A IN
CORN OIL
VERSION 1.1**

Study Number: _____

Date: _____

Analyst(s): _____

- Inject system suitability samples at the beginning of the run. It is necessary to have at least 3 acceptable injections prior to beginning the actual analysis. Calculate the peak response or concentration for each injection of the system suitability. The % relative standard deviation of the replicates should be $\leq 5\%$. Calculate the asymmetry for components B, E, and F. The asymmetry should be ≤ 3 . If any requirements are not met, assess the impact on the analysis and continue the analysis, if the failure to meet the requirements does not appear to adversely affect data quality. Notify the unit manager, study director or task leader as soon as possible.
- Inject all standards and blanks followed by the samples. Inject a drift immediately before the first dose injection and every eight to twelve injections thereafter.

VIII. Calculations

- Examine the integration of the test substance peaks. Modify, if necessary, to obtain the optimum integration. Ensure that the response of the standards bracket the response for all dose samples.
- If possible, allow the CDS to perform all necessary calculations. If the CDS cannot automatically perform all calculations, take the following steps:
 1. Calculate the peak response for each injection.
 2. Calculate the exact concentration of each vehicle standard in the final dilution.
 3. Calculate the linear regression equation by relating the peak response of each standard (y-axis) to test substance concentration (x-axis) in the final dilution. Refer to Table 7 for regression parameters. Omit the blanks.

**DOSE ANALYSIS OF C₉-C₁₆ AROMATIC FRACTION OF JET-A IN
CORN OIL
VERSION 1.1**

Study Number: _____
Date: _____
Analyst(s): _____

Table 7 - Regression Parameters for Analysis

Regression Parameters	Settings
Model	Linear
Response	Area
Weighting	none
Intercept	CALCULATE, DO NOT FORCE THROUGH ZERO

4. Calculate the relative error for all standards. If the relative error of any standard is greater than 10% evaluate the impact of omitting that standard from the curve. One standard may be omitted from the curve, if deemed technically necessary. All dose responses must be bracketed by the remaining standards.
5. Using the peak responses of the standards for Components B, E and F and their corresponding regression equations. Calculate the concentration of test substance in the final dilution of each sample. Calculate the concentration of the dose by using the total dilution factor and the calibration curve. Calculate the concentrations of each dose based on analysis of individual Components B, E and F. Calculate the final reported concentrations by averaging the calculated concentrations based on Components B, E and F.
6. Calculate E/O by dividing the averaged concentration of replicate 1 by the averaged concentration of replicate 2. Be sure to express the determined concentration of the dose in the same units on the dose labels and/or chain of custody forms.
7. If more than two aliquots of a dose are analyzed, examine any potential outliers using the Q-test with a 95% confidence interval. Calculate s and percent RSD rather than the E/O.

IX. Results

A. System Suitability

Table 8 - System Suitability Results

Parameter	Acceptance Limit	Determined Value
Asymmetry *	≤3	Component B _____ Component E _____ Component F _____
%RSD	≤5	

* on test substance peaks

**DOSE ANALYSIS OF C₉-C₁₆ AROMATIC FRACTION OF JET-A IN
CORN OIL
VERSION 1.1**

Study Number: _____
Date: _____
Analyst(s): _____

- Specify the software and version for the spreadsheet. Specify the method for data entry into the spreadsheet. Report all values with concentrations below the specified limit of quantitation as "BLOQ".
- Include copies of the chromatograms, load list, summary report, data processing parameters, Chains of Custody and an Out of Specification form (if the determined value is more than 10% from target and these are not animal room samples) in the data packet.

X. Acceptance Criteria

- The percent relative error of the system suitabilities must be less than or equal to 5. The drifts should not differ by more than 10% from the average of the system suitabilities.
- If the correlation coefficient is <0.99, repeat the preparation and analysis of the standard curve.
- If the E/O is less than 0.9 or greater than 1.1 for any set of duplicates, analyze at least two additional aliquots for that dose.
- For Pre-Administration, if the concentration differs from target by more than 10%, notify the unit manager, study director or task leader immediately.
- For Post-Administration, if the concentration differs significantly from the Pre-Administration value (if analyzed) or more than 10% from target (if unanalyzed), notify the unit manager, study director or task leader immediately.

XI. Comments

XII. Conclusions

**DOSE ANALYSIS OF C₉-C₁₆ AROMATIC FRACTION OF JET-A IN
CORN OIL
VERSION 1.1**

Study Number: _____

Date: _____

Analyst(s): _____

Analyst Signature:

QC Review:

Technical Review:

Revision Comments:

Version 1.1-Volumetric pipets added to Equipment table. Dose preparation dilution scheme modified to reflect changes in formulated concentrations.

APPENDIX F

Pathology Report from the United States Air Force F-2

ANATOMIC PATHOLOGY REPORT OF THE 90-DAY ORAL GAVAGE TOXICITY
STUDY OF C₉-C₁₆ AROMATIC FRACTION OF JET-A IN FEMALE SPRAGUE-
DAWLEY CD RATS AND MALE C57BL/6 MICE

Study Pathologist: William H. Baker

Purpose of Study

The purpose of this study was to evaluate the potential toxicity of C₉-C₁₆ Aromatic Fraction of JET-A fuel following oral gavage administration of 0, 20, 100, or 500 mg/kg/day in mice and rats for 90 consecutive days. Assessment of potential toxicity will be based on clinical observations, body weight and food consumption changes, clinical pathology, gross necropsy findings, organ weight differences, and histopathology. The histopathology results are addressed in this report.

Summary

There were no lesions observed in any of the animals which were attributed to the test substance.

Necropsy

Post-mortem examinations, organ weighing and tissue collection from rats and mice were performed by Battelle on November 2 and 3, 1998 for rats and mice, respectively.

Histopathology

Fixed tissues were received for routine histopathology processing and assessment by the Operational Toxicology Branch at Wright-Patterson Air Force Base (AFRL/HEST) on November 10, 1998. Tissues samples from the 15 rats in the control group (Group 1) and 15 rats in the high dose group (Group 4), and the 15 mice in the control group (Group 5) and 15 mice in the high dose group (Group 8) were dehydrated, paraffin embedded, and sectioned at 5 micrometers. Sections were stained using hematoxylin and eosin. These tissues included the following:

adrenal glands	liver (w/gallbladder for mouse)	skin (ventral)
aorta	lung with bronchi	spinal cord (cross & longitudinal cuts)
brain	lymph nodes (mandibular, mesenteric)	spleen
cecum/colon	mammary gland	sternum
duodenum	nasopharynx (3 sections)	stomach
epididymides	ovaries (w/ oviducts)	testes
esophagus	pancreas	thymus
femur/marrow	pituitary gland	thyroid gland (w/parathyroids)
Harderian glands	prostate	
ileum	rectum	

eyes w/ optic nerve	salivary glands	tongue
jejunum	sciatic nerve	trachea
heart	seminal vesicles	urinary bladder
kidneys	skeletal muscle (biceps femoris)	uterus
		vagina

Histopathologic assessment was made by a Board Certified Veterinary Pathologist. Microscopic lesions are presented in Appendices 1 through 4 for Study Groups 1, 4, 5, and 8, respectively. As well as being organized by treatment group, the data sheets are in order by AFRL/HEST accession number. Translation tables (Tables 1a and 1b) are provided to identify samples by Battelle study numbers. A consolidated list of lesion frequencies is presented in Tables 2a and 2b, for rats and mice, respectively. The intervening treatment groups were not processed due to the absence of lesions attributable to the test agent in the high dose group.

Comments

Phase 1 (Rats):

The vast majority of lesions noted in tissues from the rat phase of this study are considered to be normal background lesions or fixation/processing induced changes.

Central nervous system lesions consisted of demyelination within segments of the spinal cord, retinal degeneration and vascular medial hyperplasia within the brain. All of these lesions were of low incidence and are considered insignificant findings. The vacuolar change noted in the spinal cord was interpreted as a processing artifact and therefore insignificant.

Hepatic lesions consisted of inflammation, vacuolar change and foci of cellular alteration. The inflammatory lesions were multifocal aggregates of macrophages and lymphocytes scattered randomly throughout the parenchyma. This change was equally noted in control and treatment animals with no differences in severity. This is a common age related change in rats and considered insignificant. The vacuolar change noted in one control and one treated animal is suggestive of a local metabolic change within hepatocytes possibly due to decreased local vascular perfusion. This observation is also insignificant. In one treated animal, foci of cellular alteration, one basophilic and one eosinophilic, were observed. The possible role of such foci as precursors of hepatic neoplasm is controversial. Such foci may arise spontaneously and are age related. For example in F344 rats they are common by 6-12 months of age and found essentially in 100% of F344 rats by 2 years (1). Given the frequency and severity of the two observations this finding is considered incidental and of minimal significance. Although liver weights in the high dose group were elevated, no significant microscopic findings were observed supporting this change in organ weight.

Respiratory lesions included focal respiratory epithelial hyperplasia and alveolar histiocytosis. The latter observation is a common incidental finding and epithelial hyperplasia is a focal proliferative process in response to an unidentified source.

Renal inflammation and intratubular mineralization were interpreted as early changes associated with chronic progressive nephropathy, a spontaneous renal disease of rats. These changes are insignificant. Bilateral hydronephrosis, as noted in one control animal, maybe congenital or acquired. Determination of the cause of the lesion is not possible given the limited history and gross observations. Regardless of cause, the lesion is considered insignificant.

Cystic changes observed in the thyroid gland (ultimobranchial cysts), thymus (thymic epithelial cysts), kidney, and tongue (epithelial) are congenital in nature and are insignificant.

Incidental inflammatory responses were noted in the tongue of one control animal and in the vagina of a treated animal. The sources of inflammation were not determined. Likewise, an unidentified source of immune stimulation was suggested as the cause of lymphoid hyperplasia within the cecum observed in 4 control animals. Again this is an incidental finding and not significant.

Decidual alteration, infrequently seen in young adult female rats, is a proliferative response that mimics normal decidual implantation sites. Uterine dilatation, as noted in 2 control and 2 treated animals was most likely the effect of accumulation of proestral fluids within the organ lumen. Both decidual alteration and uterine dilatation are insignificant findings.

Only one neoplasm was diagnosed in the group of rats examined (15 controls and 15 treated). A poorly differentiated spindle cell neoplasm was observed in the luminal surface of the left ventricular free wall of the heart of a control animal. Comparing this lesion to findings in a previous study of 96 cardiac neoplasms in Fischer 344 rats, this mass is most probably a Schwannoma (2). In the earlier study, endocardial Schwannomas were diagnosed in sixty (62%) of the 96 cardiac neoplasms and always involved the left ventricle, the location of our mass. For this study, this particular finding is interpreted as a background lesion and considered insignificant.

Phase 2 (Mice):

Central nervous system lesions included dilatation of the ventricular system and a focal observation of pigmentation in the meninges deep within the cerebrum. The former change was interpreted as a processing artifact in that it was unaccompanied by other obvious lesions and that the change was equally present in control and treated individuals. The latter was considered an incidental finding.

Ocular lesions consisted of retinal atrophy in one control animal and retinal dysplasia in one control and one dosed animal. Changes in the Harderian gland, acinar lumen dilatation and focal epithelial hyperplasia, were considered incidental findings.

Pigmentation within cardiac valves was noted in 5 control and 2 dosed individuals. This is considered a background change and insignificant. Epicardial mineralization and focal fibrosis with mineralization within the right ventricular free wall were noted independently in two control animals. Cardiac mineralization can occur spontaneously, and as in the first animal above, is considered an incidental finding. Mineralization can also occur as a sequela to fibrosis as noted in the second animal above. The source of fibrosis in that animal, however, was not evident.

Tissues surrounding the aorta of one treated animal that died on study (608-98) displayed multiple foci of acute inflammatory infiltrates admixed with numerous clusters of coccoid bacteria and mild amounts of fibrin. Other information regarding this lesion and its interpretation are described further immediately below.

Within the respiratory tree, minimal tracheal epithelial hyperplasia was noted in one treated mouse. This lesion was considered an incidental finding. In another treated animal, multiple fibrin tags were noted on the pleural surface. This particular animal (608-98) died on study and was described at necropsy as having "food caked around the lungs". This change is consistent with pleuritis, a condition most probably secondarily induced by dosing injury.

Minimal inflammatory changes in the liver were noted with equal frequency in the control and high dose group. These lesions consisted of focal to multifocal admixtures of macrophages and lymphocytes and are considered background lesions and interpreted as insignificant. Minimal, multifocal, hepatocellular necrosis was noted in the one high dose group animal that died on study. The hepatic necrosis most probably is indicative of the septic state of the animal. Another change deemed insignificant was a mild diffuse aggregation of granulocytes in the submucosa of the gallbladder in a control animal.

Changes within the gastrointestinal tract included inflammation and lymphoid hyperplasia. Chronic inflammatory changes were noted in the salivary gland of 2 of 11 glands assessed in treated mice and in the esophagus of one control mouse. Submandibular lymphoid hyperplasia was noted in one of the treated mice displaying chronic salivary adenitis and in the one control mouse with chronic esophagitis. An additional control animal displayed submandibular lymphoid hyperplasia without accompanying inflammatory changes in surrounding tissues examined.

In the stomach, acute inflammation was noted in the glandular region of 2 of 14 stomachs from treated mice. In the squamous portion of one control and one treated mouse, minimal epithelial hyperplasia was observed. These changes in the stomach as well as esophageal lesions noted above were interpreted as possible changes induced mechanically by the gavage process.

Changes noted in the pancreas included islet cell hyperplasia in 2 control mice and lymphoid hyperplasia in 2 of 13 pancreases examined in treated animals. Minimal acute gastritis was a concomitant lesion in one of the 2 animals with pancreatic lymphoid hyperplasia. The other animal displayed no accompanying lesions.

Lymphoid hyperplasia was noted in the cecum of one control animal, but no local source for immune stimulation was observed.

Within the testes and epididymis alterations interpreted as degenerative changes were noted, however, the frequency of these changes were similar within the two groups examined. Testicular changes in 11 and 10 control and treated mice, respectively, consisted of focal to multifocal, intratubular multinucleated giant cells occasionally associated with minimal tubular germinal epithelial hypoplasia. In epididymides, there were focal to multifocal regions of epithelial attenuation characterized by shortening of epithelial height from tall columnar to short cuboidal cell shape. This latter change was observed in 12 and 13 control and treated mice, respectively. There was one observation of unilateral sperm granuloma in the epididymis of one control animal. The only other observation within the reproductive tract was epithelial hyperplasia within the seminal vesicles of 2 control animals, a change considered insignificant.

Notation of vacuolar change within the adrenal gland cortex was made with equal frequency in control and treated animals. This observation is considered an incidental finding as was the one observation of an adrenal medullary cyst in a high dose animal. One other treated animal displayed minimal cortical hypertrophy, a change not uncommonly seen in mice and attributed in part to stress.

C-cell hyperplasia within the thyroid gland was diagnosed when clusters of C-cells numbered greater than 4. Using this criteria 13 of 15 control and 9 of 14 treated mice displayed minimal C-cell hyperplasia. This change is considered insignificant and probably reflects the normal condition in this strain of mice.

Incidental findings were noted in several other miscellaneous tissues. Splenic lymphoid hyperplasia was noted in one treated mouse and in a control animal, minimal, focal, chronic inflammation was noted in adipose tissue adjacent to the sample section of skeletal muscle. One observation of a thymic medullary cyst was made in a control animal and thymic mineralization in one other control mouse.

Discussion:

The above histopathologic changes noted in rats and mice were considered to be within limits observed in normal animals. Indeed, many of the observations were noted with similar frequency in control and animals from the high dose groups. The two on study deaths (rat phase – AFRL/HEST# 582-98/Battelle 407 and mouse phase – AFRL/HEST# 608-98/Battelle 803) that occurred during the study were both attributed to

dosing injury. The only neoplasm, a Schwannoma, observed was in a rat from the control group. This neoplastic change was considered a background lesion. In mice, lymphoid hyperplasia was seen in the several foci within the intestinal tract, but a source for the immune stimulation was not evident microscopically.

Similar 90-day, oral gavage studies in Sprague-Dawley (SD) rats have been conducted using JP-8 (4,5). JP-8 components share considerable commonality with the test agent used in this study. One of the earlier studies was performed with male SD rats dosed at 0, 750, 1500, and 3000 mg/kg neat agent (4), while the other study used female SD rats dosed at 0, 325, 750, 1500 mg/kg neat agent (5). In both of these studies there were gross and microscopic evidence of perianal dermatitis, a finding not noted in our study. Likewise, inflammatory and proliferative changes were observed in the squamous portion of the stomach in both studies, but not in this C₉-C₁₆ study. These changes suggest that an additional component of JP-8, not present in the C₉-C₁₆ fraction, may have been responsible for sufficient gastrointestinal irritation that may have precipitated the above noted lesions. Additionally, it might be speculated that the significant decreases in body weights noted in the male and female rats in the two earlier studies may have also been associated with these gastrointestinal changes. Supporting this speculation is the fact that the minimal decrease of body weight in our high-dose group rats was not significant. Of course, these conclusions must be interpreted in light of the relative doses of C₉-C₁₆ or a C₉-C₁₆ -equivalent administered in the earlier studies compared to the 0, 20, 100, and 500 mg/kg/day of C₉-C₁₆ fraction received by the animals in this study.

Regarding hepatic involvement in this study, a significant increase in liver weight was noted in the C₉-C₁₆ fraction high dose group. A similar response was observed in female SD rats in the mid- and high-dose groups treated with JP-8 (5), however, the males in the other JP-8 study (4) did not demonstrate a significant change in liver weights. Although male rat liver weights were within normal limits, they did display elevated levels of hepatic enzymes (AST and ALT), albeit not in a dose-dependent manner. Females, on the other hand, from both the earlier study and the present study demonstrated no statistically significant changes in the levels of these two enzymes. Histopathologic changes were not observed in liver samples from any of the three studies. Conclusions reached by this study suggest that within the time frame and dosages of exposure, the C₉-C₁₆ fraction did not induce any adverse histopathologic changes despite the liver enlargement noted in high dose group rats.

References:

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4. Mattie DR, Marit GB, Flemming CD, and Cooper JR. The effects of JP-8 jet fuel on male Sprague-Dawley rats after a 90-day exposure by oral gavage. *Toxicology and Industrial Health* 11(4): 423-435, 1995.
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TABLE 1a. TRANSLATION TABLE FOR AFRL/HEST AND BATTELLE
ACCESSION NUMBERS

RATS

CONTROLS (GROUP 1)		HIGH DOSE 500 mg/kg (GROUP 4)	
<u>AFRL/HEST ACCESSION #</u>	<u>BATTELLE ANIMAL #</u>	<u>AFRL/HEST ACCESSION #</u>	<u>BATTELLE ANIMAL #</u>
561-98	115	576-98	401
562-98	114	577-98	402
563-98	113	578-98	403
564-98	112	579-98	404
565-98	111	580-98	405
566-98	110	581-98	406
567-98	109	582-98	407
568-98	108	583-98	408
569-98	107	584-98	409
570-98	106	585-98	410
571-98	105	586-98	411
572-98	104	587-98	412
573-98	103	588-98	413
574-98	102	589-98	414
575-98	101	590-98	415

TABLE 1b. TRANSLATION TABLE FOR AFRL/HEST AND BATTELLE
ACCESSION NUMBERS (continued)

MICE

CONTROLS (GROUP 5)		HIGH DOSE 500 mg/kg (GROUP 8)	
<u>AFRL/HEST</u> <u>ACCESSION #</u>	<u>BATTELLE</u> <u>ANIMAL #</u>	<u>AFRL/HEST</u> <u>ACCESSION #</u>	<u>BATTELLE</u> <u>ANIMAL #</u>
591-98	501	606-98	801
592-98	502	607-98	802
593-98	503	608-98	803
594-98	504	609-98	804
595-98	505	610-98	805
596-98	506	611-98	806
597-98	507	612-98	807
598-98	508	613-98	808
599-98	509	614-98	809
600-98	510	615-98	810
601-98	511	616-98	811
602-98	512	617-98	812
603-98	513	618-98	813
604-98	514	619-98	814
605-98	515	620-98	815

TABLE 2a. FREQUENCY OF MICROSCOPIC LESIONS
FROM CONTROL AND HIGH DOSE GROUP RATS

	<u>CONTROL</u>	<u>HIGH DOSE</u> <u>500 mg/kg</u>
Spinal Cord		
Vacuolar change	11/15	12/15
Demyelination	1/15	1/15
Brain		
Vascular medial hyperplasia	1/15	0/15
Eye		
Retinal degeneration	1/15	0/15
Liver		
Inflammation, chronic, multifocal	13/15	11/15
Inflammation, chronic, multifocal w/necrosis	2/15	3/15
Vacuolar change	1/15	1/15
Foci of cellular alteration eosinophilic	0/15	1/15
basophilic	0/15	1/15
Heart		
Tumor - Schwannoma	1/15	0/15
Lung		
Respiratory epithelial hyperplasia	1/15	0/15
Alveolar histiocytosis	5/15	5/15
Thyroid		
Ultimobranchial cyst	2/15	8/15
Thymus		
Epithelial cyst	3/15	3/15
Kidney		
Inflammation, subacute, interstitial	0/15	2/15
Cyst	0/15	1/15
Hydronephrosis	1/15	0/15
Mineralization, intratubular	1/15	2/15

TABLE 2a. FREQUENCY OF MICROSCOPIC LESIONS
FROM CONTROL AND HIGH DOSE GROUP RATS

	<u>CONTROL</u>	<u>HIGH DOSE</u> <u>500 mg/kg</u>
Tongue		
Inflammation	1/15	0/15
Epithelial cyst	0/15	1/15
Cecum		
Lymphoid hyperplasia	4/15	0/15
Uterus		
Dilatation	2/15	2/15
Decidual alteration	0/15	1/15
Vagina		
Inflammation	0/15	1/15

TABLE 2b. FREQUENCY OF MICROSCOPIC LESIONS
FROM CONTROL AND HIGH DOSE GROUP MICE

	<u>CONTROL</u>	<u>HIGH DOSE</u> <u>500 mg/kg</u>
Brain		
Ventricular dilatation	9/15	10/15
Focal meningeal pigmentation	0/15	1/15
Eye		
Retinal atrophy	1/15	0/15
Retinal dysplasia	1/15	1/15
Harderian gland		
Acinar dilatation	1/15	0/15
Epithelial hyperplasia	0/15	2/13
Liver		
Inflammation, chronic, multifocal, random	6/15	7/15
Necrosis	0/15	1/15
Gallbladder		
Submucosal accumulation of granulocytes	1/15	0/15
Heart		
Valvular pigmentation	5/15	2/15
Epicardial mineralization	1/15	0/15
Right ventricular free wall fibrosis w/ mineralization	1/15	0/15
Aorta		
Associated peritoneum Peritonitis, acute, diffuse	0/15	1/15
Lung w/ bronchi		
Pleural fibrin tags	0/15	1/15
Trachea		
Epithelial hyperplasia	0/15	1/15

Salivary gland		
Inflammation, chronic	0/15	2/11
Submandibular lymph node		
Lymphoid hyperplasia	2/13	1/9
Esophagus		
Inflammation, chronic	1/15	0/15
Stomach		
Squamous region		
Epithelial hyperplasia	1/15	1/15
Glandular region		
Inflammation, acute	0/15	2/14
Pancreas		
Islet hyperplasia	2/15	0/15
Lymphoid hyperplasia	0/15	2/13
Cecum		
Lymphoid hyperplasia	1/15	0/15
Urinary bladder		
Transitional cell hyperplasia	1/15	2/15
Testes		
Degeneration, w/ tubular epithelial hypoplasia &/or multinucleated giant cells	11/15	10/15
Epididymis		
Epithelial attenuation	12/15	13/15
Seminal vesicle		
Epithelial hyperplasia	2/15	0/15
Spleen		
Lymphoid hyperplasia	0/15	1/14
Thymus		
Medullary cyst	1/13	0/15
Mineralization	1/13	0/15

Adrenal gland		
Vacuolar change	11/15	11/14
Medullary cyst	0/15	1/14
Cortical hypertrophy	0/15	1/14
Thyroid gland		
C-cell hyperplasia	13/15	9/14
Muscle		
(Adjacent adipose tissue)		
Inflammation, chronic	1/15	0/15

APPENDIX 1. MICROSCOPIC FINDINGS GROUP 1
(CONTROL RATS)

Accession Number: 561-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1 -Within Normal Limits
A2	Nasal 2 -Within Normal Limits
A3	Sternum-Within Normal Limits
A4	Femur -Within Normal Limits
B1	Adrenal -Within Normal Limits
	Pituitary -Within Normal Limits
	Thyroid -Within Normal Limits
	Parathyroid -Tissue Not Present
B2	Submandibular LN-Tissue Not Present
	Salivary Gland-Tissue Not Present
	Harderian Gland -Within Normal Limits
C	Trachea -Within Normal Limits
	Esophagus -Within Normal Limits
	Lung w/ Bronchi-Within Normal Limits
D1	Heart -Within Normal Limits
	Thymus -Within Normal Limits
D2	Liver-Inflammation, chronic, random, mild w/ subendothelial and subcapsular foci
	Spleen-Within Normal Limits
D3	Aorta -Within Normal Limits
E1	Kidney-Within Normal Limits

- E2** Skin-Within Normal Limits
 - Muscle-Within Normal Limits
 - Nerve-Within Normal Limits
 - Mammary -Within Normal Limits
 - F1** Stomach -Within Normal Limits
 - Pancreas -Within Normal Limits
 - Duodenum-Within Normal Limits
 - Jejunum-Within Normal Limits
 - F2** Ileum-Tissue Not Present
 - Colon-Within Normal Limits
 - Cecum-Within Normal Limits
 - F3** Rectum-Within Normal Limits
 - G1** Ovaries-Within Normal Limits
 - Uterus-Within Normal Limits
 - G2** Urinary Bladder-Within Normal Limits
 - G3** Vagina-Within Normal Limits
 - H** Brain-Within Normal Limits
 - I** Eye-Within Normal Limits
 - J** Tongue-Within Normal Limits
- K1, 2, 3** Spinal Cord-vacuolar change, cervical dorsal horn, minimal

Accession Number: 562-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1 Within Normal Limits
A2	Nasal 2 Within Normal Limits
A3	Sternum-Within Normal Limits
A4	Femur-Within Normal Limits
B1	Adrenal- Within Normal Limits Pituitary- Within Normal Limits Thyroid- Within Normal Limits Parathyroid-Within Normal Limits
B2	Submandibular LN-Tissue misidentified (thymus) Salivary Gland-Within Normal Limits Harderian Gland-Tissue Not Present
C	Trachea-Within Normal Limits Esophagus-Within Normal Limits Lung w/ Bronchi-Alveolar histiocytosis, multifocal, minimal
D1	Heart-Within Normal Limits Thymus-see B2 thymic epithelial cysts, multiple, minimal
D2	Liver-Inflammation, chronic, random, multifocal, mild w/ occasional single cell hepatocellular necrosis -vacuolar change, random, focal, mild suggestive of increased intracellular lipid content Spleen-Within Normal Limits
D3	Aorta -Within Normal Limits
E1	Kidney-Within Normal Limits
E2	Skin-Within Normal Limits

Muscle-Within Normal Limits

Nerve-Within Normal Limits

Mammary-Within Normal Limits

F1 Stomach-Within Normal Limits

Pancreas--Within Normal Limits (see D1)

Duodenum-Within Normal Limits

Jejunum-Within Normal Limits

F2 Ileum -Within Normal Limits

Colon-Within Normal Limits

Cecum-Within Normal Limits

F3 Rectum-Within Normal Limits

G1 Ovaries-Within Normal Limits

Uterus-Within Normal Limits

G2 Urinary Bladder-Within Normal Limits

G3 Vagina-Within Normal Limits

H Brain -Within Normal Limits

I Eye-Within Normal Limits

J Tongue-Within Normal Limits

K1, 2, 3 Spinal Cord-x.s. vacuolar change, thoracic dorsal horn, mild

Accession Number: 563-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1 –Within Normal Limits
A2	Nasal 2–Within Normal Limits
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal–Within Normal Limits
	Pituitary–Within Normal Limits
	Thyroid–Within Normal Limits
	Parathyroid–Within Normal Limits
B2	Submandibular LN–Within Normal Limits
	Salivary Gland–Within Normal Limits
	Harderian Gland–Within Normal Limits (see I)
C	Trachea–Within Normal Limits
	Esophagus–Within Normal Limits
	Lung w/ Bronchi-Alveolar histiocytosis, multifocal, minimal
D1	Heart–Within Normal Limits
	Thymus-Thymic, epithelial cyst, focal, mild
D2	Liver-Inflammation, chronic, random, multifocal, minimal
	Spleen–Within Normal Limits
D3	Aorta–Within Normal Limits
E1	Kidney–Within Normal Limits
E2	Skin–Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye-Retinal degeneration, external nuclear layer, diffuse, moderate
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord-x.s. vacuolar change, cervical & thoracic dorsal horn, mild

Accession Number: 564-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1 –Within Normal Limits
A2	Nasal 2–Within Normal Limits
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal–Within Normal Limits
	Pituitary–Within Normal Limits
	Thyroid–Within Normal Limits
	Parathyroid–Within Normal Limits
B2	Submandibular LN–Within Normal Limits
	Salivary Gland–Within Normal Limits
	Harderian Gland–Within Normal Limits
C	Trachea–Within Normal Limits
	Esophagus–Within Normal Limits
	Lung w/ Bronchi–Hyperplasia, bronchiolar epithelial cell, multifocal, mild
D1	Heart–Within Normal Limits
	Thymus–Within Normal Limits
D2	Liver-Inflammation, chronic, subepithelial, multifocal, minimal
	Spleen–Within Normal Limits
D3	Aorta–Within Normal Limits
E1	Kidney-Hydronephrosis, bilateral, moderate
E2	Skin–Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain (cerebrum)-vascular medial hyperplasia, focal severe
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord-x.s. vacuolar change, thoracic dorsal horn, minimal

Accession Number: 565-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1 –Within Normal Limits
A2	Nasal 2–Within Normal Limits
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal–Within Normal Limits
	Pituitary–Within Normal Limits
	Thyroid-Ultimobranchial cyst, multifocal, minimal
	Parathyroid-Tissue Not Present
B2	Submandibular LN–Within Normal Limits
	Salivary Gland–Within Normal Limits
	Harderian Gland–Within Normal Limits
C	Trachea–Within Normal Limits
	Esophagus–Within Normal Limits
	Lung w/ Bronchi–Within Normal Limits
D1	Heart–Within Normal Limits
	Thymus–Within Normal Limits
D2	Liver–Within Normal Limits
	Spleen–Within Normal Limits
D3	Aorta–Within Normal Limits
E1	Kidney–Within Normal Limits
E2	Skin–Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Hyperplasia, lymphoid, diffuse, moderate
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—x.s. vacuolar change, cervical & thoracic dorsal horn, minimal and mild, respectively

Accession Number: 566-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1 –Within Normal Limits
A2	Nasal 2–Within Normal Limits
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal–Within Normal Limits
	Pituitary–Within Normal Limits
	Thyroid–Ultimobranchial cysts, multifocal, minimal
	Parathyroid–Within Normal Limits
B2	Submandibular LN–Within Normal Limits
	Salivary Gland–Within Normal Limits
	Harderian Gland–Within Normal Limits
C	Trachea–Within Normal Limits
	Esophagus-Tissue Not Present
	Lung w/ Bronchi–Within Normal Limits
D1	Heart–Within Normal Limits
	Thymus–Within Normal Limits
D2	Liver-Inflammation, chronic, random, multifocal, minimal
	Spleen–Within Normal Limits
D3	Aorta, adjacent brown fat-steatitis, subacute, minimal
E1	Kidney–Within Normal Limits
E2	Skin–Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum-Lymphoid hyperplasia, diffuse, mild
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord-x.s. vacuolar change, thoracic & lumbar dorsal horn, minimal

Accession Number: 567-98

Slide Tissue

- A1** Nasal 1–Within Normal Limits
- A2** Nasal 2–Within Normal Limits
- A3** Sternum–Within Normal Limits
- A4** Femur–Within Normal Limits
- B1** Adrenal- Within Normal Limits
Pituitary–Within Normal Limits
Thyroid–Within Normal Limits
Parathyroid-Tissue Not Present
- B2** Submandibular LN–Within Normal Limits
Salivary Gland–Within Normal Limits
Harderian Gland–Within Normal Limits
- C** Trachea–Within Normal Limits
Esophagus-Tissue Not Present
Lung w/ Bronchi–Alveolar histiocytosis, multifocal, minimal
- D1** Heart–Within Normal Limits
Thymus–Within Normal Limits
- D2** Liver–Inflammation, chronic, subendothelial, focal, minimal
Spleen–Within Normal Limits
- D3** Aorta–Within Normal Limits
- E1** Kidney–Within Normal Limits
- E2** Skin–Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum-Lymphoid hyperplasia, transmural, diffuse, mild
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord-x.s. vacuolar change, cervical dorsal horn, mild
 - Thoracic & lumbar-x.s. Tissue Not Present
 - Cervical-l.s. Tissue Not Present

Accession Number: 568-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1 –Within Normal Limits
A2	Nasal 2–Within Normal Limits
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal–Within Normal Limits Pituitary–Within Normal Limits Thyroid–Within Normal Limits Parathyroid-Tissue Not Present
B2	Submandibular LN–Within Normal Limits Salivary Gland–Within Normal Limits Harderian Gland–Within Normal Limits
C	Trachea–Within Normal Limits Esophagus–Within Normal Limits Lung w/ Bronchi–Within Normal Limits
D1	Heart–Within Normal Limits Thymus–Within Normal Limits
D2	Liver-Inflammation, chronic, multifocal, random, minimal Spleen–Within Normal Limits
D3	Aorta–Within Normal Limits
E1	Kidney–Within Normal Limits
E2	Skin–Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Tissue Not Present
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye—One Section Present
- J** Tongue—Glossitis, acute, focal, minimal
- K1, 2, 3** Spinal Cord—x.s. vacuolar change, thoracic dorsal horn, minimal
-demyelination, focal, minimal

Accession Number: 569-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1–Within Normal Limits
A2	Nasal 2–Within Normal Limits
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal–Within Normal Limits
	Pituitary–Within Normal Limits
	Thyroid–Within Normal Limits
	Parathyroid–Within Normal Limits
B2	Submandibular LN–Within Normal Limits
	Salivary Gland–Within Normal Limits
	Harderian Gland–Within Normal Limits
C	Trachea–Within Normal Limits
	Esophagus–Within Normal Limits
	Lung w/ Bronchi–Within Normal Limits
D1	Heart–Within Normal Limits
	Thymus–Within Normal Limits
D2	Liver–Within Normal Limits
	Spleen-Tissue Not Present
D3	Aorta–Within Normal Limits
E1	Kidney–Within Normal Limits
E2	Skin–Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord-x.s. vacuolar change, thoracic dorsal horn, minimal

Accession Number: 570-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Within Normal Limits
	Pituitary—Within Normal Limits
	Thyroid—Within Normal Limits
	Parathyroid—Within Normal Limits
B2	Submandibular LN—Within Normal Limits
	Salivary Gland—Within Normal Limits
	Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits
	Esophagus-Tissue Not Present
	Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits
	Thymus—Within Normal Limits
D2	Liver-Inflammation, chronic, subendothelial, focal, minimal
	Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney, right-mineralization, intratubular, focal, minimal
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Tissue Not Present
- Colon—Within Normal Limits
- Cecum—Hyperplasia, lymphoid, diffuse, mild
- F3** Rectum—Within Normal Limits (see G3)
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits (see F3)
- H** Brain —Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—x.s. vacuolar change, cervical dorsal horn, minimal
-l.s. vacuolar change, lumbar dorsal horn, minimal

Accession Number: 571-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1--Within Normal Limits
A2	Nasal 2--Within Normal Limits
A3	Sternum--Within Normal Limits
A4	Femur--Within Normal Limits
B1	Adrenal--Within Normal Limits
	Pituitary--Within Normal Limits
	Thyroid--Within Normal Limits
	Parathyroid-Tissue Not Present
B2	Submandibular LN--Within Normal Limits
	Salivary Gland--Within Normal Limits
	Harderian Gland--Within Normal Limits
C	Trachea--Within Normal Limits
	Esophagus--Within Normal Limits
	Lung w/ Bronchi-Alveolar histiocytosis, multifocal, minimal
D1	Heart--Within Normal Limits
	Thymus--Within Normal Limits
D2	Liver--Within Normal Limits
	Spleen--Within Normal Limits
D3	Aorta-Tissue Not Present
E1	Kidney--Within Normal Limits
E2	Skin--Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—One Section Present
- Uterus, uterine horn—dilation, mild
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—x.s. vacuolar change, thoracic & lumbar dorsal horn, minimal
-x.s. cervical Tissue Not Present

Accession Number: 572-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1–Within Normal Limits
A2	Nasal 2–Within Normal Limits
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal–Within Normal Limits
	Pituitary–Within Normal Limits
	Thyroid–Within Normal Limits
	Parathyroid–Within Normal Limits
B2	Submandibular LN–Within Normal Limits
	Salivary Gland–Within Normal Limits
	Harderian Gland–Within Normal Limits
C	Trachea–Within Normal Limits
	Esophagus–Within Normal Limits
	Lung w/ Bronchi–Within Normal Limits
D1	Heart–Within Normal Limits
	Thymus–Within Normal Limits
D2	Liver–Within Normal Limits
	Spleen–Within Normal Limits
D3	Aorta–Within Normal Limits
E1	Kidney–Within Normal Limits
E2	Skin–Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits (thoracic & lumbar x.s. Tissue Not Present)

Accession Number: 573-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1 –Within Normal Limits
A2	Nasal 2–Within Normal Limits
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal–Within Normal Limits
	Pituitary–Within Normal Limits
	Thyroid–Within Normal Limits
	Parathyroid-Tissue Not Present
B2	Submandibular LN–Within Normal Limits
	Salivary Gland–Within Normal Limits
	Harderian Gland–Within Normal Limits
C	Trachea–Within Normal Limits
	Esophagus-Tissue Not Present
	Lung w/ Bronchi–Within Normal Limits
D1	Heart-Poorly differentiated spindle cell neoplasm
	Thymus–Within Normal Limits
D2	Liver-Inflammation, chronic, subendothelial, multifocal, minimal
	Spleen–Within Normal Limits
D3	Aorta–Within Normal Limits
E1	Kidney–Within Normal Limits
E2	Skin–Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 574-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1–Within Normal Limits
A2	Nasal 2–Within Normal Limits
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal–Within Normal Limits
	Pituitary–Within Normal Limits
	Thyroid–Within Normal Limits
	Parathyroid–Within Normal Limits
B2	Submandibular LN–Within Normal Limits
	Salivary Gland–Within Normal Limits
	Harderian Gland–Within Normal Limits
C	Trachea–Within Normal Limits
	Esophagus-Tissue Not Present
	Lung w/ Bronchi–Within Normal Limits
D1	Heart–Within Normal Limits
	Thymus-Thymic epithelial cysts, multifocal, minimal
D2	Liver-Inflammation, chronic, subendothelial, minimal
	Spleen–Within Normal Limits
D3	Aorta–Within Normal Limits
E1	Kidney–Within Normal Limits
E2	Skin–Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum-Tissue Not Present
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus, uterine horn-dilation, minimal
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 575-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1–Within Normal Limits
A2	Nasal 2–Within Normal Limits
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal–Within Normal Limits
	Pituitary–Within Normal Limits
	Thyroid–Within Normal Limits
	Parathyroid-Tissue Not Present
B2	Submandibular LN–Within Normal Limits
	Salivary Gland–Within Normal Limits
	Harderian Gland–Within Normal Limits
C	Trachea–Within Normal Limits
	Esophagus–Within Normal Limits
	Lung w/ Bronchi-Alveolar histiocytosis, multifocal, mild
D1	Heart–Within Normal Limits
	Thymus–Within Normal Limits
D2	Liver–Within Normal Limits
	Spleen–Within Normal Limits
D3	Aorta–Within Normal Limits
E1	Kidney–Within Normal Limits
E2	Skin–Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain—Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

APPENDIX 2. MICROSCOPIC FINDINGS GROUP 4
(500 mg/kg, RATS)

Accession Number: 576-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Within Normal Limits Pituitary—Within Normal Limits Thyroid—Ultimobranchial cyst, focal, mild Parathyroid—Within Normal Limits
B2	Submandibular LN—Within Normal Limits Salivary Gland—Within Normal Limits Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits Esophagus—Tissue Not Present Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits Thymus—Thymic epithelial cyst, focal, mild
D2	Liver—Inflammation, chronic, subendothelial, multifocal, minimal Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney, left—nephritis, subacute, interstitial, minimal

-mineralization, intratubular w/ epithelial degeneration, focal, minimal

- E2** Skin—Within Normal Limits
- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits (see G3)
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 577-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1–Within Normal Limits
A2	Nasal 2–Within Normal Limits
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal–Within Normal Limits
	Pituitary–Within Normal Limits
	Thyroid–Ultimobranchial cyst, focal, mild
	Parathyroid–Within Normal Limits
B2	Submandibular LN–Within Normal Limits
	Salivary Gland–Within Normal Limits
	Harderian Gland–Within Normal Limits
C	Trachea–Within Normal Limits
	Esophagus–Within Normal Limits
	Lung w/ Bronchi–Alveolar histiocytosis, multifocal, minimal
D1	Heart–Within Normal Limits
	Thymus–Thymic epithelial cyst, multifocal, minimal
D2	Liver–Inflammation, chronic, random, multifocal, minimal
	Spleen–Within Normal Limits
D3	Aorta–Within Normal Limits
E1	Kidney–Within Normal Limits
E2	Skin–Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord-x.s. vacuolar change, thoracic dorsal horn, minimal

Accession Number: 578-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1 –Within Normal Limits (this is Nasal 2)
A2	Nasal 2–Within Normal Limits (this is Nasal 1)
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal–Within Normal Limits Pituitary–Within Normal Limits Thyroid–Ultimobranchial cyst, focal, mild Parathyroid-Tissue Not Present
B2	Submandibular LN–Within Normal Limits Salivary Gland–Within Normal Limits Harderian Gland–Within Normal Limits
C	Trachea–Within Normal Limits Esophagus–Within Normal Limits Lung w/ Bronchi–Within Normal Limits
D1	Heart–Within Normal Limits Thymus–Within Normal Limits
D2	Liver–Within Normal Limits Spleen–Within Normal Limits
D3	Aorta–Within Normal Limits
E1	Kidney–Within Normal Limits
E2	Skin–Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord, thoracic-demyelination, multifocal, minimal

Accession Number: 579-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1–Within Normal Limits
A2	Nasal 2–Within Normal Limits
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal–Within Normal Limits
	Pituitary–Within Normal Limits
	Thyroid–Ultimobranchial cyst, focal, mild
	Parathyroid–Within Normal Limits
B2	Submandibular LN–Within Normal Limits
	Salivary Gland–Within Normal Limits
	Harderian Gland–Within Normal Limits
C	Trachea–Within Normal Limits
	Esophagus–Within Normal Limits
	Lung w/ Bronchi–Within Normal Limits
D1	Heart–Within Normal Limits
	Thymus–Within Normal Limits
D2	Liver–Within Normal Limits
	Spleen–Within Normal Limits
D3	Aorta–Within Normal Limits
E1	Kidney–Within Normal Limits
E2	Skin–Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Gastritis, acute, focal, minimal
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord-x.s. vacuolar change, cervical & thoracic dorsal horn, mild & minimal, respectively

Accession Number: 580-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1–Within Normal Limits
A2	Nasal 2–Within Normal Limits
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal–Within Normal Limits Pituitary–Within Normal Limits Thyroid–Ultimobranchial cyst, multifocal, minimal Parathyroid–Within Normal Limits
B2	Submandibular LN–Within Normal Limits Salivary Gland–Within Normal Limits Harderian Gland–Within Normal Limits
C	Trachea–Within Normal Limits Esophagus–Within Normal Limits Lung w/ Bronchi–Within Normal Limits
D1	Heart–Within Normal Limits Thymus–Tissue misidentified (pancreas)
D2	Liver–Inflammation, chronic, random, multifocal, mild -vacuolar change, scattered, random, minimal Spleen–Within Normal Limits
D3	Aorta–Within Normal Limits
E1	Kidney–Within Normal Limits
E2	Skin–Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain—Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord-x.s. vacuolar change, cervical & thoracic dorsal horn, minimal
-lumbar x.s. Tissue Not Present

Accession Number: 581-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1--Within Normal Limits
A2	Nasal 2--Within Normal Limits
A3	Sternum--Within Normal Limits
A4	Femur--Within Normal Limits
B1	Adrenal--Within Normal Limits
	Pituitary--Within Normal Limits
	Thyroid-Ultimobranchial cyst, focal, minimal
	Parathyroid-Tissue Not Present
B2	Submandibular LN--Within Normal Limits
	Salivary Gland--Within Normal Limits
	Harderian Gland--Within Normal Limits
C	Trachea--Within Normal Limits
	Esophagus-Tissue Not Present
	Lung w/ Bronchi-Alveolar histiocytosis, multifocal, minimal
D1	Heart--Within Normal Limits
	Thymus--Within Normal Limits
D2	Liver--Within Normal Limits
	Spleen--Within Normal Limits
D3	Aorta--Within Normal Limits
E1	Kidney, right-mineralization, convoluted tubule, focal, minimal
E2	Skin--Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus, uterine horns-dilation, moderate
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord-x.s. vacuolar change, thoracic dorsal horn, minimal

Accession Number: 582-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1–Within Normal Limits
A2	Nasal 2–Within Normal Limits
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal–Within Normal Limits
	Pituitary–Within Normal Limits
	Thyroid–Within Normal Limits
	Parathyroid–Within Normal Limits
B2	Submandibular LN–Within Normal Limits
	Salivary Gland–Within Normal Limits
	Harderian Gland–Within Normal Limits
C	Trachea–Within Normal Limits
	Esophagus–Within Normal Limits
	Lung w/ Bronchi–Within Normal Limits
D1	Heart–Within Normal Limits
	Thymus–Within Normal Limits
D2	Liver–Within Normal Limits
	Spleen–Within Normal Limits
D3	Aorta–Within Normal Limits
E1	Kidney, left-cortical cyst, focal, mild
E2	Skin–Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—decidual alteration, diffuse, mild
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain—Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—x.s. vacuolar change, cervical dorsal horn, minimal

Accession Number: 583-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1--Within Normal Limits
A2	Nasal 2--Within Normal Limits
A3	Sternum--Within Normal Limits
A4	Femur--Within Normal Limits
B1	Adrenal--Within Normal Limits
	Pituitary--Within Normal Limits
	Thyroid-Ultimobranchial cyst, focal, minimal
	Parathyroid-Tissue Not Present
B2	Submandibular LN-Tissue Not Present
	Salivary Gland--Within Normal Limits
	Harderian Gland--Within Normal Limits
C	Trachea--Within Normal Limits
	Esophagus-Tissue Not Present
	Lung w/ Bronchi--Within Normal Limits
D1	Heart--Within Normal Limits
	Thymus--Within Normal Limits
D2	Liver-Inflammation, chronic, random, multifocal, minimal
	Spleen--Within Normal Limits
D3	Aorta--Within Normal Limits
E1	Kidney--Within Normal Limits
E2	Skin--Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum-Tissue Not Present
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain—Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord-x.s. vacuolar change, thoracic dorsal horn, mild

Accession Number: 584-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1 –Within Normal Limits
A2	Nasal 2–Within Normal Limits
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal–Within Normal Limits Pituitary–Within Normal Limits Thyroid–Within Normal Limits Parathyroid–Within Normal Limits
B2	Submandibular LN–Within Normal Limits Salivary Gland–Within Normal Limits Harderian Gland–Within Normal Limits
C	Trachea–Within Normal Limits Esophagus-Tissue Not Present Lung w/ Bronchi–Within Normal Limits
D1	Heart–Within Normal Limits Thymus–Within Normal Limits
D2	Liver-Inflammation, chronic, random, multifocal, minimal w/ occasional hepatocellular necrosis Spleen–Within Normal Limits
D3	Aorta–Within Normal Limits
E1	Kidney–Within Normal Limits
E2	Skin–Within Normal Limits

- Muscle—Within Normal Limits
 - Nerve—Within Normal Limits
 - Mammary—Within Normal Limits
 - F1** Stomach—Within Normal Limits
 - Pancreas—Within Normal Limits
 - Duodenum—Within Normal Limits
 - Jejunum—Within Normal Limits
 - F2** Ileum—Within Normal Limits
 - Colon—Within Normal Limits
 - Cecum—Within Normal Limits
 - F3** Rectum—Within Normal Limits
 - G1** Ovaries—Within Normal Limits
 - Uterus—Within Normal Limits
 - G2** Urinary Bladder—Within Normal Limits
 - G3** Vagina—Within Normal Limits
 - H** Brain —Within Normal Limits
 - I** Eye—Within Normal Limits
 - J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord-x.s. vacuolar change, thoracic & lumbar dorsal horn, mild

Accession Number: 585-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1–Within Normal Limits
A2	Nasal 2–Within Normal Limits
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal–Within Normal Limits
	Pituitary–Within Normal Limits
	Thyroid–Within Normal Limits
	Parathyroid–Within Normal Limits
B2	Submandibular LN–Within Normal Limits
	Salivary Gland–Within Normal Limits
	Harderian Gland–Within Normal Limits
C	Trachea–Within Normal Limits
	Esophagus–Within Normal Limits
	Lung w/ Bronchi–Within Normal Limits
D1	Heart–Within Normal Limits
	Thymus–Within Normal Limits
D2	Liver–Inflammation, chronic, random, multifocal w/ occasional subendothelial foci
	Spleen–Within Normal Limits
D3	Aorta–Within Normal Limits
E1	Kidney–Within Normal Limits
E2	Skin–Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain—Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord-x.s. vacuolar change, cervical & lumbar dorsal horn, minimal

Accession Number: 586-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1--Within Normal Limits
A2	Nasal 2--Within Normal Limits
A3	Sternum--Within Normal Limits
A4	Femur--Within Normal Limits
B1	Adrenal--Within Normal Limits
	Pituitary--Within Normal Limits
	Thyroid--Within Normal Limits
	Parathyroid--Within Normal Limits
B2	Submandibular LN--Within Normal Limits
	Salivary Gland--Within Normal Limits
	Harderian Gland--Within Normal Limits
C	Trachea--Within Normal Limits
	Esophagus-Tissue Not Present
	Lung w/ Bronchi-Alveolar histiocytosis, focal, minimal
D1	Heart--Within Normal Limits
	Thymus--Within Normal Limits
D2	Liver--Within Normal Limits
	Spleen--Within Normal Limits
D3	Aorta--Within Normal Limits
E1	Kidney--Within Normal Limits
E2	Skin--Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain—Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue-epithelial cyst, focal, mild
- K1, 2, 3** Spinal Cord-x.s. vacuolar change, thoracic dorsal horn, minimal

Accession Number: 587-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1--Within Normal Limits
A2	Nasal 2--Within Normal Limits
A3	Sternum--Within Normal Limits
A4	Femur--Within Normal Limits
B1	Adrenal--Within Normal Limits
	Pituitary--Within Normal Limits
	Thyroid--Within Normal Limits
	Parathyroid--Within Normal Limits
B2	Submandibular LN--Within Normal Limits
	Salivary Gland--Within Normal Limits
	Harderian Gland--Within Normal Limits
C	Trachea--Within Normal Limits
	Esophagus--Within Normal Limits
	Lung w/ Bronchi--Within Normal Limits
D1	Heart--Within Normal Limits
	Thymus--Within Normal Limits
D2	Liver-Inflammation, chronic, random, focal, minimal
	Spleen--Within Normal Limits
D3	Aorta--Within Normal Limits
E1	Kidney--Within Normal Limits
E2	Skin--Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus, uterine horns-dilation, mild
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain—Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord-x.s. vacuolar change, cervical, thoracic, & lumbar dorsal horn, mild

Accession Number: 588-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits (see A4)
A4	Femur-Tissue Not Present
B1	Adrenal—Within Normal Limits Pituitary—Within Normal Limits Thyroid—Within Normal Limits Parathyroid—Within Normal Limits
B2	Submandibular LN—Within Normal Limits Salivary Gland—Within Normal Limits Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits Esophagus—Within Normal Limits Lung w/ Bronchi-Alveolar histiocytosis, multifocal, mild
D1	Heart—Within Normal Limits Thymus—Within Normal Limits
D2	Liver-Inflammation, chronic, random, multifocal, minimal w/ occasional hepatocellular necrosis Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Within Normal Limits
- H** Brain—Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord-x.s. vacuolar change, cervical & thoracic dorsal horn, minimal

Accession Number: 589-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1–Within Normal Limits
A2	Nasal 2–Within Normal Limits
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal–Within Normal Limits
	Pituitary–Within Normal Limits
	Thyroid–Ultimobranchial cyst, multifocal, minimal
	Parathyroid–Within Normal Limits
B2	Submandibular LN–Within Normal Limits
	Salivary Gland–Within Normal Limits
	Harderian Gland–Within Normal Limits
C	Trachea–Within Normal Limits
	Esophagus–Within Normal Limits
	Lung w/ Bronchi–Within Normal Limits
D1	Heart–Within Normal Limits
	Thymus–Thymic epithelial cyst, focal, minimal
D2	Liver–Inflammation, chronic, random, multifocal w/ subcapsular & subendothelial foci
	Spleen–Within Normal Limits
D3	Aorta–Within Normal Limits
E1	Kidney–Within Normal Limits
E2	Skin–Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Ovaries—Within Normal Limits
- Uterus—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- G3** Vagina—Inflammation, subacute, focal, minimal
- H** Brain—Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 590-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Within Normal Limits Pituitary—Within Normal Limits Thyroid—Within Normal Limits Parathyroid—Within Normal Limits
B2	Submandibular LN—Within Normal Limits Salivary Gland—Within Normal Limits Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits Esophagus—Within Normal Limits Lung w/ Bronchi-Alveolar histiocytosis, multifocal, minimal
D1	Heart—Within Normal Limits Thymus—Within Normal Limits
D2	Liver-Eosinophilic focus of cellular alteration, focal, minimal -Basophilic focus of cellular alteration, focal, minimal -Inflammation, chronic, random, multifocal, minimal Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney, left-Inflammation, interstitial, subacute, minimal

- E2** Skin–Within Normal Limits
- Muscle–Within Normal Limits
- Nerve–Within Normal Limits
- Mammary–Within Normal Limits
- F1** Stomach–Within Normal Limits
- Pancreas–Within Normal Limits
- Duodenum–Within Normal Limits
- Jejunum–Within Normal Limits
- F2** Ileum –Within Normal Limits
- Colon–Within Normal Limits
- Cecum–Within Normal Limits
- F3** Rectum–Within Normal Limits
- G1** Ovaries–Within Normal Limits
- Uterus–Within Normal Limits
- G2** Urinary Bladder–Within Normal Limits
- G3** Vagina–Within Normal Limits
- H** Brain –Within Normal Limits
- I** Eye–Within Normal Limits
- J** Tongue–Within Normal Limits

K1, 2, 3 Spinal Cord-x.s. vacuolar change, cervical, thoracic & lumbar dorsal horn, minimal

APPENDIX 3. MICROSCOPIC FINDINGS GROUP 5 (CONTROL MICE)

Accession Number: 591-98

Slide	Tissue
A1	Nasal 1 –Within Normal Limits
A2	Nasal 2–Within Normal Limits
A3	Sternum–Within Normal Limits
A4	Femur–Within Normal Limits
B1	Adrenal—Vacuolar change, multifocal, minimal Pituitary—Tissue Not Present Thyroid—C-cell hyperplasia, focal, minimal Parathyroid—Tissue Not Present
B2	Submandibular LN–Within Normal Limits Salivary Gland–Within Normal Limits Harderian Gland–Within Normal Limits
C	Trachea–Within Normal Limits Esophagus–Within Normal Limits Lung w/ Bronchi–Within Normal Limits
D1	Heart, valve—pigmentation, minimal Thymus–Within Normal Limits
D2	Liver–Within Normal Limits Spleen–Within Normal Limits
D3	Aorta–Within Normal Limits
E1	Kidney–Within Normal Limits

- E2** Skin—Within Normal Limits
- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Within Normal Limits
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain—Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 592-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Vacuolar change, multifocal, minimal Pituitary—Within Normal Limits Thyroid—C-cell hyperplasia, multifocal, minimal Parathyroid—Within Normal Limits
B2	Submandibular LN—Within Normal Limits Salivary Gland—Within Normal Limits Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits Esophagus—Within Normal Limits Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits Thymus—Within Normal Limits
D2	Liver—Inflammation, chronic, multifocal, random minimal Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Inadequate Sample

- Muscle, associated adipose tissue—Inflammation, chronic, focal, minimal
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, focal, minimal w/ multinucleated giant cell
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Within Normal Limits
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain—Tissue Not Present
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 593-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Inadequate Sample
	Pituitary—Tissue Not Present
	Thyroid—C-cell hyperplasia, minimal
	Parathyroid—Within Normal Limits
B2	Submandibular LN—Tissue Not Present
	Salivary Gland—Within Normal Limits
	Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits
	Esophagus—Within Normal Limits
	Lung w/ Bronchi—Within Normal Limits
D1	Heart, epicardium—mineralization, multifocal, minimal
	Thymus, medulla—cyst, focal, minimal
D2	Liver—Within Normal Limits
	Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits

- Mammary—Within Normal Limits

- F1** Stomach—Within Normal Limits
- Pancreas, islet—hyperplasia, focal, minimal
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits

- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits

- F3** Rectum—Within Normal Limits

- G1** Testes—degeneration, minimal w/ minimal segmental loss of germinal epithelium

- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits

- G3** Epididymis—epithelial attenuation, multifocal, minimal

- G4** Seminal Vesicle—Within Normal Limits

- H** Brain, ventricles—dilatation, minimal

- I** Eye—Within Normal Limits

- J** Tongue—Within Normal Limits

- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 594-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Vacuolar change, multifocal, minimal Pituitary—Within Normal Limits Thyroid—C-cell hyperplasia, focal, minimal Parathyroid—Within Normal Limits
B2	Submandibular LN—Within Normal Limits Salivary Gland—Within Normal Limits Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits Esophagus—Within Normal Limits Lung w/ Bronchi—Within Normal Limits
D1	Heart, valve—pigmentation, focal, minimal Right ventricular free wall, chamber surface—fibrosis, focal, mild w/ mineralization Thymus—Within Normal Limits
D2	Liver—Within Normal Limits Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits

- E2** Skin—Within Normal Limits
 - Muscle—Within Normal Limits
 - Nerve—Within Normal Limits
 - Mammary—Within Normal Limits
- F1** Stomach, squamous region—epithelial hyperplasia, diffuse, minimal
 - Pancreas—Within Normal Limits
 - Duodenum—Within Normal Limits
 - Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
 - Colon—Within Normal Limits
 - Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
 - Prostate—Within Normal Limits
- G3** Epididymis—epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain, ventricles—dilatation, minimal
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 595-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—vacuolar change, multifocal, minimal Pituitary—Within Normal Limits Thyroid—Within Normal Limits Parathyroid—Tissue Not Present
B2	Submandibular LN—lymphoid hyperplasia, mild Salivary Gland—Within Normal Limits Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits Esophagus—Within Normal Limits Lung w/ Bronchi—Within Normal Limits
D1	Heart, valve—pigmentation, focal, minimal Thymus—Within Normal Limits
D2	Liver—Within Normal Limits Spleen—Within Normal Limits
D3	Aorta—Tissue Not Present
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, multifocal, minimal w/ giant cell
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 596-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Vacuolar change, multifocal, minimal Pituitary—Within Normal Limits Thyroid—C-cell hyperplasia, minimal Parathyroid—Within Normal Limits
B2	Submandibular LN—Within Normal Limits Salivary Gland—Within Normal Limits Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits Esophagus—Within Normal Limits Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits Thymus—Within Normal Limits
D2	Liver—Inflammation, chronic, multifocal, random w/ occasional single cell necrosis Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Tissue Not Present

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, minimal w/ multifocal, multinucleated giant cells
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Epithelial hyperplasia, diffuse, mild
- H** Brain, ventricles—Dilatation, minimal
- I** Eye—Within Normal Limits
- J** Tongue—Inadequate Sample
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 597-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Vacuolar change, focal, minimal Pituitary—Within Normal Limits Thyroid—C-cell hyperplasia, minimal Parathyroid—Tissue Not Present
B2	Submandibular LN—Within Normal Limits Salivary Gland—Within Normal Limits Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits Esophagus—Within Normal Limits Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits Thymus—Within Normal Limits
D2	Liver—Inflammation, chronic, multifocal, random, minimal Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Tissue Not Present
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, minimal w/ focal multinucleated giant cell
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 598-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Within Normal Limits
	Pituitary—Within Normal Limits
	Thyroid—C-cell hyperplasia, focal, minimal
	Parathyroid—Tissue Not Present
B2	Submandibular LN—Within Normal Limits
	Salivary Gland—Within Normal Limits
	Harderian Gland, acini—Dilatation, multifocal, minimal
C	Trachea—Within Normal Limits
	Esophagus—Within Normal Limits
	Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits
	Thymus—Within Normal Limits
D2	Liver—Inflammation, chronic, multifocal, random, minimal w/ minimal single cell necrosis
	Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Tissue Not Present
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, minimal w/ focal multinucleated giant cell
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, focal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain—Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 599-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Vacuolar change, multifocal, minimal
	Pituitary—Within Normal Limits
	Thyroid—C-cell hyperplasia, focal, minimal
	Parathyroid—Within Normal Limits
B2	Submandibular LN—Tissue Not Present
	Salivary Gland—Within Normal Limits
	Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits
	Esophagus—Within Normal Limits
	Lung w/ Bronchi—Within Normal Limits
D1	Heart, valve—Pigmentation, focal, minimal
	Thymus—Mineralization, multifocal, minimal
D2	Liver—Within Normal Limits
	Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas, islet—Hyperplasia, multifocal, minimal
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Tissue Not Present
- Cecum—Lymphoid hyperplasia, focal, minimal
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, minimal w/ multifocal, multinucleated giant cells
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 600-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Within Normal Limits
	Pituitary—Within Normal Limits
	Thyroid—C-cell hyperplasia, focal, minimal
	Parathyroid—Tissue Not Present
B2	Submandibular LN—Within Normal Limits
	Salivary Gland—Within Normal Limits
	Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits
	Esophagus—Within Normal Limits
	Lung w/ Bronchi—Within Normal Limits
D1	Heart, valve—Pigmentation, focal, minimal
	Thymus—Within Normal Limits
D2	Liver, gallbladder, submucosa—granulocytic accumulation, diffuse, mild
	Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
 - Pancreas, islet—Hyperplasia, focal, mild
 - Duodenum—Within Normal Limits
 - Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
 - Colon—Within Normal Limits
 - Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, minimal w/ multifocal, multinucleated giant cells and focal tubular epithelial hypoplasia
- G2** Urinary Bladder—Within Normal Limits
 - Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain, ventricles—Dilatation, minimal
- I** Eye—Within Normal Limits
- J** Tongue—Inadequate Sample
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 601-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Vacuolar change, focal, minimal Pituitary—Within Normal Limits Thyroid—Within Normal Limits Parathyroid—Tissue Not Present
B2	Submandibular LN—Tissue Not Present Salivary Gland—Within Normal Limits Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits Esophagus—Inflammation, chronic, focal, minimal Lung w/ Bronchi—Within Normal Limits
D1	Heart, valve—Pigmentation, focal, minimal Thymus—Within Normal Limits
D2	Liver—Within Normal Limits Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain—Within Normal Limits
- I** Eye—Retinal atrophy, focal, moderate
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 602-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Vacuolar change, multifocal, minimal Pituitary—Within Normal Limits Thyroid—C-cell hyperplasia, focal, minimal Parathyroid—Within Normal Limits
B2	Submandibular LN—Tissue Not Present Salivary Gland—Within Normal Limits Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits Esophagus—Within Normal Limits Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits Thymus—Within Normal Limits
D2	Liver—Within Normal Limits Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Tissue Not Present
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, minimal w/ multifocal, multinucleated giant cells
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis--Inflammation, chronic, mild w/ extensive peri-ductal fibrosis
--Hypospermia, multifocal, mild
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain—Within Normal Limits
- I** Eye—Dysplasia, unilateral, moderate
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 603-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Within Normal Limits
	Pituitary—Within Normal Limits
	Thyroid—Within Normal Limits
	Parathyroid—Tissue Not Present
B2	Submandibular LN—Within Normal Limits
	Salivary Gland—Within Normal Limits
	Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits
	Esophagus—Within Normal Limits
	Lung w/ Bronchi—Within Normal Limits
D1	Heart, valve—Pigmentation, multifocal, minimal
	Thymus—Tissue Not Present
D2	Liver—Within Normal Limits
	Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Inadequate Sample
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, minimal w/ multifocal tubular epithelial hypoplasia w/ focal multinucleated giant cells
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, focal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain, ventricles—Dilatation, minimal
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 604-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Vacuolar change, multifocal, minimal Pituitary—Within Normal Limits Thyroid—C-cell hyperplasia, multifocal, minimal Parathyroid—Tissue Not Present
B2	Submandibular LN—Within Normal Limits Salivary Gland—Within Normal Limits Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits Esophagus—Within Normal Limits Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits Thymus—Tissue Not Present
D2	Liver—Inflammation, chronic, multifocal, random, minimal Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Inflammation, granulomatous, focal, severe
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain, ventricles—Dilatation, minimal
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 605-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Vacuolar change, focal, mild
	Pituitary—Within Normal Limits
	Thyroid—C-cell hyperplasia, multifocal, minimal
	Parathyroid—Tissue Not Present
B2	Submandibular LN—Lymphoid hyperplasia, diffuse, minimal
	Salivary Gland—Within Normal Limits
	Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits
	Esophagus—Within Normal Limits
	Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits
	Thymus—Within Normal Limits
D2	Liver—Inflammation, chronic, focal, minimal
	Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, minimal w/ multifocal tubular epithelial hypoplasia w/ occasional multinucleated giant cells
- G2** Urinary Bladder—Epithelial hyperplasia, diffuse, minimal
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Epithelial hyperplasia, focal, minimal
- H** Brain, ventricles—Dilatation, minimal
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

APPENDIX 4. MICROSCOPIC FINDINGS GROUP 8
(500 mg/kg MICE)

Accession Number: 606-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Tissue Not Present
B1	Adrenal—Within Normal Limits
	Pituitary—Within Normal Limits
	Thyroid—Within Normal Limits
	Parathyroid—Within Normal Limits
B2	Submandibular LN—Tissue Not Present
	Salivary Gland—Within Normal Limits
	Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits
	Esophagus—Tissue Not Present
	Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits
	Thymus—Within Normal Limits
D2	Liver—Inflammation, chronic, multifocal, random, minimal w/ single cell necrosis
	Spleen—Within Normal Limits
D3	Aorta—Tissue Not Present
E1	Kidney—Within Normal Limits

- E2** Skin—Within Normal Limits
- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Tissue Not Present
- G1** Testes—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain, ventricle—Dilatation, unilateral, minimal
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 607-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Within Normal Limits
	Pituitary—Within Normal Limits
	Thyroid—C-cell hyperplasia, focal, minimal
	Parathyroid—Tissue Not Present
B2	Submandibular LN—Tissue Not Present
	Salivary Gland—Tissue Not Present
	Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits
	Esophagus—Within Normal Limits
	Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits
	Thymus—Within Normal Limits
D2	Liver—Inflammation, chronic, multifocal, minimal
	Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Tissue Not Present
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain, ventricle—Dilatation, minimal
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 608-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Tissue Not Present
	Pituitary—Within Normal Limits
	Thyroid—C-cell hyperplasia, focal, minimal
	Parathyroid—Tissue Not Present
B2	Submandibular LN—Tissue Not Present
	Salivary Gland—Tissue Not Present
	Harderian Gland—Within Normal Limits
C	Trachea—Insufficient Sample
	Esophagus—Insufficient Sample
	Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits
	Thymus—Tissue Not Present
D2	Liver—Necrosis, multifocal, minimal
	Spleen—Tissue Not Present
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach, squamous region—Epithelial hyperplasia, diffuse, mild
- Pancreas—Tissue Not Present
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, minimal w/ occasional vacuoles and multinucleated giant cells
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Within Normal Limits
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain, ventricles—Dilatation, minimal
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 609-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Vacuolar change, multifocal, minimal
	Pituitary—Within Normal Limits
	Thyroid—Tissue Not Present
	Parathyroid—Tissue Not Present
B2	Submandibular LN—Tissue Not Present
	Salivary Gland—Tissue Not Present
	Harderian Gland—Within Normal Limits
C	Trachea—Tissue Not Present
	Esophagus—Within Normal Limits
	Lung w/ Bronchi—Within Normal Limits
D1	Heart, valve—Pigmentation, multifocal, mild
	Thymus—Within Normal Limits
D2	Liver—Inflammation, chronic, multifocal, minimal
	Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Tissue Not Present
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Tissue Not Present
- G1** Testes—Degeneration, minimal w/ minimal, multifocal, multinucleated giant cells
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, focal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain, ventricles—Dilatation, minimal
- I** Eye—Inadequate samples for assessing retina
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 610-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal, medulla—Cyst, focal, minimal Pituitary—Within Normal Limits Thyroid—C-cell hyperplasia, focal, minimal Parathyroid—Tissue Not Present
B2	Submandibular LN—Tissue Not Present Salivary Gland—Within Normal Limits Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits Esophagus—Within Normal Limits Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits Thymus—Tissue Not Present
D2	Liver—Within Normal Limits Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Tissue Not Present
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, minimal w/ focal multinucleated giant cell
- G2** Urinary Bladder—Transitional cell hyperplasia, multifocal, minimal
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain—Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 611-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Tissue Not Present
A4	Femur—Within Normal Limits
B1	Adrenal—Vacuolar change, multifocal , minimal Pituitary—Within Normal Limits Thyroid—C-cell hyperplasia, minimal Parathyroid—Within Normal Limits
B2	Submandibular LN—Tissue Not Present Salivary Gland—Within Normal Limits Harderian Gland—Tissue Not Present
C	Trachea—Within Normal Limits Esophagus—Within Normal Limits Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits Thymus—Within Normal Limits
D2	Liver—Inflammation, chronic, multifocal, random, minimal Spleen—Within Normal Limits
D3	Aorta—Tissue Not Present
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, multifocal, minimal
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain, ventricles—Dilatation, minimal
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 612-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Vacuolar change, multifocal, minimal Pituitary—Tissue Not Present Thyroid—C-cell hyperplasia, minimal Parathyroid—Within Normal Limits
B2	Submandibular LN—Lymphoid hyperplasia, diffuse, mild Salivary Gland—Inflammation, chronic, focal, minimal Harderian Gland, acini—Epithelial hyperplasia, focal, minimal
C	Trachea—Epithelial hyperplasia, focal, minimal Esophagus—Within Normal Limits Lung w/ Bronchi—Within Normal Limits
D1	Heart, valve—Pigmentation, focal, minimal Thymus—Within Normal Limits
D2	Liver—Within Normal Limits Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, focal, minimal w/ multinucleated giant cells and focal tubular hypoplasia (w/ remnant spermatogonia & few Sertoli cells)
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain—Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 613-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Vacuolar change, multifocal, minimal Pituitary—Within Normal Limits Thyroid—C-cell hyperplasia, multifocal, minimal Parathyroid—Within Normal Limits
B2	Submandibular LN—Tissue Not Present Salivary Gland—Within Normal Limits Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits Esophagus—Within Normal Limits Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits Thymus—Within Normal Limits
D2	Liver—Within Normal Limits Spleen—Lymphoid hyperplasia, diffuse, mild
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Tissue Not Present

- Muscle—Within Normal Limits
- Nerve—Tissue Not Present
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Tissue Not Present
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, segmental, multifocal, minimal w/ giant cells & focal tubular hypoplasia
- G2** Urinary Bladder—Epithelial hyperplasia, minimal
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain—Within Normal Limits
- I** Eye—Retinal degeneration, focal, mild
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 614-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Vacuolar change, multifocal, minimal Pituitary—Within Normal Limits Thyroid—C-cell hyperplasia, minimal Parathyroid—Within Normal Limits
B2	Submandibular LN—Within Normal Limits Salivary Gland—Within Normal Limits Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits Esophagus—Within Normal Limits Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits Thymus—Within Normal Limits
D2	Liver—Within Normal Limits Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Within Normal Limits
- G2** Urinary Bladder—Epithelial hyperplasia, multifocal, minimal
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain, ventricles—Dilatation, mild
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 615-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Inadequate Sample
B1	Adrenal—Vacuolar change, multifocal, minimal Pituitary—Within Normal Limits Thyroid—Within Normal Limits Parathyroid—Tissue Not Present
B2	Submandibular LN—Within Normal Limits Salivary Gland—Inflammation, chronic, minimal Harderian Gland, acini—Epithelial hyperplasia, focal, minimal
C	Trachea—Within Normal Limits Esophagus—Tissue Not Present Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits Thymus—Within Normal Limits
D2	Liver—Inflammation, chronic, multifocal, random, minimal w/ infrequent single cell hepatocellular necrosis Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits (insufficient glandular portion)
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, focal, minimal w/ occasional vacuolar change and giant cells
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain, ventricles—Dilatation, mild
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 616-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Tissue Not Present
A4	Femur—Within Normal Limits
B1	Adrenal—Within Normal Limits
	Pituitary—Within Normal Limits
	Thyroid—C-cell hyperplasia, focal, minimal
	Parathyroid—Tissue Not Present
B2	Submandibular LN—Tissue Not Present
	Salivary Gland—Tissue Not Present
	Harderian Gland—Tissue Not Present
C	Trachea—Inadequate Sample
	Esophagus—Inadequate Sample
	Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits
	Thymus—Within Normal Limits
D2	Liver—Within Normal Limits
	Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Tissue Not Present
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain —Within Normal Limits
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 617-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Vacuolar change, multifocal, minimal Pituitary—Within Normal Limits Thyroid—Within Normal Limits Parathyroid—Within Normal Limits
B2	Submandibular LN—Within Normal Limits Salivary Gland—Inflammation, chronic, focal, minimal Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits Esophagus—Tissue Not Present Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits Thymus—Within Normal Limits
D2	Liver—Within Normal Limits Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach, glandular—Inflammation, acute, focal, mild
- Pancreas—Lymphoid hyperplasia, focal, minimal
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, focal, minimal w/ loss of germinal epithelium
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain, ventricles—Dilatation, minimal
- I** Eye—Within Normal Limits
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 618-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Vacuolar change, multifocal, minimal Pituitary—Within Normal Limits Thyroid—Within Normal Limits Parathyroid—Within Normal Limits
B2	Submandibular LN—Within Normal Limits Salivary Gland—Within Normal Limits Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits Esophagus—Within Normal Limits Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits Thymus—Within Normal Limits
D2	Liver—Inflammation, chronic, multifocal, random, minimal Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum—Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, minimal w/ focal, giant cell
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, multifocal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain, ventricles—Dilatation, minimal
- I** Eye—Retinal dysplasia, mild w/ retinal-retinal pigmented epithelial scar
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 619-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Vacuolar change, multifocal, minimal
	Pituitary—Within Normal Limits
	Thyroid—C-cell hyperplasia, focal, minimal
	Parathyroid—Tissue Not Present
B2	Submandibular LN—Tissue Not Present
	Salivary Gland—Tissue Not Present
	Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits
	Esophagus—Within Normal Limits
	Lung w/ Bronchi—Within Normal Limits
D1	Heart—Within Normal Limits
	Thymus—Within Normal Limits
D2	Liver—Within Normal Limits
	Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach—Within Normal Limits
 - Pancreas—lymphoid hyperplasia, focal, minimal
 - Duodenum—Within Normal Limits
 - Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
 - Colon—Within Normal Limits
 - Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Degeneration, multifocal, minimal w/ giant cells
- G2** Urinary Bladder—Within Normal Limits
 - Prostate—Within Normal Limits
- G3** Epididymis—Epithelial attenuation, focal, minimal
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain—Pigment, deep meningeal, minimal
- I** Eye, cornea—Epithelial hyperplasia, minimal
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

Accession Number: 620-98

<u>Slide</u>	<u>Tissue</u>
A1	Nasal 1—Within Normal Limits
A2	Nasal 2—Within Normal Limits
A3	Sternum—Within Normal Limits
A4	Femur—Within Normal Limits
B1	Adrenal—Vacuolar change, focal, minimal Pituitary—Within Normal Limits Thyroid—Within Normal Limits Parathyroid—Tissue Not Present
B2	Submandibular LN—Within Normal Limits Salivary Gland—Within Normal Limits Harderian Gland—Within Normal Limits
C	Trachea—Within Normal Limits Esophagus—Within Normal Limits Lung w/ Bronchi—Within Normal Limits
D1	Heart, valve—Pigmentation, minimal Thymus—Within Normal Limits
D2	Liver, gallbladder—Inflammation, acute, minimal w/ multifocal, minimal, intraepithelial microabscesses Liver—Inflammation, chronic, multifocal, minimal Spleen—Within Normal Limits
D3	Aorta—Within Normal Limits
E1	Kidney—Within Normal Limits
E2	Skin—Within Normal Limits

- Muscle—Within Normal Limits
- Nerve—Within Normal Limits
- Mammary—Within Normal Limits
- F1** Stomach, glandular—Inflammation, chronic-active, focal, minimal
- Pancreas—Within Normal Limits
- Duodenum—Within Normal Limits
- Jejunum—Within Normal Limits
- F2** Ileum —Within Normal Limits
- Colon—Within Normal Limits
- Cecum—Within Normal Limits
- F3** Rectum—Within Normal Limits
- G1** Testes—Within Normal Limits
- G2** Urinary Bladder—Within Normal Limits
- Prostate—Within Normal Limits
- G3** Epididymis—Within Normal Limits
- G4** Seminal Vesicle—Within Normal Limits
- H** Brain, ventricles—Dilatation, minimal
- I** Eye—Retinal dysplasia, mild
- J** Tongue—Within Normal Limits
- K1, 2, 3** Spinal Cord—Within Normal Limits

APPENDIX G

Stability Evaluation Report from Equilon Enterprises, L. L. C. G-2



August 10, 1999

File No. 481b

Peter Smith, M.S.
 Battelle
 Pharmaceutical Product Development
 505 King Avenue
 Columbus, OH 43201-2693

Re: Study Numbers G003493-A and G003493-B – Stability of Test Material

Dear Mr. Smith:

I analyzed the test material used in the above-referenced 90-day study. The test material consists of the C₉-C₁₆ aromatic fraction of JET-A fuel. We analyzed an aliquot of test material prior to commencement of the study on August 18, 1998, and we analyzed a second aliquot after the study was completed on February 15, 1999. These samples were analyzed at Equilon's Westhollow Technology Center using both gas chromatography/flame ionization detection (GC/FID) and gas chromatography/mass spectrometry (GC/MS). GC/MS chromatograms for each sample are attached. Figures 1 and 2 represent the Total Ion Chromatograms (TICs) of the sample analyzed in August of 1998 and the sample analyzed in February of 1999, respectively. Visual inspection of these chromatograms seems to indicate that the two samples are the same material. A comparison of area ratios of selected analytes to 1,2,4-Trimethylbenzene from the August '98 sample to those of the February '99 sample further support their similarity. The compounds used in these ratios encompass the entire range of the material tested.

Ratios with 1,2,4-Trimethylbenzene

<u>Analytes</u>	<u>August 18, 1998</u>	<u>February 15, 1999</u>
Ethyl Benzene	0.05	0.06
m- and p-Xylene	0.14	0.15
o-Xylene	0.09	0.09
Unk. Aromatic at ~14min	0.91	1.7
Unk. Aromatic at ~18min	0.93	1.7

Given these results, it is my opinion that the composition of the test material did not change significantly over the course of the study.

Sincerely,

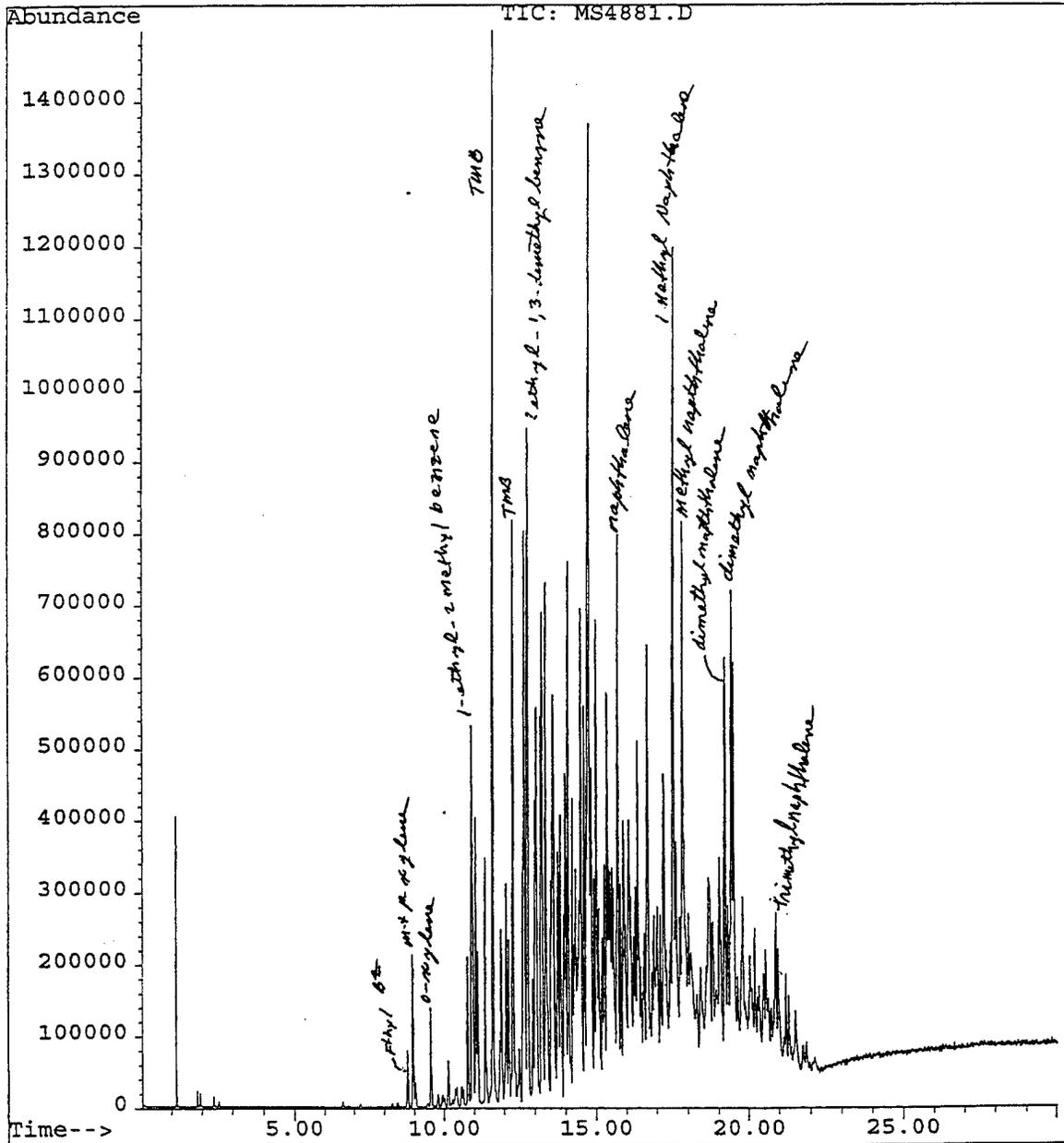
Dr. Ileana A.L. Rhodes
 Environmental Analysis & Air Quality

cc: David Mattie, Wright-Patterson Air Force Base
 Donna Vorhees, Menzie-Cura & Associates, Inc.
 Lorraine Twerdok, American Petroleum Institute

Westhollow Technology Center
 P. O. Box 1380
 Houston, TX 77251-1380

Figure 1

File : C:\HPCHEM\1\DATA\MS4881.D
Operator : JAM
Acquired : 20 Aug 98 11:53 am using AcqMethod USAF
Instrument : 5971 - GC
Sample Name: JET FUEL; AROMATICS ; - USAF DI
Misc Info : 08/20/98
Vial Number: 1



1.0 INTRODUCTION

The objective of this study was to characterize the potential toxic effects elicited by the daily oral administration of C₉-C₁₆ aromatic fraction of Jet-A in female rats and male mice for 90 days. Menzie-Cura & Associates, Inc. was the Sponsor of the study. Donna Vorhees was the Sponsor's Study Monitor. Menzie-Cura & Associates, Inc. were acting as the agent of their primary client, the U.S. Air Force's Occupational Toxicology Branch of the Air Force Research Laboratory. The study protocol, amendments to the protocol, and protocol deviations are contained in Appendix A.

Rodents are the preferred species for general toxicity testing (EPA, 1990). Members of the total petroleum hydrocarbon criteria working group (TPHCWG) evaluated the "data gaps" on animal toxicity of petroleum hydrocarbons and suggested that data from two species (rats and mice) would be of greater value than data from a single species for establishing a test substance reference dose. However, toxicity data from male rats may be difficult to interpret due to the development of α -2-microglobulin nephropathy, induced by most hydrocarbons. To keep animal numbers to a minimum, one sex of each species was considered appropriate for meeting the objectives of this study. Thus, female rats and male mice were selected. Except for the development of α -2-microglobulin nephropathy in male rats, differences between the sexes were not observed in the biological endpoints monitored. Both the Fischer 344 rat and the C57BL/6 mouse were used extensively for the toxicity testing of jet fuels from 1973 to 1983 by the Air Force.

The study was performed at Battelle (Columbus, OH) under the direction of Peter B. Smith, Study Director. The experimental start date (first day of dosing) was August 4, 1998 and the in-life phase was completed (final necropsy) on November 3, 1998.

2.0 EXPERIMENTAL DESIGN

Sixty Sprague-Dawley (CD) female rats and sixty Charles River C57BL/6 male mice were each allocated into 4 treatment groups comprised of fifteen animals. Each animal received a daily oral gavage administration of vehicle or test substance as specified below. All animals were necropsied after a 90-day treatment period.

Study Design Summary Table

Group Number	Number of Animals	Treatment	Dose Level (mg/kg/day)
1	15 female rats	Carrier Control	0
2	15 female rats	Jet-A ^a	20
3	15 female rats	Jet-A ^a	100
4	15 female rats	Jet-A ^a	500
5	15 male mice	Carrier Control	0
6	15 male mice	Jet-A ^a	20
7	15 male mice	Jet-A ^a	100
8	15 male mice	Jet-A ^a	500

a. Jet-A = C₉-C₁₆ aromatic fraction of Jet-A.

Data collection included:

- detailed clinical observations for signs of toxicity approximately one to two hours after dosing and a second observation at least six hours after dosing, twice-daily mortality and morbidity observations
- body weights at time of group assignment (Day 4 for rats and Day 5 for mice), prior to initiation of dosing (Day 1), weekly during the study and prior to necropsy (Day 91)
- weekly total food consumption measurements
- hematology and serum chemistry evaluations of animals at study termination
- complete necropsy of all animals
- measurement of organ weights and calculation of organ weights relative to brain and body weight
- microscopic examination of histologically prepared tissue samples

The study protocol, amendments and deviations are provided in Appendix A. Detailed methods for all phases of the study are specified in subsequent sections of this report.