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Institute Report No. 364

Acute Intravenous Toxicity Study of  
Hypertonic Saline/Dextran 70® and its Constituents  
in New Zealand White Rabbits

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DIVISION OF TOXICOLOGY

April 1989

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Acute Intravenous Toxicity Study of Hypertonic Saline/Dextran 70® and its Constituents in  
New Zealand White Rabbits (Toxicology Series 246) --Zaucha *et al*

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*Edwin S. Beatrice* 11 Apr 89

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| 19 ABSTRACT (Continue on reverse if necessary and identify by block number)<br>The acute toxicity following intravenous administration of a proposed HSD (Hypertonic Saline-Dextran) mixture, hypertonic saline-Dextran 70® (HSD), was evaluated in New Zealand White rabbits. Animals received a single bolus injection of 1.5 ml/kg, 1.5 ml/kg over a 5-minute period, in an attempt to induce maximum tolerated dose. Equal volumes of each HSD component, 7.5% dextrose in water (HSD), and 6% Dextran 70® (D70) in normal saline, and Ringer's lactate were also evaluated. The animals in each group were divided into two groups and sacrificed for necropsy, either Day 3 or Day 14 after dosing. Blood samples were taken for serum chemistry and hematologic analyses at Day 0, Day 3, and Day 14. Observations were made at 1, 2, and 3 hours post-dose and daily on the day of dosing and twice daily thereafter. Ringer's lactate was administered with a 10% emulsion at the start of injection in 6 of 20 rabbits. The results indicated that animals receiving HSD, the HSD and HSD groups exhibited |   |  |                                       |
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IV. SPECIFIC TERMS (cont.)

Resuscitation Fluid, New Zealand White Rabbits

V. ABSTRACT (cont.)

Increased incidence of bruising of the injected ear, inactivity, disorientation, and tremors. Compared to the controls, all groups exhibited increased respiratory rate. Except for decreased serum iron in the HS group 3 days after administration, no consistent changes were seen in serum chemistry measurements. No significant changes outside of normal limits were observed in the hematology measurements. Body weights and water consumption were unaffected by the dosing and no gross or microscopic lesions could be attributed to HSD or its constituents. These data suggest that the lethality of HS was due to an acute hemodynamic effect of the volume administered, and that the rabbit was less sensitive to HSD or D70 than to HS. Since the proposed therapeutic dose of HSD is only 4 ml/kg, these findings indicate minimal adverse effects should be anticipated with the therapeutic administration of HSD.

## ABSTRACT

The acute toxicity following intravenous administration of a proposed resuscitation fluid, hypertonic saline/ Dextran 70® (HSD), was evaluated in male and female New Zealand White rabbits. Animals received a single intravenous dose of HSD, 4 ml/kg over a 5-minute period, in an attempt to define maximum tolerated dosage. Equal volumes of each HSD component, 7.5% hypertonic saline (HS) and 6% Dextran 70® (D70) in normal saline, and Ringer's lactate (RL) were also evaluated. The animals in each group were divided into two subgroups according to necropsy, either Day 3 or Day 14 after dosing. Blood samples were collected for serum chemistry and hematologic analyses at necropsy on Day 3, and on Day 13. Observations were made at 1, 2, and 4 hours after administration on the day of dosing and twice daily thereafter. HS produced death within 12 minutes of the start of injection in 6 of 20 rabbits. Compared to the control animals receiving RL, the HS and HSD groups exhibited increased incidence of bruising of the injected ear, inactivity, disorientation, and tremors. Compared to the controls, all groups exhibited increased respiratory rate. Except for decreased serum iron in the HS group 3 days after administration, no consistent changes were seen in serum chemistry measurements. No significant changes outside of normal limits were observed in the hematology measurements. Animal weights and water consumption were unaffected by the treatment and no gross or microscopic lesions could be attributed to HSD or its constituents. These data suggest that the lethality of HS was due to an acute hemodynamic effect of the volume administered, and that the rabbit was more sensitive to HSD or D70 than to HS. Since the proposed therapeutic dose of HSD is only 4 ml/kg, these findings indicate minimal adverse effects should be anticipated with therapeutic administration of HSD.

• **Keywords:** Acute Toxicity, Intravenous Injection, Maximum Tolerated Dose, Hypertonic Saline/Dextran 70®, Hypertonic Saline, Dextran 70®, Ringer's Lactate, Resuscitation Fluid, New Zealand White Rabbits

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## PREFACE

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PROJECT/WORK UNIT/APC: 3S463807D836/087/TLRO

GLP STUDY NUMBER: 88002

STUDY DIRECTOR: Don W. Korte, Jr., PhD, LTC, MSC  
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DATA MANAGER: Yvonne C. LeTellier, BS

REPORT AND DATA MANAGEMENT: A copy of the final report,  
study protocols, retired SOPs,  
raw data, analytical and  
stability data, and an aliquot  
of the test compound will be  
retained in the LAIR Archives.

TEST SUBSTANCE: Hypertonic Saline/Dextran 70®

INCLUSIVE STUDY DATES: 24 August 88 - 4 October 88

OBJECTIVE: The objective of this study was to determine  
the acute toxicity of hypertonic saline/Dextran  
70® following intravenous administration in male  
and female New Zealand White rabbits.

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SPC Dean K. Magnuson, BS, SPC Eric Dahlberg, BS, and SPC Vilmar O. L. Villa provided assistance in dose preparation and administration; SGT Tammie Heineman, SGT Barbara D. Green, and Richard Katona provided data collection, animal care, and facility management.

**SIGNATURES OF PRINCIPAL SCIENTISTS AND MANAGERS  
INVOLVED IN THE STUDY**

We, the undersigned, declare that GLP study number 88002 was performed under our supervision, according to the procedures described herein, and that this report is an accurate record of the results obtained.

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Study Director

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DEPARTMENT OF THE ARMY  
LETTERMAN ARMY INSTITUTE OF RESEARCH  
PRESIDIO OF SAN FRANCISCO, CALIFORNIA 94129-6800

REPLY TO  
ATTENTION OF:

SGRD-ULZ-QA

28 March 1988

MEMORANDUM FOR RECORD

SUBJECT: GLP Compliance for GLP Study 88002

1. This is to certify that in relation to LAIR GLP Study 88002, the following inspections were made:

|                   |                                  |
|-------------------|----------------------------------|
| 27 January 1988   | - Protocol Review                |
| 17 June 1988      | - Animal Receipt/Room Inspection |
| 06 July 1988      | - Randomization                  |
| 11 July 1988      | - Dosing                         |
| 25 July 1988      | - Necropsy                       |
| 25 July 1988      | - Test Chemical Log              |
| 25 August 1988    | - Animal Receipt                 |
| 12 September 1988 | - Randomization                  |
| 13 September 1988 | - Dosing                         |
| 13 September 1988 | - Observations/Scoring           |
| 16 September 1988 | - Interim Sacrifice              |
| 26 September 1988 | - Weighing Water Bottles         |
| 27 September 1988 | - Necropsy                       |
| 27 September 1988 | - Serum Chemistry Check          |

2. The institute report entitled "Hypertonic Saline/Dextran 70® and its Constituents in New Zealand White Rabbits," Toxicology Series 246, was audited on 24 February 1989.

*Walter G. Bell*  
WALTER G. BELL  
SFC, USA  
Quality Assurance Auditor

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**Acute Intravenous Toxicity Study of Hypertonic  
Saline/Dextran 70® and Its Constituents in New  
Zealand White Rabbits -- Zaucha et al**

**INTRODUCTION**

During conventional land warfare it has been estimated that 90% of the deaths occur either in the field or en route to a fixed medical treatment facility and that 50% of those deaths occur due to hemorrhage (1). Conventional treatment of hemorrhage has involved infusion of isotonic resuscitation fluids at volumes equivalent to two or three times the volume of blood lost (2). Supplying this volume of resuscitation fluid on the battlefield for treatment of multiple casualties is not feasible.

Hypertonic crystalloid solutions have been used for the past 70 years in the treatment of hemorrhage (3). However, the consensus has been that unless followed by replacement of the lost blood volume, the beneficial effects of treatment with hyperosmotic solutions are transient (4). Recently, the addition of a hyperoncotic colloid, 6% Dextran 70®, to the hypertonic crystalloid, 7.5% saline, has significantly extended 96-hour survival rates compared with those obtained with normal saline or 7.5% saline (5). Should the effectiveness of this hypertonic saline/Dextran therapy be verified by clinical trial, it would provide a significant advance in the treatment of blood loss due to traumatic injuries.

As with any new treatment regimen, there are potential risks. Low molecular weight dextran could cause bleeding abnormalities and phlebitis or possibly interfere with the cross-matching of blood (6). Hypertonic solutions could cause neurologic abnormalities induced by the rapid increases in osmolalities (7-9) or cardiac arrhythmias induced by the hypokalemia associated with the rapid expansion of extracellular space (2, 10). Consequently, the Division of Toxicology, Letterman Army Institute of Research, was tasked to provide an acute and subchronic toxicity profile of the 7.5% hypertonic saline/6% Dextran 70® resuscitation fluid (HS/SD). This report describes the results of an acute toxicity study of hypertonic saline/Dextran 70® following intravenous administration of the maximum tolerated dose in male and female New Zealand white rabbits.

Objective of Study

The objective of this study was to determine the acute toxicity of hypertonic saline/Dextran 70® following intravenous administration in male and female New Zealand White rabbits.

**MATERIALS**

Test Substance

Name: Hypertonic saline/Dextran 70® (HSD)

LAIR Compound Code: TP96

Lot Number: NC 54845

Expiration Date: September 1989

Composition per 100 ml: Dextran 70® 6 g  
sodium chloride 7.5 g  
water for injection to 100 ml

Source: Pharmacia LEO Pharmaceuticals  
Uppsala, Sweden

Test Substance Constituents

Name: Hypertonic (7.5%) saline (HS)

LAIR Compound Code: TP98

Lot Number: I 318712

Expiration Date: 31 December 1988

Composition per 100 ml: sodium chloride 7.5 g  
water for injection to 100 ml

Source: Pharmacia LEO Pharmaceuticals  
Uppsala, Sweden

Name: Dextran 70® (D70)

LAIR Compound Code: TP95

Lot Number: NE 54941

Expiration Date: 31 May 1989

Composition per 100 ml: Dextran 70® 6 g  
sodium chloride 0.9 g  
water for injection to 100 ml

Source: Pharmacia LEO Pharmaceuticals  
Uppsala, Sweden

Control

Name: Ringer's lactate (RL)

LAIR Compound Code: TP97

Lot Number: NC 54847

Expiration Date: September 1989

Composition per 100 ml: sodium chloride 600 mg  
potassium chloride 30 mg  
calcium chloride  
dihydrate 20 mg  
sodium lactate 310 mg  
water for injection to 100 ml

Source: Pharmacia LEO Pharmaceuticals  
Uppsala, Sweden

Other test substance information is presented in  
Appendix A.

Animal Data

Forty male and 40 female New Zealand White rabbits (Hazleton Research Products, Inc., Swampbridge Rd., Denver, PA 17517) were assigned to this study. They were identified individually with ear tags. The animal weights on receipt (24 August 88) ranged from 2.447 to 3.732 kg. Additional animal data are presented in Appendix B.

Husbandry

Study animals were individually housed in stainless steel battery-type cages with screen bottoms, in racks equipped with automatically flushing dump tanks. The diet, fed *ad libitum*, consisted of Certified Purina Rabbit Chow® 5322 (Ralston Purina Company, St. Louis, MO); water, purified by reverse osmosis, was provided by individual water bottles with sipper tubes. The animal room temperature and humidity were monitored continuously by hygrothermograph. The

temperature was maintained in a range from 17.2°C to 23.3°C. The relative humidity was maintained in a range of 27% to 65% with occasional spikes to as high as 90% during room cleaning. The photoperiod was 12 hours of light per day (0600 - 1800 hours).

## METHODS

This study was conducted in accordance with FDA guidelines (11) and LAIR SOP-OP-STX-113, "Acute Intravenous Toxicity Study" (12).

### Group Assignment/Acclimation

The animals were randomized into four groups of 10 male and 10 female animals each. Since animals were to be terminated at two different time intervals following dosing, the first 5 male and 5 female animals of each group were designated for interim sacrifice (Day 3) with the remainder designated for terminal sacrifice (Day 14) (Table 1). Allocation was accomplished using a computer-based, stratified, weight-biased method. The XYBION Path/Tox AESLCT Animal Allocation Program was used in conjunction with a VAX 750 Computer.

Table 1

### DOSE GROUPS

| Group | n<br>(each sex) | Solution                      | Sacrifice<br>Day |
|-------|-----------------|-------------------------------|------------------|
| 1     | 5               | hypertonic saline             | 3                |
| 1     | 5               | hypertonic saline             | 14               |
| 2     | 5               | hypertonic saline/Dextran 70® | 3                |
| 2     | 5               | hypertonic saline/Dextran 70® | 14               |
| 3     | 5               | Dextran 70/normal saline      | 3                |
| 3     | 5               | Dextran 70/normal saline      | 14               |
| 4     | 5               | Ringer's lactate              | 3                |
| 4     | 5               | Ringer's lactate              | 14               |

The male and female study animals were acclimated for 19 and 26 days, respectively, before the day of dosing. During this period they were checked daily for signs of illness, and weighed weekly.

#### Dose Levels, Preparation, and Analysis

The maximum tolerated intravenous dose of HSD administered over a 5-minute period was determined to be 20 ml/kg in preliminary pilot studies. Equal volumes of HS, D70, and RL were administered to animals in the corresponding dose groups. Solutions were used as supplied by the manufacturer, Pharmacia LEO Pharmaceuticals. Analysis of the dosing solutions was provided by Pharmacia LEO Pharmaceuticals. Additional chemical data are presented in Appendix A.

#### Test Procedures

The acute intravenous toxicity of hypertonic saline/Dextran 70® (HSD) was evaluated in parallel with solutions of its major constituents, hypertonic (7.5%) saline (HS) and Dextran 70® (6%) in normal saline (D70), with Ringer's lactate (RL) serving as the control. The dosing solutions were administered via the marginal ear veins. Injections were made using 60 cc syringes (Becton Dickinson & Co., Rutherford, NJ 07070, Lot No. 5M516) and 23-gauge, 1-inch needles (Becton Dickinson & Co., Rutherford, NJ 07070, Lot No. 7F018). A 12-inch length of PE-50 polyethylene tubing (Clay Adams, Division of Becton Dickinson & Co., Parsippany, NJ 07054, Lot No. 93590, exp. date 3/93) was used to attach a second, hubless needle to the needle on the syringe to facilitate completion of the injections. Immediately following the injection, digital pressure was applied to control any bleeding from the injection site.

#### Observations

Clinical observations were accomplished 1, 2, and 4 hours after dosing on Day 0, and then at least twice daily for the remainder of the observation period. Body weights were recorded upon receipt of the animals, weekly during the quarantine and observation periods, before dosing, and at necropsy. Water consumption was monitored for a twenty-four hour period, weekly during quarantine, daily for the first week of the study, and at 14 days. Blood was collected for serum chemistry and hematology analyses at necropsy on Day 3 and on Day 13. All samples for serum chemistry and clotting

time determinations were centrifuged after collection and the serum or plasma frozen for a week before being analyzed.

Necropsy

Animals that died spontaneously after dosing were immediately submitted for necropsy. Interim and terminal sacrifice animals were submitted for necropsy on Days 3 and 14, respectively, immediately after sacrifice by barbiturate overdose. Histopathologic examination was performed on the heart, liver, kidney, brain, lung, spleen, and all gross lesions.

Statistical Analysis

Clinical signs were tabulated by groups. The means and standard deviations for the body weights, water consumption, serum chemistry, and hematology data for each group were calculated. For the body weights, serum chemistry, and hematology data, an analysis of variance and the Bartlett's test for homogeneity were performed using the XYBION PATH/TOX software package. If the F-statistic was significant for an analysis of variance for a particular measurement, differences from the control were evaluated using the Dunnett's test for homogeneous data and the Modified T test for nonhomogeneous data. Using the BMDP statistical software package, the equality of the variances for the groups' water consumption was tested by the Levene test. If equal, the standard one-way analysis of variance was performed. If unequal, the Welch's one-way analysis of variance was performed. If the F-statistic was significant for an analysis of variance for a particular measurement, differences among the groups were evaluated using the Newman-Keuls test (13). For total bilirubin, the Kruskal-Wallis nonparametric one-way analysis of variance was performed (13). Gross and microscopic pathology findings were described for each animal and tabulated by groups.

Duration of Study

Appendix C is a complete listing of historical events.

Changes/Deviations

Water consumption was not recorded on Day 7 and Day 14 for the males and females, respectively. Body weights were not recorded for the females on Day 7. Terminal sacrifice blood samples were taken from the central artery of the ear on Day 13 instead of Day 14 to avoid hemolysis induced by pentobarbital anesthesia at euthanasia and necropsy. The

prothrombin time and activated partial thromboplastin time data are designated as "NT" when hemolysis and clumping of the samples interfered with the test procedure. Hematology data are unavailable for animals 88F00-301, 308, 324, 336, 338, and 344 due to clotting or lack of sufficient sample obtained at interim sacrifice. The protocol schedule refers to the day of dosing as Day 0. Since XYBION programming refers to the day of dosing as Day 1, a one-day discrepancy exists between the actual study day and the day listed in the XYBION printouts for Serum Chemistry, Hematology, and Pathology appendices. Day 4, 14, and 15 listed in each of these appendices refers to study days 3, 13, and 14, respectively. In an attempt to equalize the number of animals scheduled for Interim Sacrifice and Terminal Sacrifice, animal # 310, originally scheduled for Terminal sacrifice, was moved up into the Interim Sacrifice group. The need to reschedule was due to 3 deaths in the HS Interim sacrifice group.

It is believed that these changes had no adverse effects on the results of this study.

#### Storage of Raw Data and Final Report

A copy of the final report, study protocol, raw data, retired SCPs, and an aliquot of the test compound will be retained in the Letterman Army Institute of Research Archives.

## RESULTS

### Clinical Observations

The clinical signs observed were grouped into the following categories: behavioral, respiratory, injection site reactions, death, ocular, reflexive, food consumption, and gastrointestinal.

The category of signs most frequently observed was behavioral. Inactivity (27 of 80 animals) was observed throughout the study period in males and females, but was most frequently seen on Day 0 (14 animals) following dosing. In the males, inactivity was seen with equal distribution among dose groups. However, in the female animals, the HSD and HS groups were primarily affected (7 and 6 animals, respectively). Disorientation (22 of 80) was observed on Day 1 in both sexes with greatest incidence in the females. Disorientation was observed most frequently in the HS (10 animals) and HSD (8 animals) groups. Tremors (12 of 80) were

also observed primarily in the HS and HSD groups and only on Day 0. Males and females were affected equally with tremors. Infrequently observed behavioral signs included aggression (4 of 80), hyperactivity (3 of 80), and irritability (1 of 80). These signs were sporadically observed among the different dose groups.

The second major category of clinical signs observed in the study was respiratory signs. Increased respiratory rate was observed in 33 of 80 animals on Day 0. Respiratory rate returned to normal in all affected animals by Day 1. The increase in respiratory rate occurred primarily in female animals receiving HSD, HS, or D70.

Bruising of the injected ear was observed in 12 animals (8 males and 4 females) from the HSD- and HS-treated groups. Fluid or bloody discharge, discoloration, and necrosis of the injection site also occurred in several HSD and HS animals.

Six animals receiving HS (3 males and 3 females) died within 12 minutes of the start of the infusion. No other mortalities were observed during the study period.

Ocular signs were observed in 2 of 80 animals. Both animals were HS-treated males. The eyes of these animals became pale or a lighter red in color. The pale eyes were first observed on Day 0 with the condition persisting for 1 and 3 days in each respective animal.

Other signs were isolated in nature and occurred sporadically among the different groups. Increased startle reflex (reflexive), diarrhea (gastrointestinal), and decreased appetite (food consumption) were observed in one animal each.

A summary of clinical observations is presented in Table 2. Individual animal histories are presented in Appendix D.

#### Body Weights

Animal body weights were not significantly ( $p \leq 0.05$ ) affected by dosing. Group mean body weights are presented in Table 3. Individual animal body weights are presented in Appendix E.

#### Water Consumption

Water consumption was not significantly ( $p \leq 0.05$ ) affected by dosing. Group mean water consumption data are

presented in Table 4. Individual animal water consumption data are presented in Appendix F.

#### Serum Chemistry

Group mean serum chemistry data are presented in Table 5. Individual serum chemistry data are presented in Appendix G. At interim sacrifice, the mean iron of the male HS group was significantly less than that of the controls ( $p = 0.01$ ), with all 3 interim sacrifice HS males having abnormally low values (14). The mean iron of the female HS group was also reduced at interim sacrifice, but the difference from the controls was not statistically significant ( $p \leq 0.05$ ). The mean triglyceride values of the male HSD, HS, and D70 groups were significantly greater than that of the controls ( $p = 0.05$ ) at interim sacrifice, but the values were within accepted normal limits (15). The magnesium of the female HS group was significantly less than that of the controls at interim sacrifice ( $p = 0.05$ ), but the value was within normal limits (14). At terminal sacrifice, the male HSD and HS groups had mean alanine amino-transferase levels significantly less than that of the controls ( $p = 0.01$  and 0.05, respectively), but the values were within normal limits (14). The serum chemistries of the female dose groups were not significantly different from those of the controls at terminal sacrifice.

#### Hematology

Group mean hematology data are presented in Table 6. Individual hematology data are presented in Appendix H. Hematology parameters of the females study animals at interim sacrifice were not significantly affected by dosing ( $p \leq 0.05$ ). At interim sacrifice, the male animals receiving HS had a mean erythrocyte count significantly less than that of the controls ( $p = 0.05$ ), but the value was within normal limits (16). At terminal sacrifice, the male HSD group had a mean reticulocyte count significantly less than that of the control group ( $p = 0.05$ ), but this value was also within normal limits (16). The mean prothrombin times of the female HSD and D70 groups were significantly greater than that of the control group at terminal sacrifice ( $p = 0.05$ ), but the values remained within acceptable limits.

#### Necropsy Findings

No gross or microscopic pathological lesions attributable to the test compound or its constituents were reported. The Veterinary Pathologist's report is presented in Appendix I.

## DISCUSSION

The acute intravenous toxicity of HSD in rabbits was evaluated by dosing the animals with an apparent maximum tolerated dose via the marginal ear vein. This dose was established in preliminary studies as 20 ml/kg administered over 5 minutes. This dose, 20 ml/kg, is five times the proposed therapeutic dose of 4 ml/kg (2). In addition to dosing with HSD, groups of rabbits were dosed with equal volumes of HS, D70, or RL. No mortalities were observed when HSD was administered at a rate of 20 ml/kg over 5 minutes. However, the HS caused death in 3 of 10 males and 3 of 10 females dosed, suggesting that the HS component has greater toxicity than the HSD mixture, and the maximum tolerated dose is less than 20 ml/kg for the HS component alone. The deaths were very rapid, occurring within 3 - 12 minutes of the initiation of the infusion. Since death occurred rapidly and only in the group receiving hypertonic saline, the deaths could be attributed to cardiac dysrhythmia arising from the putative hypokalemia produced by the saline infusion. This is consistent with the observation that dextran is well tolerated when administered intravenously at doses up to 40 ml/kg in various animal models (G. Jonsson, Pharmacia Pharmaceuticals AB, personal communication).

An equal volume of RL was administered as a control. Since the RL is an isotonic solution, it would only permit comparison of the effects of the volume administered. Therefore, differences between the RL group and the HSD, HS, and D70 groups can be attributed to the volume expansion capabilities of the latter groups.

Inactivity, disorientation, tremors, increased respiratory rate, bruising of the injection site, and pale eyes were observed at an increased rate in the HS and HSD-treated groups. The D70-treated animals also exhibited a greater incidence of increased respiratory rate when compared to the controls.

The increased incidence of behavioral signs appeared to be limited to animals receiving HS-containing solutions, which again suggests that the toxicity of HSD is due to the HS component, although behavioral signs were also noted in the female D70 group.

**Table 2**  
**CLINICAL OBSERVATIONS SUMMARY\***

| Group<br>(n)<br><u>Observation</u> | RL<br>(10) | HSD<br>(10) | HS<br>(10) | D70<br>(10) |
|------------------------------------|------------|-------------|------------|-------------|
| Males                              |            |             |            |             |
| NORMAL/NO SIGNIFICANT SIGNS        | 7          | 3           | 0          | 7           |
| <b>BEHAVIOR</b>                    |            |             |            |             |
| TREMORS                            | 0          | 2           | 3          | 0           |
| DISORIENTED                        | 0          | 1           | 5          | 0           |
| INACTIVE                           | 3          | 3           | 3          | 2           |
| HYPERACTIVE                        | 0          | 1           | 1          | 0           |
| IRRITABLE                          | 0          | 0           | 1          | 0           |
| <b>RESPIRATION</b>                 |            |             |            |             |
| INCREASED RESPIRATORY RATE         | 0          | 0           | 2          | 2           |
| <b>OCULAR</b>                      |            |             |            |             |
| PALE EYES                          | 0          | 0           | 2          | 0           |
| <b>INJECTION SITE REACTION</b>     |            |             |            |             |
| BRUISE                             | 0          | 3           | 5          | 0           |
| FLUID DISCHARGE                    | 0          | 0           | 1          | 0           |
| BLOOD DRAINAGE                     | 0          | 0           | 2          | 0           |
| <b>FOOD CONSUMPTION</b>            |            |             |            |             |
| DECREASED APPETITE                 | 0          | 0           | 1          | 0           |
| DEATH                              | 0          | 0           | 3          | 0           |

\* Data presented as number of animals affected.

**Table 2 (cont.)**  
**CLINICAL OBSERVATIONS SUMMARY\***

| Group<br>(n)                | RL<br>(10) | HSD<br>(10) | HS<br>(10) | D70<br>(10) |
|-----------------------------|------------|-------------|------------|-------------|
| <u>Observation</u>          |            |             |            |             |
|                             |            | Females     |            |             |
| NORMAL/NO SIGNIFICANT SIGNS | 4          | 0           | 0          | 0           |
| BEHAVIOR                    |            |             |            |             |
| TREMORS                     | 0          | 2           | 4          | 1           |
| DISORIENTED                 | 1          | 7           | 5          | 3           |
| INACTIVE                    | 0          | 7           | 6          | 3           |
| HYPERACTIVE                 | 0          | 0           | 0          | 1           |
| AGGRESSIVE                  | 0          | 1           | 1          | 2           |
| RESPIRATION                 |            |             |            |             |
| INCREASED RESPIRATORY RATE  | 5          | 10          | 7          | 7           |
| INJECTION SITE REACTION     |            |             |            |             |
| BRUISE                      | 0          | 4           | 0          | 0           |
| DRIED BLOODY MATERIAL       | 1          | 0           | 2          | 0           |
| DISCOLORATION               | 1          | 1           | 0          | 1           |
| NECROSIS                    | 0          | 2           | 0          | 0           |
| GASTROINTESTINAL            |            |             |            |             |
| DIARRHEA                    | 0          | 1           | 0          | 0           |
| REFLEXES                    |            |             |            |             |
| INCREASED STARTLE REFLEX    | 1          | 0           | 0          | 0           |
| DEATH                       | 0          | 0           | 3          | 0           |

\* Data presented as number of animals affected.

Table 3

## GROUP MEAN BODY WEIGHT (kg)

| Group  | Day of Study                       |                      |                      |                      |                      |                     |                     |
|--------|------------------------------------|----------------------|----------------------|----------------------|----------------------|---------------------|---------------------|
|        | -19                                | -13                  | -7                   | 0                    | 3†                   | 7                   | 14                  |
| Male   |                                    |                      |                      |                      |                      |                     |                     |
| RL     | 2.87 <sup>¶</sup><br>±0.08<br>(10) | 3.04<br>0.07<br>(10) | 3.12<br>0.06<br>(10) | 3.31<br>0.07<br>(10) | 3.45<br>0.08<br>(5)  | 3.27<br>0.06<br>(5) | 3.36<br>0.08<br>(5) |
| HSD    | 2.89<br>±0.07<br>(10)              | 3.06<br>0.09<br>(10) | 3.20<br>0.08<br>(10) | 3.30<br>0.08<br>(10) | 3.40<br>0.07<br>(5)  | 3.30<br>0.15<br>(5) | 3.38<br>0.15<br>(5) |
| HS     | 2.88<br>±0.07<br>(10)              | 3.10<br>0.06<br>(10) | 3.21<br>0.06<br>(10) | 3.33<br>0.06<br>(10) | 3.42<br>0.09<br>(3)  | 3.32<br>0.09<br>(4) | 3.41<br>0.12<br>(4) |
| D70    | 2.87<br>±0.06<br>(10)              | 3.03<br>0.06<br>(10) | 3.16<br>0.07<br>(10) | 3.26<br>0.06<br>(10) | 3.37<br>0.11<br>(5)  | 3.33<br>0.06<br>(5) | 3.38<br>0.04<br>(5) |
| Group  | Day of Study                       |                      |                      |                      |                      |                     |                     |
|        | -29                                | -20                  | -14                  | -7                   | 0                    | 3†                  | 14                  |
| Female |                                    |                      |                      |                      |                      |                     |                     |
| RL     | 3.16<br>±0.08<br>(10)              | 3.42<br>0.09<br>(10) | 3.61<br>0.09<br>(10) | 3.82<br>0.10<br>(10) | 3.95<br>0.10<br>(10) | 4.05<br>0.16<br>(5) | 4.02<br>0.16<br>(5) |
| HSD    | 3.26<br>±0.06<br>(10)              | 3.40<br>0.11<br>(10) | 3.60<br>0.08<br>(10) | 3.75<br>0.09<br>(10) | 3.94<br>0.07<br>(10) | 3.82<br>0.05<br>(5) | 4.08<br>0.09<br>(5) |
| HS     | 3.20<br>±0.10<br>(10)              | 3.45<br>0.09<br>(10) | 3.62<br>0.09<br>(10) | 3.84<br>0.09<br>(10) | 3.98<br>0.07<br>(10) | 3.93<br>0.24<br>(3) | 3.99<br>0.04<br>(4) |
| D70    | 3.18<br>±0.08<br>(10)              | 3.43<br>0.09<br>(10) | 3.55<br>0.09<br>(10) | 3.74<br>0.08<br>(10) | 3.86<br>0.08<br>(10) | 3.81<br>0.12<br>(5) | 4.03<br>0.09<br>(5) |

<sup>†</sup> Day 3 body weights include only interim sacrifice animals.

<sup>¶</sup> Data are presented as mean ± standard error of the mean with the number of animals, n, in parenthesis.

Table 4

## GROUP MEAN WATER CONSUMPTION (ml/day)

| Group  | Study Day                      |                   |                   |                   |                   |                  |                  |                  |                  |                  |
|--------|--------------------------------|-------------------|-------------------|-------------------|-------------------|------------------|------------------|------------------|------------------|------------------|
|        | -13                            | -7                | 1                 | 2                 | 3                 | 4                | 5                | 6                | 7                | 14               |
| Male   |                                |                   |                   |                   |                   |                  |                  |                  |                  |                  |
| RL     | 292 <sup>a</sup><br>±17<br>(9) | 277<br>16<br>(9)  | 258<br>28<br>(10) | 292<br>22<br>(10) | 247<br>17<br>(9)  | 249<br>22<br>(5) | 245<br>18<br>(5) | 357<br>30<br>(5) | 235<br>(1)       | 233<br>20<br>(5) |
| HSD    | 320<br>±22<br>(10)             | 338<br>17<br>(10) | 311<br>21<br>(10) | 276<br>15<br>(10) | 263<br>18<br>(10) | 267<br>17<br>(5) | 300<br>47<br>(4) | 356<br>34<br>(5) | NR<br>(0)        | 254<br>17<br>(5) |
| HS     | 284<br>±27<br>(9)              | 298<br>20<br>(10) | 304<br>50<br>(7)  | 225<br>51<br>(7)  | 240<br>24<br>(6)  | 257<br>38<br>(4) | 257<br>24<br>(4) | 277<br>59<br>(4) | 200<br>4<br>(2)  | 183<br>7<br>(4)  |
| D70    | 301<br>±16<br>(10)             | 313<br>25<br>(10) | 254<br>17<br>(10) | 276<br>26<br>(10) | 238<br>17<br>(10) | 307<br>21<br>(5) | 341<br>41<br>(5) | 354<br>31<br>(5) | 280<br>(1)       | 248<br>45<br>(5) |
| Group  | Study Day                      |                   |                   |                   |                   |                  |                  |                  |                  |                  |
|        | -14                            | -6                | 1                 | 2                 | 3                 | 4                | 5                | 6                | 7                | 14               |
| Female |                                |                   |                   |                   |                   |                  |                  |                  |                  |                  |
| RL     | 316<br>±21<br>(10)             | 277<br>27<br>(9)  | 269<br>29<br>(10) | 292<br>26<br>(10) | 274<br>33<br>(5)  | 184<br>37<br>(5) | 356<br>32<br>(5) | 384<br>31<br>(5) | 274<br>41<br>(5) | NR<br>(0)        |
| HSD    | 325<br>±25<br>(10)             | 315<br>19<br>(10) | 367<br>20<br>(10) | 295<br>31<br>(10) | 321<br>29<br>(5)  | 188<br>47<br>(5) | 343<br>31<br>(5) | 356<br>31<br>(5) | 312<br>49<br>(5) | NR<br>(0)        |
| HS     | 333<br>±22<br>(10)             | 324<br>23<br>(10) | 332<br>42<br>(7)  | 279<br>43<br>(7)  | 330<br>29<br>(4)  | 281<br>46<br>(4) | 369<br>37<br>(4) | 389<br>21<br>(4) | 359<br>16<br>(4) | NR<br>(0)        |
| D70    | 307<br>±17<br>(10)             | 309<br>29<br>(10) | 324<br>15<br>(10) | 297<br>19<br>(10) | 295<br>21<br>(4)  | 200<br>28<br>(5) | 301<br>29<br>(5) | 376<br>30<br>(5) | 316<br>13<br>(5) | NR<br>(0)        |

<sup>a</sup> Data are presented as mean ± standard error of the mean with the number of animals, n, in parenthesis.

Table 5  
SERUM CHEMISTRY SUMMARY

| PARAMETER/<br>UNITS                 | STUDY<br>DAY | MEAN              | RL<br>SD         | N | MEAN              | HSD<br>SD        | N | MEAN              | HS<br>SD          | N | MEAN              | D 70<br>SD        | N |
|-------------------------------------|--------------|-------------------|------------------|---|-------------------|------------------|---|-------------------|-------------------|---|-------------------|-------------------|---|
|                                     |              |                   |                  |   |                   |                  |   |                   |                   |   |                   |                   |   |
| ASPARTATE AMINO-<br>TRANSFERASE U/l | 3<br>13      | 45.42<br>12.88    | 10.97<br>2.23    | 5 | 47.10<br>11.58    | 10.29<br>1.25    | 5 | 38.83<br>15.45    | 18.56<br>3.98     | 3 | 166.62<br>15.54   | 166.35<br>4.75    | 5 |
| BLOOD UREA<br>NITROGEN mg/dl        | 3<br>13      | 19.14<br>17.68    | 5.05<br>1.79     | 5 | 20.14<br>17.48    | 1.84<br>1.81     | 5 | 14.93<br>16.03    | 2.65<br>1.84      | 3 | 21.80<br>16.20    | 5.78<br>0.97      | 5 |
| CREATINE<br>PHOSPHOKINASE U/l       | 3<br>13      | 1994.38<br>637.06 | 952.61<br>281.72 | 5 | 1413.39<br>599.67 | 181.98<br>170.98 | 5 | 1623.31<br>485.80 | 1031.82<br>263.26 | 3 | 4691.68<br>809.46 | 4902.42<br>421.37 | 5 |
| ALBUMIN<br>g/dL                     | 3<br>13      | 3.95<br>4.82      | 0.25<br>0.18     | 3 | 4.00<br>4.52      | 0.41<br>0.18     | 5 | 3.53<br>4.55      | 0.15<br>0.13      | 3 | 3.97<br>4.94      | 0.32<br>0.26      | 3 |
| TOTAL BILIRUBIN<br>mg/dl            | 3<br>13      | 0.00<br>0.00      | 0.00<br>0.00     | 5 | 0.00<br>0.00      | 0.00<br>0.00     | 5 | 0.00<br>0.00      | 0.00<br>0.00      | 3 | 0.00<br>0.00      | 0.00<br>0.00      | 5 |
| CHLORIDE<br>Meq/dl                  | 3<br>13      | 106.80<br>102.40  | 3.03<br>5.13     | 5 | 108.20<br>102.40  | 1.48<br>1.95     | 5 | 103.33<br>103.75  | 1.53<br>1.26      | 3 | 105.20<br>103.60  | 2.78<br>3.85      | 5 |
| GLUCOSE<br>mg/dl                    | 3<br>13      | 170.86<br>112.38  | 47.64<br>15.71   | 5 | 157.56<br>120.86  | 17.09<br>30.69   | 5 | 181.93<br>107.58  | 19.32<br>6.60     | 3 | 177.08<br>118.16  | 103.81<br>18.61   | 5 |
| IRON<br>μg/dl                       | 3<br>13      | 193.40<br>145.20  | 42.07<br>33.66   | 5 | 191.80<br>163.80  | 22.33<br>41.76   | 5 | 65.67†<br>141.50  | 21.50<br>57.02    | 3 | 225.60<br>136.80  | 58.16<br>30.03    | 5 |

Mean value of the group is significantly different from that of the control at  $p = 0.01$ .

Table 5 (cont.)  
**SERUM CHEMISTRY SUMMARY**

| PARAMETER/<br>UNITS               | STUDY<br>DAY | MEAN             | SD              | N      | MEAN             | SD              | N      | MEAN             | SD             | N      | MEAN             | SD              | N      | D 70 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|-----------------------------------|--------------|------------------|-----------------|--------|------------------|-----------------|--------|------------------|----------------|--------|------------------|-----------------|--------|------|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
|                                   |              |                  |                 |        |                  |                 |        |                  |                |        |                  |                 |        |      |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| MALES                             |              |                  |                 |        |                  |                 |        |                  |                |        |                  |                 |        |      |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|                                   |              |                  |                 |        |                  |                 |        |                  |                |        |                  |                 |        |      |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| GAMMA GLUTAMYL<br>TRANSFERASE U/l | 3<br>13      | 7.40<br>8.24     | 2.01<br>0.92    | 5<br>5 | 7.10<br>8.24     | 1.28<br>2.52    | 5<br>5 | 7.87<br>10.00    | 3.68<br>3.43   | 3<br>4 | 4.22<br>9.30     | 0.89<br>2.01    | 5<br>5 |      |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ALKALINE<br>PHOSPHATASE U/l       | 3<br>13      | 82.14<br>105.10  | 33.57<br>34.88  | 5<br>5 | 113.56<br>81.00  | 27.14<br>21.81  | 5<br>5 | 42.07<br>85.78   | 5.60<br>49.51  | 3<br>4 | 138.12<br>96.48  | 72.33<br>20.90  | 5<br>5 |      |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| LACTATE<br>DEHYDROGENASE U/l      | 3<br>13      | 385.78<br>110.98 | 162.43<br>53.56 | 5<br>5 | 328.40<br>88.40  | 104.87<br>27.56 | 5<br>5 | 356.03<br>96.28  | 96.69<br>49.34 | 3<br>4 | 541.02<br>145.80 | 164.48<br>84.89 | 5<br>5 |      |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| MAGNESIUM<br>mg/dl                | 3<br>13      | 2.18<br>2.05     | 0.24<br>0.17    | 5<br>5 | 2.25<br>1.85     | 0.20<br>0.08    | 5<br>5 | 1.96<br>1.99     | 0.14<br>0.26   | 3<br>4 | 2.32<br>2.07     | 0.13<br>0.24    | 5<br>5 |      |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| SODIUM<br>Meq/l                   | 3<br>13      | 149.42<br>146.38 | 1.73<br>4.23    | 5<br>5 | 150.02<br>145.04 | 1.07<br>0.50    | 5<br>5 | 147.47<br>146.85 | 0.78<br>2.90   | 3<br>4 | 149.54<br>148.34 | 5.98<br>2.72    | 5<br>5 |      |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CALCIUM<br>mg/dl                  | 3<br>13      | 12.76<br>14.18   | 0.38<br>0.11    | 5<br>5 | 13.10<br>14.08   | 0.27<br>0.40    | 5<br>5 | 12.83<br>14.10   | 0.21<br>0.29   | 3<br>4 | 12.58<br>14.54   | 0.74<br>0.18    | 5<br>5 |      |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| PHOSPHORUS<br>mg/dl               | 3<br>13      | 5.48<br>3.80     | 0.67<br>0.55    | 5<br>5 | 5.50<br>3.92     | 0.45<br>0.55    | 5<br>5 | 5.07<br>3.88     | 0.78<br>0.46   | 3<br>4 | 5.26<br>3.96     | 0.91<br>0.65    | 5<br>5 |      |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CHOLESTEROL<br>mg/dl              | 3<br>13      | 21.34<br>24.60   | 5.85<br>8.27    | 5<br>5 | 28.24<br>27.48   | 6.09<br>5.67    | 5<br>5 | 51.80<br>30.50   | 40.46<br>22.58 | 3<br>4 | 19.66<br>21.88   | 10.69<br>8.76   | 5<br>5 |      |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

Table 5 (cont.)  
SERUM CHEMISTRY SUMMARY

| PARAMETER/<br>UNITS               | STUDY<br>DAY | MEAN            | RL<br>SD       | N      | MEAN                          | HSD<br>SD      | N      | MEAN                         | HS<br>SD       | N      | MEAN                          | D 70<br>SD     | N |
|-----------------------------------|--------------|-----------------|----------------|--------|-------------------------------|----------------|--------|------------------------------|----------------|--------|-------------------------------|----------------|---|
|                                   |              |                 |                |        |                               |                |        | MALES                        |                |        |                               |                |   |
| CREATININE<br>mg/dl               | 3<br>13      | 0.96<br>1.04    | 0.18<br>0.15   | 5<br>5 | 1.16<br>1.12                  | 0.21<br>0.11   | 5<br>5 | 0.90<br>1.15                 | 0.20<br>0.10   | 3<br>4 | 1.02<br>1.16                  | 0.04<br>0.19   | 5 |
| ALANINE AMINO-<br>TRANSFERASE U/l | 3<br>13      | 38.72<br>51.00  | 11.50<br>9.57  | 5<br>5 | 52.24<br>28.54 <sup>†</sup>   | 9.23<br>5.35   | 5<br>5 | 47.93<br>36.35*              | 10.95<br>3.23  | 3<br>4 | 69.32<br>39.50                | 44.08<br>11.13 | 5 |
| TOTAL PROTEIN<br>g/dl             | 3<br>13      | 4.70<br>6.56    | 0.65<br>0.28   | 3<br>5 | 5.04<br>6.28                  | 0.45<br>0.30   | 5<br>5 | 4.70<br>6.47                 | 0.26<br>0.37   | 3<br>4 | 5.17<br>6.66                  | 0.21<br>0.28   | 3 |
| URIC ACID<br>mg/dl                | 3<br>13      | 0.10<br>0.04    | 0.07<br>0.05   | 5<br>5 | 0.12<br>0.00                  | 0.08<br>0.00   | 5<br>5 | 0.07<br>0.03                 | 0.12<br>0.05   | 3<br>4 | 0.14<br>0.00                  | 0.09<br>0.00   | 5 |
| POTASSIUM<br>Meq/l                | 3<br>13      | 5.12<br>4.44    | 0.52<br>0.42   | 5<br>5 | 5.18<br>4.34                  | 0.58<br>0.58   | 5<br>5 | 4.87<br>4.35                 | 0.51<br>0.60   | 3<br>4 | 6.06<br>4.40                  | 2.34<br>0.39   | 5 |
| TRIGLYCERIDE<br>mg/dl             | 3<br>13      | 76.60<br>179.00 | 6.84<br>114.16 | 5<br>5 | 124.60 <sup>*</sup><br>107.20 | 35.11<br>45.43 | 5<br>5 | 114.33 <sup>*</sup><br>82.50 | 13.20<br>22.25 | 3<br>4 | 138.20 <sup>*</sup><br>121.60 | 44.46<br>47.17 | 5 |
| ALBUMIN-<br>GLOBULIN RATIO        | 3<br>13      | 6.90<br>2.88    | 4.12<br>0.62   | 3<br>5 | 4.16<br>2.56                  | 1.33<br>0.30   | 5<br>5 | 3.23<br>2.43                 | 1.33<br>0.34   | 3<br>4 | 3.67<br>2.84                  | 1.59<br>0.39   | 3 |

<sup>†</sup> Mean value of the group is significantly different from that of the control at p = 0.01.

\* Mean value of the group is significantly different from that of the control at p = 0.05.

Table 5 (cont.)  
SERUM CHEMISTRY SUMMARY

| PARAMETER/<br>UNITS                 | STUDY<br>DAY | MEAN              | SD               | N      | HSD               |                  |   | HS                | SD                | N      | MEAN              | SD               | N | D 70 |
|-------------------------------------|--------------|-------------------|------------------|--------|-------------------|------------------|---|-------------------|-------------------|--------|-------------------|------------------|---|------|
|                                     |              |                   |                  |        | MEAN              | SD               | N |                   |                   |        |                   |                  |   |      |
| FEMALES                             |              |                   |                  |        |                   |                  |   |                   |                   |        |                   |                  |   |      |
| ASPARTATE AMINO-<br>TRANSFERASE U/l | 3<br>13      | 33.86<br>16.04    | 12.42<br>7.84    | 5<br>5 | 64.10<br>13.14    | 74.79<br>1.19    | 5 | 29.03<br>14.45    | 5.35<br>4.40      | 3<br>4 | 38.04<br>17.20    | 17.21<br>13.72   | 5 |      |
| BLOOD UREA<br>NITROGEN mg/dl        | 3<br>13      | 20.52<br>22.52    | 1.73<br>3.31     | 5<br>5 | 19.28<br>23.60    | 2.33<br>3.05     | 5 | 18.23<br>20.50    | 2.80<br>5.55      | 3<br>4 | 17.50<br>20.88    | 1.61<br>1.35     | 5 |      |
| CREATINE<br>PHOSPHOKINASE U/l       | 3<br>13      | 2013.34<br>653.04 | 737.41<br>305.65 | 5<br>5 | 1900.74<br>871.54 | 805.37<br>321.11 | 5 | 2316.11<br>552.53 | 1030.59<br>187.11 | 3<br>4 | 1055.75<br>634.86 | 377.79<br>418.66 | 5 |      |
| ALBUMIN<br>g/dl                     | 3<br>13      | 4.20<br>5.00      | 0.20<br>0.34     | 3<br>5 | 3.78<br>4.68      | 0.10<br>0.22     | 4 | 3.73<br>4.80      | 0.32<br>0.29      | 3<br>4 | 3.80<br>4.98      | 0.30<br>0.30     | 5 |      |
| TOTAL BILIRUBIN<br>mg/dl            | 3<br>13      | 0.00<br>0.01      | 0.00<br>0.01     | 5<br>5 | 0.00<br>0.00      | 0.00<br>0.00     | 5 | 0.00<br>0.00      | 0.00<br>0.00      | 3<br>4 | 0.00<br>0.00      | 0.00<br>0.00     | 5 |      |
| CHLORIDE<br>Meg/l                   | 3<br>13      | 105.60<br>110.60  | 3.36<br>4.51     | 5<br>5 | 101.60<br>110.00  | 2.88<br>3.74     | 5 | 104.67<br>106.75  | 2.52<br>3.30      | 3<br>4 | 104.60<br>110.80  | 7.77<br>3.56     | 5 |      |
| GLUCOSE<br>mg/dl                    | 3<br>13      | 124.82<br>119.92  | 33.91<br>10.50   | 5<br>5 | 159.36<br>107.68  | 58.65<br>6.21    | 5 | 177.67<br>109.80  | 17.93<br>10.33    | 3<br>4 | 127.78<br>115.48  | 33.98<br>11.41   | 5 |      |
| IRON<br>μg/dl                       | 3<br>13      | 173.60<br>212.00  | 57.77<br>39.13   | 5<br>5 | 197.20<br>171.00  | 61.25<br>18.47   | 5 | 133.67<br>148.50  | 63.52<br>27.54    | 3<br>4 | 175.40<br>202.20  | 13.20<br>70.56   | 5 |      |

Table 5 (cont.)  
SERUM CHEMISTRY SUMMARY

| PARAMETER/<br>UNITS               | STUDY<br>DAY | MEAN             | RL<br>SD        | N | MEAN             | HSD<br>SD       | N | MEAN             | HS<br>SD        | N | MEAN             | D 70<br>SD      | N |
|-----------------------------------|--------------|------------------|-----------------|---|------------------|-----------------|---|------------------|-----------------|---|------------------|-----------------|---|
|                                   |              |                  |                 |   | FEMALES          |                 |   |                  |                 |   |                  |                 |   |
| GAMMA GLUTAMYL<br>TRANSFERASE U/l | 3<br>13      | 4.56<br>6.98     | 1.09<br>1.74    | 5 | 12.54<br>7.66    | 6.41<br>1.42    | 5 | 6.47<br>8.38     | 3.19<br>2.16    | 3 | 4.68<br>4.50     | 1.80<br>1.67    | 5 |
| ALKALINE<br>PHOSPHATASE U/l       | 3<br>13      | 55.86<br>87.24   | 25.39<br>9.21   | 5 | 81.04<br>46.62   | 35.10<br>11.89  | 5 | 38.40<br>74.22   | 15.40<br>21.63  | 3 | 79.14<br>82.22   | 19.09<br>49.86  | 5 |
| LACTATE<br>DEHYDROGENASE U/l      | 3<br>13      | 558.92<br>140.16 | 254.56<br>59.01 | 5 | 445.66<br>172.20 | 270.41<br>59.31 | 5 | 440.50<br>100.53 | 133.30<br>36.51 | 3 | 344.40<br>273.28 | 73.95<br>400.25 | 5 |
| MAGNESIUM<br>mg/dl                | 3<br>13      | 2.55<br>1.95     | 0.23<br>0.22    | 5 | 2.19<br>1.96     | 0.28<br>0.21    | 5 | 2.01*            | 0.13            | 3 | 2.30             | 0.20            | 5 |
| SODIUM<br>Meq/l                   | 3<br>13      | 147.98<br>143.28 | 2.35<br>2.97    | 5 | 145.74<br>145.12 | 1.08<br>2.69    | 5 | 146.83<br>142.75 | 0.74<br>3.28    | 3 | 143.04<br>145.88 | 6.37<br>1.09    | 5 |
| CALCIUM<br>mg/dl                  | 3<br>13      | 11.88<br>14.16   | 0.83<br>0.24    | 5 | 11.62<br>12.44   | 0.28<br>3.10    | 5 | 11.97<br>13.88   | 0.06<br>0.62    | 3 | 12.02<br>14.42   | 0.19<br>0.28    | 5 |
| PHOSPHORUS<br>mg/dl               | 3<br>13      | 4.90<br>3.86     | 0.52<br>0.50    | 5 | 4.74<br>3.26     | 0.48<br>0.49    | 5 | 4.53<br>3.92     | 0.42<br>0.30    | 3 | 4.44<br>3.68     | 0.42<br>0.31    | 5 |
| CHOLESTEROL<br>mg/dl              | 3<br>13      | 65.24<br>55.12   | 25.83<br>14.57  | 5 | 49.84<br>60.76   | 8.07<br>14.66   | 5 | 58.00<br>71.30   | 12.62<br>10.91  | 3 | 42.04<br>55.32   | 19.68<br>21.61  | 5 |

\* Mean value of the group is significantly different from that of the control at  $p = 0.05$ .

Table 5 (cont.)  
SERUM CHEMISTRY SUMMARY

| PARAMETER/<br>UNITS               | STUDY<br>DAY | RL    |       | HSD |       | HS    |   | MEAN   |       | D 70 |        |
|-----------------------------------|--------------|-------|-------|-----|-------|-------|---|--------|-------|------|--------|
|                                   |              | MEAN  | SD    | N   | MEAN  | SD    | N | MEAN   | SD    | N    | SD     |
| FEMALES                           |              |       |       |     |       |       |   |        |       |      |        |
| CREATININE<br>mg/dl               | 3            | 1.10  | 0.19  | 5   | 1.04  | 0.15  | 5 | 0.90   | 0.20  | 3    | 1.00   |
|                                   | 13           | 1.08  | 0.08  | 5   | 1.20  | 0.16  | 5 | 1.15   | 0.19  | 4    | 1.10   |
| ALANINE AMINO-<br>TRANSFERASE U/l | 3            | 35.14 | 7.82  | 5   | 60.06 | 22.94 | 5 | 27.90  | 3.03  | 3    | 38.02  |
|                                   | 13           | 45.56 | 11.54 | 5   | 32.26 | 3.17  | 5 | 43.45  | 17.40 | 4    | 36.28  |
| TOTAL PROTEIN<br>g/dl             | 3            | 5.77  | 0.31  | 3   | 4.90  | 0.51  | 4 | 5.13   | 0.40  | 3    | 5.00   |
|                                   | 13           | 6.70  | 0.21  | 5   | 6.64  | 0.31  | 5 | 6.68   | 0.34  | 4    | 6.98   |
| URIC ACID<br>mg/dl                | 3            | 0.00  | 0.00  | 5   | 0.00  | 0.00  | 5 | 0.03   | 0.06  | 3    | 0.00   |
|                                   | 13           | 0.06  | 0.05  | 5   | 0.04  | 0.05  | 5 | 0.08   | 0.05  | 4    | 0.02   |
| POTASSIUM<br>Meq/l                | 3            | 5.52  | 1.94  | 5   | 5.04  | 0.57  | 5 | 4.80   | 0.40  | 3    | 7.54   |
|                                   | 13           | 4.68  | 0.77  | 5   | 4.64  | 0.23  | 5 | 4.30   | 0.36  | 4    | 5.00   |
| TRIGLYCERIDE<br>mg/dl             | 3            | 65.60 | 26.56 | 5   | 52.20 | 17.08 | 5 | 106.00 | 45.64 | 3    | 55.40  |
|                                   | 13           | 70.20 | 30.64 | 5   | 67.60 | 23.08 | 5 | 74.75  | 20.63 | 4    | 106.40 |
| ALBUMIN-<br>GLOBULIN RATIO        | 3            | 2.80  | 0.50  | 3   | 4.20  | 2.60  | 4 | 2.57   | 0.15  | 3    | 3.18   |
|                                   | 13           | 3.02  | 0.57  | 5   | 2.46  | 0.55  | 5 | 2.70   | 0.64  | 4    | 2.83   |

Table 6  
HEMATOLOGY SUMMARY

| PARAMETER/<br>UNITS                          | STUDY<br>DAY | MEAN           | RL<br>SD     | N | MEAN           | HSD<br>SD    | N | MEAN           | HS<br>SD     | N | MEAN           | D 70<br>SD   | N |
|--|--------------|----------------|--------------|---|----------------|--------------|---|----------------|--------------|---|----------------|--------------|---|
|  |              |                |              |   |                |              |   | MALES          |              |   |                |              |   |
| WHITE BLOOD CELL<br>COUNT X10 <sup>3</sup>   | 3<br>13      | 4.00<br>7.52   | 2.19<br>1.76 | 5 | 5.10<br>7.80   | 0.57<br>2.43 | 5 | 4.25<br>10.65  | 1.91<br>2.77 | 2 | 4.44<br>8.40   | 1.49<br>1.64 | 5 |
| RED BLOOD CELL<br>COUNT X10 <sup>6</sup>     | 3<br>13      | 5.75<br>6.07   | 0.32<br>0.57 | 5 | 5.43<br>5.65   | 0.33<br>0.87 | 5 | 4.90*          | 0.38         | 2 | 6.07<br>6.03   | 0.33<br>0.63 | 5 |
| HEMOGLOBIN<br>g/dl                           | 3<br>13      | 12.14<br>13.54 | 0.91<br>1.23 | 5 | 11.76<br>12.78 | 0.69<br>1.58 | 5 | 10.75<br>14.35 | 0.07<br>1.17 | 2 | 12.42<br>13.46 | 0.70<br>0.94 | 5 |
| HEMATOCRIT<br>%                              | 3<br>13      | 37.66<br>40.54 | 2.07<br>3.19 | 5 | 36.78<br>38.14 | 2.62<br>4.80 | 5 | 33.15<br>42.28 | 0.49<br>3.37 | 2 | 40.56<br>40.50 | 2.18<br>2.80 | 5 |
| MEAN CORPUSCULAR<br>VOLUME f1                | 3<br>13      | 65.54<br>66.90 | 0.85<br>2.19 | 5 | 67.72<br>67.76 | 2.63<br>2.98 | 5 | 67.80<br>69.63 | 4.24<br>1.54 | 2 | 66.86<br>67.36 | 1.33<br>3.05 | 5 |
| MEAN CORPUSCULAR<br>HEMOGLOBIN Pg            | 3<br>13      | 21.14<br>22.34 | 0.83<br>0.63 | 5 | 21.68<br>22.74 | 0.97<br>1.17 | 5 | 22.00<br>23.63 | 1.56<br>0.84 | 2 | 20.48<br>22.40 | 1.37<br>1.04 | 5 |
| MEAN CORPUSCULAR<br>HEMOGLOBIN CONC.<br>g/dl | 3<br>13      | 32.22<br>33.60 | 1.03<br>0.55 | 5 | 32.02<br>33.52 | 0.63<br>0.33 | 5 | 32.40<br>33.95 | 0.28<br>0.83 | 2 | 30.66<br>33.24 | 1.72<br>0.32 | 5 |

\* Mean value of the group is significantly different from that of the control at p = 0.05.

**Table 6 (cont.)**  
**HEMATOLOGY SUMMARY**

| PARAMETER/<br>UNITS                | STUDY<br>DAY | RL     |        |   | HSD    |        |   | HS     |       |   | D 70   |        |   |
|------------------------------------|--------------|--------|--------|---|--------|--------|---|--------|-------|---|--------|--------|---|
|                                    |              | MEAN   | SD     | N | MEAN   | SD     | N | MEAN   | SD    | N | MEAN   | SD     | N |
| MALES                              |              |        |        |   |        |        |   |        |       |   |        |        |   |
| PLATELET COUNT<br>X10 <sup>3</sup> | 3            | 262.20 | 111.83 | 5 | 335.80 | 115.83 | 5 | 440.50 | 84.15 | 2 | 536.00 | 293.75 | 5 |
|                                    | 13           | 309.80 | 88.72  | 5 | 246.00 | 69.35  | 5 | 342.75 | 80.86 | 4 | 322.60 | 86.41  | 5 |
| SEGMENTED<br>NEUTROPHILS<br>%      | 3            | 55.60  | 11.08  | 5 | 41.80  | 13.52  | 5 | 33.50  | 2.12  | 2 | 55.40  | 27.52  | 5 |
|                                    | 13           | 29.00  | 13.10  | 5 | 28.60  | 17.39  | 5 | 38.25  | 20.39 | 4 | 27.60  | 14.19  | 5 |
| BAND<br>NEUTROPHILS<br>%           | 3            | 0.00   | 0.00   | 5 | 0.00   | 0.00   | 5 | 0.00   | 0.00  | 2 | 0.00   | 0.00   | 5 |
|                                    | 13           | 0.20   | 0.45   | 5 | 0.00   | 0.00   | 5 | 0.00   | 0.00  | 4 | 0.20   | 0.45   | 5 |
| EOSINOPHILS<br>%                   | 3            | 2.00   | 2.12   | 5 | 2.80   | 0.84   | 5 | 3.50   | 0.71  | 2 | 1.40   | 1.14   | 5 |
|                                    | 13           | 1.80   | 1.64   | 5 | 1.80   | 2.17   | 5 | 3.50   | 2.52  | 4 | 2.20   | 1.79   | 5 |
| BASOPHILS<br>%                     | 3            | 2.40   | 2.88   | 5 | 3.00   | 1.41   | 5 | 0.50   | 0.71  | 2 | 2.60   | 3.05   | 5 |
|                                    | 13           | 2.60   | 2.70   | 5 | 3.40   | 2.07   | 5 | 2.25   | 0.50  | 4 | 1.60   | 1.14   | 5 |
| LYMPHOCYTES<br>%                   | 3            | 32.60  | 13.90  | 5 | 44.80  | 10.85  | 5 | 58.50  | 2.12  | 2 | 33.20  | 29.47  | 5 |
|                                    | 13           | 56.80  | 15.87  | 5 | 60.20  | 19.98  | 5 | 44.75  | 26.42 | 4 | 61.60  | 13.16  | 5 |
| MONOCYTES<br>%                     | 3            | 2.20   | 2.39   | 5 | 1.60   | 1.52   | 5 | 2.00   | 1.41  | 2 | 2.40   | 1.95   | 5 |
|                                    | 13           | 2.00   | 1.41   | 5 | 1.00   | 1.73   | 5 | 3.00   | 2.16  | 4 | 3.20   | 2.68   | 5 |

Table 6 (cont.)  
HEMATOLOGY SUMMARY

| PARAMETER/<br>UNITS                             | STUDY<br>DAY | MEAN           | RL<br>SD     | N      | MEAN          | HSD<br>SD    | N      | MEAN         | HS<br>SD     | N      | MEAN         | D 70<br>SD   | N      |
|---|--------------|----------------|--------------|--------|---------------|--------------|--------|--------------|--------------|--------|--------------|--------------|--------|
|   |              |                |              |        |               |              |        |              |              |        |              |              |        |
| ATYPICAL<br>LYMPHOCYTES<br>%                    | 3<br>13      | 5.20<br>4.20   | 1.30<br>2.28 | 5<br>5 | 6.00<br>4.80  | 3.46<br>3.19 | 5<br>5 | 2.00<br>6.50 | 1.41<br>2.65 | 2<br>4 | 5.40<br>3.60 | 3.91<br>2.61 | 5<br>5 |
| NRBC/100 WBC                                    | 3<br>13      | 3.40<br>1.80   | 3.05<br>2.49 | 5<br>5 | 6.00<br>0.00  | 3.08<br>0.00 | 5<br>5 | 4.00<br>0.25 | 0.00<br>0.50 | 2<br>4 | 7.00<br>2.60 | 3.46<br>2.51 | 5<br>5 |
| PROTHROMBIN<br>TIME sec                         | 3<br>13      | 9.50<br>4.85   | 0.00<br>4.45 | 1<br>2 | -<br>7.85     | -<br>2.33    | 2<br>2 | -<br>5.07    | -<br>2.75    | -<br>3 | -<br>6.05    | -<br>1.89    | -<br>4 |
| ACTIVATED PARTIAL<br>THROMBOPLASTIN TIME<br>sec | 3<br>13      | 34.50<br>18.60 | 0.00<br>1.27 | 1<br>2 | -<br>40.90    | -<br>0.00    | 1<br>1 | -<br>23.20   | -<br>18.70   | -<br>3 | -<br>25.35   | -<br>15.37   | -<br>4 |
| RETICULOCYTES<br>%                              | 3<br>13      | 3.54<br>3.88   | 1.76<br>0.48 | 5<br>5 | 2.68<br>2.20* | 1.76<br>1.07 | 5<br>5 | 0.75<br>2.33 | 1.06<br>0.96 | 2<br>4 | 3.14<br>3.26 | 0.92<br>1.11 | 5<br>5 |

\* Mean value of the group is significantly different from that of the control at  $p = 0.05$ .

Table 6 (cont.)  
HEMATOLOGY SUMMARY

| PARAMETER/<br>UNITS                          | STUDY<br>DAY | MEAN  | SD   | N | D 70 |  |
|--|--------------|-------|------|---|-------|------|---|-------|------|---|-------|------|---|------|--|
|  |              |       |      |   |       |      |   |       |      |   |       |      |   |      |  |
| FEMALES                                      |              |       |      |   |       |      |   |       |      |   |       |      |   |      |  |
| WHITE BLOOD CELL<br>COUNT X10 <sup>3</sup>   | 3            | 3.73  | 1.53 | 3 | 3.83  | 2.45 | 4 | 1.53  | 0.67 | 3 | 6.13  | 0.55 | 3 |      |  |
|  | 13           | 6.20  | 1.73 | 5 | 7.28  | 1.65 | 5 | 7.03  | 1.31 | 4 | 6.40  | 2.38 | 5 |      |  |
| RED BLOOD CELL<br>COUNT X10 <sup>6</sup>     | 3            | 4.74  | 0.50 | 3 | 4.73  | 0.52 | 4 | 4.07  | 0.87 | 3 | 4.62  | 0.24 | 3 |      |  |
|  | 13           | 5.48  | 0.71 | 5 | 5.21  | 0.37 | 5 | 5.46  | 0.16 | 4 | 5.05  | 0.92 | 5 |      |  |
| HEMOGLOBIN<br>g/dl                           | 3            | 11.20 | 0.70 | 3 | 10.80 | 1.00 | 4 | 9.53  | 1.76 | 3 | 10.77 | 0.72 | 3 |      |  |
|  | 13           | 12.36 | 1.42 | 5 | 12.22 | 0.99 | 5 | 12.80 | 0.52 | 4 | 11.60 | 2.01 | 5 |      |  |
| HEMATOCRIT<br>%                              | 3            | 33.60 | 2.72 | 3 | 32.68 | 2.76 | 4 | 28.30 | 5.80 | 3 | 32.60 | 1.25 | 3 |      |  |
|  | 13           | 37.04 | 4.19 | 5 | 36.58 | 3.08 | 5 | 37.95 | 1.50 | 4 | 34.08 | 6.48 | 5 |      |  |
| MEAN CORPUSCULAR<br>VOLUME f1                | 3            | 71.07 | 1.82 | 3 | 69.23 | 2.62 | 4 | 69.70 | 1.30 | 3 | 70.57 | 1.95 | 3 |      |  |
|  | 13           | 67.82 | 2.31 | 5 | 70.22 | 3.58 | 5 | 69.45 | 0.76 | 4 | 67.46 | 1.53 | 5 |      |  |
| MEAN CORPUSCULAR<br>HEMOGLICBIN pg           | 3            | 23.77 | 1.38 | 3 | 22.88 | 0.46 | 4 | 23.53 | 0.85 | 3 | 23.27 | 0.59 | 3 |      |  |
|  | 13           | 22.62 | 0.70 | 5 | 23.48 | 0.92 | 5 | 23.43 | 0.32 | 4 | 23.00 | 0.57 | 5 |      |  |
| MEAN CORPUSCULAR<br>HEMOGLOBIN CONC.<br>g/dl | 3            | 33.40 | 1.32 | 3 | 33.03 | 0.78 | 4 | 33.77 | 0.81 | 3 | 33.00 | 1.67 | 3 |      |  |
|  | 13           | 33.36 | 0.23 | 5 | 33.40 | 0.54 | 5 | 33.72 | 0.33 | 4 | 34.14 | 0.80 | 5 |      |  |

Table 6 (cont.)  
HEMATOLOGY SUMMARY

| PARAMETER /<br>UNITS            | STUDY<br>DAY | MEAN             | RL<br>SD         | N      | MEAN             | HSD<br>SD       | N      | MEAN             | HS<br>SD         | N      | MEAN             | D 70<br>SD      | N      |
|---------------------------------|--------------|------------------|------------------|--------|------------------|-----------------|--------|------------------|------------------|--------|------------------|-----------------|--------|
|                                 |              |                  |                  |        |                  |                 |        |                  |                  |        |                  |                 |        |
| PLATELET COUNT<br>$\times 10^3$ | 3<br>13      | 410.67<br>393.00 | 164.45<br>152.07 | 3<br>5 | 237.25<br>341.80 | 130.71<br>47.43 | 4<br>5 | 251.00<br>323.50 | 330.74<br>140.43 | 3<br>4 | 325.00<br>256.40 | 166.14<br>78.40 | 3<br>5 |
| SEGMENTED<br>NEUTROPHILS<br>%   | 3<br>13      | 40.67<br>41.00   | 8.50<br>16.17    | 3<br>5 | 34.50<br>40.20   | 10.02<br>17.91  | 4<br>5 | 32.00<br>51.25   | 19.08<br>8.38    | 3<br>4 | 41.67<br>42.40   | 10.21<br>15.49  | 3<br>5 |
| BAND<br>NEUTROPHILS<br>%        | 3<br>13      | 0.00<br>0.00     | 0.00<br>0.00     | 3<br>5 | 0.00<br>0.20     | 0.00<br>0.45    | 4<br>5 | 0.00<br>0.00     | 0.00<br>0.00     | 3<br>4 | 0.00<br>0.00     | 0.00<br>0.00    | 3<br>5 |
| EOSINOPHILS<br>%                | 3<br>13      | 2.00<br>2.60     | 1.00<br>2.61     | 3<br>5 | 1.25<br>0.20     | 1.50<br>0.45    | 4<br>5 | 0.33<br>3.00     | 0.58<br>1.41     | 3<br>4 | 1.00<br>2.60     | 1.00<br>2.79    | 3<br>5 |
| BASOPHILS<br>%                  | 3<br>13      | 2.00<br>0.80     | 1.73<br>0.84     | 3<br>5 | 1.75<br>0.20     | 2.36<br>0.45    | 4<br>5 | 2.00<br>0.50     | 2.00<br>1.00     | 3<br>4 | 1.00<br>0.20     | 1.73<br>0.45    | 3<br>5 |
| LYMPHOCYTES<br>%                | 3<br>13      | 50.67<br>38.60   | 10.79<br>11.08   | 3<br>5 | 59.25<br>40.20   | 11.84<br>17.60  | 4<br>5 | 61.00<br>39.25   | 18.03<br>6.02    | 3<br>4 | 48.33<br>50.00   | 9.50<br>15.12   | 3<br>5 |
| MONOCYTES<br>%                  | 3<br>13      | 1.67<br>2.40     | 0.58<br>2.51     | 3<br>5 | 1.50<br>1.60     | 1.00<br>1.52    | 4<br>5 | 1.33<br>3.75     | 1.53<br>4.27     | 3<br>4 | 3.00<br>0.80     | 1.73<br>0.84    | 3<br>5 |

**Table 6 (cont.)**  
**HEMATOLOGY SUMMARY**

| PARAMETER/<br>UNITS                             | STUDY<br>DAY | MEAN  | RL<br>SD | N | MEAN    | HSD<br>SD | N | MEAN  | HS<br>SD | N | MEAN  | D 70<br>SD | N |
|---|--------------|-------|----------|---|---------|-----------|---|-------|----------|---|-------|------------|---|
|   |              |       |          |   | FEMALES |           |   |       |          |   |       |            |   |
| ATYPICAL<br>LYMPHOCYTES<br>%                    | 3            | 3.00  | 1.73     | 3 | 1.75    | 2.22      | 4 | 3.33  | 4.16     | 3 | 5.00  | 5.29       | 3 |
|   | 13           | 6.20  | 3.35     | 5 | 2.00    | 1.00      | 5 | 2.25  | 1.71     | 4 | 4.00  | 3.81       | 5 |
| NRBC/100 WBC                                    | 3            | 0.00  | 0.00     | 3 | 0.00    | 0.00      | 4 | 0.00  | 0.00     | 3 | 0.00  | 0.00       | 3 |
|   | 13           | 0.00  | 0.00     | 5 | 0.00    | 0.00      | 5 | 0.00  | 0.00     | 4 | 0.00  | 0.00       | 5 |
| PROTHROMBIN TIME<br>sec                         | 3            | 7.00  | 0.00     | 1 | 6.65    | 0.21      | 2 | -     | -        | - | -     | -          | - |
|   | 13           | 6.08  | 0.76     | 4 | 8.80*   | 0.00      | 2 | 6.30  | 0.61     | 3 | 8.50* | 1.41       | 2 |
| ACTIVATED PARTIAL<br>THROMBOPLASTIN TIME<br>sec | 3            | 28.10 | 0.00     | 1 | 44.30   | 4.53      | 2 | -     | -        | - | -     | -          | - |
|   | 13           | 9.03  | 6.83     | 4 | 19.45   | 7.42      | 2 | 12.73 | 10.58    | 3 | 6.55  | 7.00       | 2 |
| RETICULOCYTES<br>%                              | 3            | 3.97  | 1.10     | 3 | 3.05    | 1.26      | 4 | 4.23  | 0.74     | 3 | 2.73  | 1.10       | 3 |
|   | 13           | 3.44  | 0.57     | 5 | 5.04    | 1.74      | 5 | 2.88  | 1.36     | 4 | 4.88  | 2.69       | 5 |

\* Mean value of the group is significantly different from that of the control at  $p = 0.05$ .

The bruising, discoloration, and necrosis around the injection site on the ear were observed in 7 animals receiving HSD and 5 animals receiving HS. Only 1 animal in each of the groups receiving D70 or RL exhibited any of these signs. This finding was consistent with observations made in a maximum tolerated dose study of HSD in mice in which tail sloughing was observed when HSD and HS were administered via the tail vein (17). These responses were attributed to unavoidable extravasation of injection fluid around the injection site. Since the injection technique was the same for all animals, one could assume that equivalent amounts of extravasation would occur in all dose groups. Therefore, the increased incidence of irritation in HSD and HS, but not in D70 treated animals, suggests that extravascular hypertonic saline causes tissue necrosis by a mechanism other than by an ischemic response due to increased extravascular fluid pressure. The probable mechanism for this local toxicity is a direct effect of the HS on extravascular tissues even though HS and HSD were no more irritating following paravenous administration than RL when evaluated for local irritation (18). However, the amount of fluid that was injected paravenously in the rabbit local irritation study was 0.1 ml which produced a wheal considerably smaller than that produced by the fluid that was extravasated in the rabbit maximum tolerated dose study.

In albino rabbits, the reddish color of the eyes is associated with the concentration of erythrocytes in the highly vascular retina; thus, the "pale eye" observation would suggest a reduction (or dilution) in the erythrocyte concentration. The increased incidence of pale eyes in the HS group compared with the RL group is attributed to the hyperosmotic action of the solution drawing additional fluid into the vascular compartment which results in a greater dilution of erythrocytes than the RL group.

With the exception of decreased serum iron in the HS group 3 days after administration, no consistent changes were seen in serum chemistry parameters, and no significant changes outside of normal limits were observed in the hematology parameters. Body weights and water consumption were unaffected by the dosing.

No significant treatment-related findings other than local toxicity around the injection site were observed at necropsy 3 or 14 days after administration of the fluids nor in the histological examination of selected tissues. This suggests that any morphological changes due to the administration of the volume expanders were transient, if any did occur.

These data suggest that the maximum tolerated dose of HSD administered intravenously over a 5-minute period is 20 ml/kg. The toxicity observed following HSD administration was attributable primarily to the HS component and is an expected physiological response to large volumes of hypertonic saline. The findings of lethality following HS administration suggests that the rabbit is more sensitive to the acute hemodynamic effects of HS than HSD. Since the proposed therapeutic dose of HSD is only 4 ml/kg, these findings indicate that there will be minimal adverse effects associated with the therapeutic administration of HSD.

#### **CONCLUSION**

The maximum tolerated dose of HSD following acute intravenous administration is 20 ml/kg, and the toxicity associated with the HSD administration is consistent with the administration of large volumes of hypertonic saline. Since the proposed therapeutic dose of HSD is only 4 ml/kg, these findings indicate that there will be minimal adverse effects associated with the therapeutic administration of HSD.

REFERENCES

1. Bellamy RF. The causes of death in conventional land warfare: Implications for combat casualty care research. *Milit Med* 1984; 149: 55-62.
2. Kramer GC, Perron PR, Lindsey DC. Small-volume resuscitation with hypertonic saline dextran solution. *Surgery* 1986; 100(2): 239-246.
3. Penfield WG. The treatment of severe and progressive hemorrhage by intravenous injection. *Am J Physiol* 1919; 48: 121-128.
4. Velasco IT, Pontieri V, Rocha e Silva M. Hyperosmotic NaCl and severe hemorrhagic shock. *Am J Physiol* 1980; 239: H664-H673.
5. Maningas PA, DeGuzman RL, Tillman FJ, Hinson CS, Priegnitz KJ, Volk KA, Bellamy RF. Small-volume infusion of 7.5% NaCl in 6% Dextran 70® for the treatment of severe hemorrhagic shock in swine. *Ann Emerg Med* 1986; 15(10): 1131-1137.
6. Holcroft JW, Vassar MJ, Turner JE, Derlet RW, Kramer GC. NaCl and 7.5% NaCl/dextran 70 in the resuscitation of severely injured patients. *Ann Surg* 1987; 206(3): 279-288.
7. Norenberg MD, Leslie KO, Robertson AS. Association between rise in serum sodium and central pontine myelinolysis. *Ann Neurol* 1982; 11(2): 128-135.
8. Laureno R. Central pontine myelinolysis following rapid correction of hyponatremia. *Ann Neurol* 1983; 13(3): 232-243.
9. Sterns RH, Riggs JE, Schochet SS. Osmotic demyelination syndrome following correction of hyponatremia. *N Engl J Med* 1986; 314(2): 1535-1541.
10. Shackford SR, Fortlage DA, Peters RM. Serum osmolar and electrolyte changes associated with large infusions of hypertonic sodium lactate for intravascular volume expansion of patients undergoing aortic reconstruction. *Surg Gynecol Obstet* 1987; 164(2): 127-136.
11. FDA, Nonclinical Laboratory Studies (21 CFR 58) Final Rule, 22 Dec 78 (43 FR 59986-60025).

REFERENCES (cont.)

12. Acute Intravenous Toxicity Study. LAIR Standard Operating Procedure OP-STX-113, Letterman Army Institute of Research, Presidio of San Francisco, CA, 8 June 1988.
13. Dixon DJ, ed. BMDP statistical software. Berkeley: University of California Press, 1981: 555-573.
14. Yu L, Pragay DA, Chang D, Wicher K. Biochemical parameters of normal rabbit serum. Clin Biochem 1979; 12: 83-87.
15. Harkness JE, Wagner JE. The biology and medicine of rabbits and rodents. 2nd ed. Philadelphia: Lea & Febiger, 1983.
16. Kozma C, Macklin W, Cummins LM, Mauer R. Anatomy, physiology, and biochemistry of the rabbit. In: Weisbroth SH, Flatt RE, Kraus AL, eds. The biology of the laboratory rabbit. New York: Academic Press, 1974.
17. Frost DF, Zaucha GM, Young GD, Korte DW. Acute intravenous toxicity study of hypertonic saline/Dextran 70® and its constituents in ICR mice. Toxicology Series 245. Institute Report No. 333. Presidio of San Francisco, CA: Letterman Army Institute of Research, 1989.
18. Zaucha GM, Frost DF, Young GD, Korte DW. Local irritation toxicity study of hypertonic saline/Dextran 70® in New Zealand White rabbits. Toxicology Series 244. Institute Report No. 332. Presidio of San Francisco, CA: Letterman Army Institute of Research, 1988.

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## Appendix A: CHEMICAL DATA



CERTIFICATE OF ANALYSIS 1987-10-23

6 % DEXTRAN 70 IN 7,5 %  
SODIUM CHLORIDE INJECTION

Charge No. NC 54845

|                            |                |
|----------------------------|----------------|
| Inherent viscosity         | 27 ml/g        |
| Absorbance (375 nm, 10 mm) | 0,006          |
| pH                         | 4,6            |
| Heavy metals               | < 5 ppm        |
| Sodium chloride            | 74,7 g/1000 ml |
| Dextran 70                 | 60 g/1000 ml   |
| Particulate matter         | passed test    |
| Sterility                  | passed test    |
| Pyrogens                   | passed test    |

Released for clinical trials.

---

Pharmacia AB  
Analytical Chemistry Department

Tord Jonsson

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## Appendix A (cont.): CHEMICAL DATA



CERTIFICATE OF ANALYSIS 1988-12-19

7,5 % SODIUM CHLORIDE

Charge No. I 318712

|                    |                |
|--------------------|----------------|
| Identification     | passed test    |
| Absorbance         | 0.000          |
| pH                 | 6.0            |
| Heavy metals       | < 5 ppm        |
| Sodium chloride    | 75,0 g/1000 ml |
| Particulate matter | passed test    |
| Sterility          | passed test    |
| Pyrogens           | passed test    |

Released for biological trials.

---

Pharmacia AB  
Analytical Chemistry Department

*Elisabet Fransson*

Elisabet Fransson

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## Appendix A (cont.): CHEMICAL DATA



Pharmacia

## Certificate of analysis

Name: MACRODEX 60 mg/ml in Normal saline

Item No.: 10-4510-00

Lot No.: NE 54941

| Test               |          | Result      | Tolerance limit | Method        |
|--------------------|----------|-------------|-----------------|---------------|
| Inherent viscosity | ml/g     | 26          | 25 - 28         | 03700         |
| Colour             |          | 0.01        | Max. 0.04       | 03811         |
| pH                 |          | 4.9         | 4.0 - 7.0       | USP XX p. 968 |
| Heavy metals ppm   |          | < 5         | Max. 5          | USP XX p. 909 |
| Assay for          |          |             |                 |               |
| - sodium chloride  | g/1000ml | 8.88        | 8.10 - 9.90     | 02355         |
| - dextran 70       | g/1000ml | 59          | 54 - 66         | 02356         |
| Sterility          |          | Passed test | To pass test    | 02885         |
| Pyrogens           |          | Passed test | To pass test    | 02983         |

The identity is assured through strict adherence to established GMP rules throughout the manufacturing procedures.

Released for sale: 1987-05-25

Pharmacia AB  
Quality Control Department

Mats Wiberg

M09

Pharmacia AB  
S-751 82 UPPSALA  
Sweden

Telephone  
Nat 018 - 163000  
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## Appendix A (cont.): CHEMICAL DATA

|                             |                                    |
|-----------------------------|------------------------------------|
| <b>Pharmacia</b>            | CERTIFICATE OF ANALYSIS 1987-10-23 |
| Product                     |                                    |
| LACTATED RINGER'S INJECTION |                                    |
| Charge No. NC 54847         |                                    |

|                    |                    |
|--------------------|--------------------|
| pH                 | 5,8                |
| Heavy metals       | < 5 ppm            |
| Sodium             | 127 mmol/1000 ml   |
| Potassium          | 3,91 mmol/1000 ml  |
| Calcium            | 1,30 mmol/1000 ml  |
| Chloride           | 105,5 mmol/1000 ml |
| Lactate            | 27,2 mmol/1000 ml  |
| Particulate matter | passed test        |
| Sterility          | passed test        |
| Pyrogens           | passed test        |

Released for clinical trials.

Pharmacia AB  
Analytical Chemistry Department

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**Appendix B: ANIMAL DATA**

Species: *Oryctolagus cuniculus*

Strain: New Zealand White

Source: Hazleton Research Products, Inc.  
Swampbridge Road  
Denver, PA 17517

Sex: Male and Female

Date of birth: 24 Apr 88

Method of randomization: Weight bias, stratified animal allocation (XYBION Medical Systems PATH/TOX AESLCT Program)

Animals in each group: 10 Males and 10 Females

Condition of animals at start of study: Normal

Body weight range at dosing: Males 2.906 - 3.767 kg  
Females 3.413 - 4.411 kg

Identification procedures: Supplier ear tag with corresponding LAIR animal number

Pretest conditioning: Quarantine/acclimation 25 August 1988 to 12 and 19 September 1988, males and females, respectively

Justification: The laboratory rabbit is a standard laboratory model for acute toxicity studies and is accepted by all regulatory agencies.

**Appendix C: HISTORICAL LISTING OF STUDY EVENTS**

| <u>Date</u>   | <u>Event</u>  |
|---|---|
| 24 Aug 88   | Animals arrived at LAIR. They were sexed, observed for illness, and caged in the GLP Suite. Eighty-two animals were assigned to the study.                              |
| 25 Aug 88   | Animals were identified (ear tag referenced to LAIR number).  |
| 25, 31 Aug 88<br>6, 13, 16, 20, 27<br>Sep, 4 Oct 88 | Animals were weighed.   |
| 31 Aug, 6, 14-27<br>Sep 88                          | Water consumption was monitored.  |
| 26 Aug 88   | Quality control animals were submitted for necropsy.  |
| 25 Aug 88-<br>3 Oct 88                              | Animals were observed twice daily.  |
| 31 Aug 88   | Animals were randomized into groups.  |
| 13 (M), 20 (F)<br>Sep 88                            | Animals were dosed beginning at 0900 hours. Observations were conducted one, two, and four hours after dosing.  |
| 26 Sep, 3 Oct 88                                    | Day 13 blood samples were collected.  |
| 16, 23, 27<br>Sep, 4 Oct 88                         | Animals were observed for clinical signs at approximately 0730 hours. Animals were delivered to the Necropsy Suite for blood sampling (Day 3), euthanasia and necropsy. |

**Appendix D: INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN | SEVERITY OR LOCATION |
|---------------|------------|-------------------------------|---------------|----------------------|
| 88F00262      | M/HS       | 0 / 09:20                     | DOSED         | ++                   |
|               |            | 0 / 09:26                     | FND DEAD      | ++                   |
| 88F00301      | M/HS       | 0 / 09:24                     | DOSED         | ++                   |
|               |            | 0 / 10:21                     | TREMORS       | MODERATE             |
|               |            | 0 / 11:23                     | DISORIENT     | SLIGHT               |
|               |            | 0 / 13:32                     | TREMORS       | SLIGHT               |
|               |            | 1 / 11:10                     | DISORIENT     | SLIGHT               |
|               |            | 2 / 09:05                     | INACTIVE      | SLIGHT               |
|               |            | 3 / 07:00                     | DISORIENT     | SLIGHT               |
|               |            | 0 / 09:25                     | N/EUTH        | ++                   |
| 88F00282      | M/HS       | 0 / 09:28                     | DOSED         | ++                   |
|               |            | 0 / 10:07                     | FND DEAD      | ++                   |
| 88F00298      | M/HS       | 0 / 11:07                     | DOSED         | ++                   |
|               |            | 0 / 12:08                     | INC RESP RATE | MODERATE             |
|               |            | 0 / 14:16                     | HUNCCHED      | MODERATE             |
|               |            | 1 / 11:10                     | INACTIVE      | MODERATE             |
|               |            | 2 / 10:00                     | INC RESP RATE | SLIGHT               |
|               |            | 3 / 07:00                     | HUNCCHED      | SLIGHT               |
|               |            | 0 / 12:03                     | INACTIVE      | SLIGHT               |
|               |            | 0 / 14:17                     | HUNCCHED      | SLIGHT               |
|               |            | 1 / 09:20                     | BRUISE        | SEVERE LEFT EAR      |
|               |            |                               | DISCHARGE     | SLIGHT LEFT EAR      |
| 88F00257      | M/HS       | 3 / 07:00                     | BRUISE        | SEVERE LEFT EAR      |
|               |            |                               | EUTHAN        | ++                   |
|               |            | 0 / 10:03                     | DOSED         | ++                   |
|               |            | 0 / 11:04                     | INACTIVE      | SEVERE               |
|               |            |                               | PALE EYES     | MODERATE             |
|               |            | 0 / 12:03                     | HUNCCHED      | MODERATE             |
|               |            | 0 / 14:17                     | INACTIVE      | MODERATE             |
|               |            | 1 / 09:20                     | PALE EYES     | MODERATE             |
|               |            |                               | HUNCCHED      | SEVERE               |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN   | CLINICAL SIGN   | SEVERITY OR LOCATION  |
|---------------|------------|---|---|---|
| 88F00257      | M/HS       | 1 / 09:20<br>2 / 09:07<br><br>3 / 07:00   | BRUISE<br>INACTIVE<br>PALE EYES<br>HUNCCHED<br>BRUISE<br>INACTIVE<br>PALE EYES<br>HUNCCHED<br>BRUISE<br>EUTHAN  | SEVERE LEFT EAR<br>SEVERE<br>MODERATE<br>SEVERE<br>SEVERE LEFT EAR<br>SEVERE<br>MODERATE<br>SEVERE<br>SEVERE LEFT EAR<br>++                                       |
| 88F00272      | M/HS       | 0 / 10:51<br>0 / 10:55  | DOSED<br>FND DEAD   | ++<br>++  |
| 88F00280      | M/HS       | 0 / 10:20<br>0 / 11:21<br><br>0 / 12:19<br><br>0 / 14:19<br>1 / 11:26<br>2 / 09:08<br>3 / 10:10<br>4 / 14:00<br>5 / 11:00<br>6 / 10:12<br>7 / 10:40<br>8 / 13:35<br>9 / 15:30<br>10 / 13:53<br>11 / 09:30<br>12 / 08:50<br>13 / 14:38<br>14 / 07:00 | DOSED<br>HUNCCHED<br>DISORIENT<br>HUNCCHED<br>DISORIENT<br>HUNCCHED<br>HUNCCHED<br>BRUISE<br>BRUISE<br>BRUISE<br>BRUISE<br>BRUISE<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>N/EUTH | MODERATE<br>SLIGHT<br>MODERATE<br>SLIGHT<br>SLIGHT<br>SLIGHT<br>SLIGHT LEFT EAR<br>SLIGHT LEFT EAR<br>SLIGHT LEFT EAR<br>SLIGHT LEFT EAR<br>SLIGHT LEFT EAR<br>++ |
| 88F00303      | M/HS       | 0 / 10:26<br>0 / 11:25<br><br>0 / 12:20<br><br>0 / 14:25<br>1 / 11:10<br>2 / 10:01<br>3 / 10:37   | DOSED<br>DISORIENT<br>TREMORS<br>HUNCCHED<br>HUNCCHED<br>DISORIENT<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL  | ++<br>MODERATE<br>MODERATE<br>SLIGHT<br>SLIGHT<br>MODERATE  |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN                                      | SEVERITY OR LOCATION                     |
|---------------|------------|-------------------------------|--|--|
| 88F00303      | M/HS       | 4 / 14:00                     | NORMAL   |  |
|               |            | 5 / 11:00                     | NORMAL   |  |
|               |            | 6 / 10:18                     | NORMAL   |  |
|               |            | 7 / 10:52                     | NORMAL   |  |
|               |            | 8 / 13:24                     | NORMAL   |  |
|               |            | 9 / 15:30                     | NORMAL   |  |
|               |            | 10 / 13:03                    | NORMAL   |  |
|               |            | 11 / 09:30                    | NORMAL   |  |
|               |            | 12 / 08:50                    | NORMAL   |  |
|               |            | 13 / 14:43                    | NORMAL   |  |
|               |            | 14 / 07:00                    | N/EUTH   | ++                                       |
|               |            | 0 / 10:28                     | DOSED  | ++                                       |
|               |            | 0 / 11:26                     | TREMORS<br>DISORIENT<br>HUNCHED                    | MODERATE<br>MODERATE<br>MODERATE         |
| 88F00254      | M/HS       | 0 / 12:25                     | HUNCHED<br>DISORIENT<br>TREMORS                    | SLIGHT<br>SLIGHT<br>SLIGHT               |
|               |            | 0 / 14:28                     | DISORIENT<br>HUNCHED                               | SLIGHT<br>SLIGHT                         |
|               |            | 1 / 11:26                     | HUNCHED  | SLIGHT                                   |
|               |            | 2 / 09:09                     | BRUISE   | MODERATE LEFT EAR                        |
|               |            | 3 / 10:25                     | BRUISE   | MODERATE LEFT EAR                        |
|               |            | 4 / 14:00                     | BLOOD DRN  | SLIGHT LEFT EAR                          |
|               |            | 5 / 11:00                     | BRUISE   | MODERATE LEFT EAR                        |
|               |            | 6 / 10:13                     | BRUISE   | MODERATE LEFT EAR                        |
|               |            | 7 / 10:42                     | BRUISE   | MODERATE LEFT EAR                        |
|               |            | 8 / 13:36                     | BRUISE   | MODERATE LEFT EAR                        |
|               |            | 9 / 15:30                     | BRUISE   | MODERATE LEFT EAR                        |
|               |            | 10 / 13:49                    | BRUISE   | SLIGHT LEFT EAR                          |
|               |            | 11 / 09:30                    | BRUISE   | SLIGHT LEFT EAR                          |
|               |            | 12 / 08:50                    | BRUISE   | SLIGHT LEFT EAR                          |
| 88F00297      | M/HS       | 13 / 14:35                    | BRUISE   | SLIGHT LEFT EAR                          |
|               |            | 14 / 07:00                    | BRUISE   | SLIGHT LEFT EAR                          |
|               |            | EUTHAN                        |  | ++                                       |
|               |            | 0 / 10:35                     | DOSED  | ++                                       |
|               |            | 0 / 11:33                     | HUNCHED<br>PALE EYES<br>DISORIENT<br>INC RESP RATE | MODERATE<br>SLIGHT<br>MODERATE<br>SLIGHT |
|               |            | 0 / 12:30                     | HUNCHED  | SLIGHT                                   |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN   | SEVERITY OR LOCATION   |
|---------------|------------|-------------------------------|---|--|
| 88F00297      | M/HS       | 0 / 12:30                     | DISORIENT<br>INC RESP RATE<br>HYPERACT<br>HYPERACT<br>NORMAL<br>HYPERACT<br>BRUISE<br>HYPERACT<br>BRUISE<br>BLOOD DRN<br>DEC APPET<br>DEC APPET<br>BRUISE<br>7 / 10:52<br>8 / 13:25<br>IRRITABLE<br>9 / 15:30<br>10 / 13:59<br>11 / 09:30<br>12 / 08:50<br>13 / 14:41<br>14 / 07:00 | SLIGHT<br>SLIGHT<br>MODERATE<br>MODERATE<br>SLIGHT<br>MODERATE LEFT EAR<br>SLIGHT<br>MODERATE LEFT EAR<br>SLIGHT LEFT EAR<br>MODERATE<br>MODERATE<br>MODERATE LEFT EAR<br>MODERATE LEFT EAR<br>MODERATE LEFT EAR<br>MODERATE LEFT EAR<br>MODERATE LEFT EAR<br>MODERATE LEFT EAR<br>MODERATE LEFT EAR<br>SLIGHT LEFT EAR<br>SLIGHT LEFT EAR |
|               |            | 0 / 14:34                     |   |  |
|               |            | 1 / 11:10                     |   |  |
|               |            | 2 / 10:45                     |   |  |
|               |            | 3 / 11:06                     |   |  |
|               |            | 4 / 14:00                     |   |  |
|               |            | 5 / 11:00                     |   |  |
|               |            | 6 / 10:13                     |   |  |
|               |            | 7 / 10:52                     |   |  |
|               |            | 8 / 13:25                     |   |  |
|               |            | 9 / 15:30                     |   |  |
|               |            | 10 / 13:59                    |   |  |
|               |            | 11 / 09:30                    |   |  |
|               |            | 12 / 08:50                    |   |  |
|               |            | 13 / 14:41                    |   |  |
|               |            | 14 / 07:00                    |   |  |
|               |            | EUTHAN                        |   | ++<br>++   |
| 88F00274      | M/HSD      | 0 / 08:47                     | DOSED   |  |
|               |            | 0 / 10:00                     | NORMAL  |  |
|               |            | 0 / 10:47                     | NORMAL  |  |
|               |            | 0 / 12:54                     | NORMAL  |  |
|               |            | 1 / 11:14                     | NORMAL  |  |
|               |            | 2 / 09:21                     | NORMAL  |  |
|               |            | 3 / 07:00                     | N/EUTH  | ++   |
| 88F00258      | M/HSD      | 0 / 08:50                     | DOSED   | ++   |
|               |            | 0 / 10:00                     | NORMAL  |  |
|               |            | 0 / 10:51                     | NORMAL  |  |
|               |            | 0 / 12:54                     | NORMAL  |  |
|               |            | 1 / 11:15                     | NORMAL  |  |
|               |            | 2 / 09:21                     | NORMAL  |  |
|               |            | 3 / 07:00                     | N/EUTH  | ++   |
| 88F00285      | M/HSD      | 0 / 08:47                     | DOSED   | ++   |
|               |            | 0 / 10:00                     | TREMORS   | SEVERE   |
|               |            | 0 / 10:49                     | TREMORS   | MODERATE   |
|               |            | 0 / 12:55                     | HYPERRACT   | SLIGHT   |
|               |            |                               | TREMORS   | MODERATE   |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN | SEVERITY OR LOCATION   |
|---------------|-----------|-------------------------------|---------------|--|
| 88F00285      | M/HSD     | 0 / 12:55                     | HYPERACT      | SLIGHT   |
|               |           | 1 / 11:16                     | NORMAL        |  |
|               |           | 2 / 09:22                     | NORMAL        |  |
|               |           | 3 / 07:00                     | N/EUTH        |  |
| 88F00260      | M/HSD     | 0 / 08:55                     | DOSED         | ++   |
|               |           | 0 / 10:00                     | NORMAL        |  |
|               |           | 0 / 10:52                     | NORMAL        |  |
|               |           | 0 / 12:57                     | BRUISE        |  |
|               |           | 1 / 11:17                     | BRUISE        | SEVERE LEFT EAR<br>MODERATE LEFT EAR<br>MODERATE LEFT EAR<br>MODERATE LEFT EAR   |
|               |           | 2 / 09:25                     | BRUISE        |  |
|               |           | 3 / 07:00                     | BRUISE        |  |
|               |           | EUTHAN                        |               |  |
| 88F00293      | M/HSD     | 0 / 08:56                     | DOSED         | ++<br>SLIGHT<br>SLIGHT   |
|               |           | 0 / 10:00                     | HUNCHE        |  |
|               |           | 0 / 10:56                     | HUNCHE        |  |
|               |           | 0 / 12:58                     | NORMAL        |  |
|               |           | 1 / 11:18                     | NORMAL        |  |
|               |           | 2 / 09:26                     | NORMAL        |  |
|               |           | 3 / 07:00                     | N/EUTH        |  |
|               |           | 0 / 09:02                     | DOSED         |  |
| 88F00295      | M/HSD     | 0 / 10:00                     | NORMAL        | ++<br><br>MODERATE RT EAR<br>MODERATE RT EAR<br>MODERATE RT EAR<br>MODERATE RT EAR<br>SLIGHT RT EAR<br>EUTHAN |
|               |           | 0 / 11:00                     | NORMAL        |  |
|               |           | 0 / 13:00                     | NORMAL        |  |
|               |           | 1 / 11:19                     | NORMAL        |  |
|               |           | 2 / 09:27                     | BRUISE        |  |
|               |           | 3 / 10:16                     | BRUISE        |  |
|               |           | 4 / 14:00                     | BRUISE        |  |
|               |           | 5 / 11:00                     | BRUISE        |  |
|               |           | 6 / 10:04                     | BRUISE        |  |
|               |           | 7 / 10:43                     | BRUISE        |  |
|               |           | 8 / 13:36                     | BRUISE        |  |
|               |           | 9 / 15:30                     | INACTIVE      |  |
|               |           | 10 / 13:56                    | BRUISE        |  |
|               |           | 11 / 09:30                    | BRUISE        |  |
|               |           | 12 / 08:50                    | BRUISE        |  |
|               |           | 13 / 14:41                    | BRUISE        |  |
|               |           | 14 / 07:00                    | BRUISE        |  |
| 88F00289      | M/HSD     | 0 / 09:06                     | EUTHAN        | ++<br>++   |
|               |           | 0 / 10:00                     | DOSED         |  |
|               |           |                               | NORMAL        |  |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN | SEVERITY OR LOCATION |
|---------------|------------|-------------------------------|---------------|----------------------|
| 88F00289      | M/HSD      | 0 / 11:06                     | NORMAL        |                      |
|               |            | 0 / 13:10                     | NORMAL        |                      |
|               |            | 1 / 11:19                     | NORMAL        |                      |
|               |            | 2 / 09:29                     | NORMAL        |                      |
|               |            | 3 / 10:17                     | NORMAL        |                      |
|               |            | 4 / 14:00                     | NORMAL        |                      |
|               |            | 5 / 11:00                     | NORMAL        |                      |
|               |            | 6 / 10:07                     | NORMAL        |                      |
|               |            | 7 / 10:43                     | NORMAL        |                      |
|               |            | 8 / 13:37                     | NORMAL        |                      |
|               |            | 9 / 15:30                     | NORMAL        |                      |
|               |            | 10 / 13:55                    | NORMAL        |                      |
|               |            | 11 / 09:30                    | NORMAL        |                      |
| 88F00290      | M/HSD      | 12 / 08:50                    | NORMAL        |                      |
|               |            | 13 / 14:39                    | NORMAL        |                      |
|               |            | 14 / 07:00                    | N/EUTH        | ++                   |
|               |            | 0 / 09:10                     | DOSED         | ++                   |
|               |            | 0 / 10:00                     | NORMAL        |                      |
|               |            | 0 / 11:08                     | NORMAL        |                      |
|               |            | 0 / 13:11                     | BRUISE        | SLIGHT LEFT EAR      |
|               |            | 1 / 11:20                     | BRUISE        | SLIGHT LEFT EAR      |
|               |            | 2 / 09:30                     | BRUISE        | SLIGHT LEFT EAR      |
|               |            | 3 / 10:18                     | BRUISE        | SLIGHT LEFT EAR      |
|               |            | 4 / 14:00                     | BRUISE        | SLIGHT LEFT EAR      |
|               |            | 5 / 11:00                     | BRUISE        | SLIGHT LEFT EAR      |
|               |            | 6 / 10:07                     | BRUISE        | SLIGHT LEFT EAR      |
| 88F00279      | M/HSD      | 7 / 10:44                     | INACTIVE      | SLIGHT               |
|               |            | 8 / 13:38                     | BRUISE        | SLIGHT LEFT EAR      |
|               |            | 9 / 15:30                     | INACTIVE      | SLIGHT               |
|               |            | 10 / 13:55                    | BRUISE        | SLIGHT LEFT EAR      |
|               |            | 11 / 09:30                    | NORMAL        |                      |
|               |            | 12 / 08:50                    | NORMAL        |                      |
|               |            | 13 / 14:40                    | NORMAL        |                      |
|               |            | 14 / 07:00                    | N/EUTH        | ++                   |
|               |            | 0 / 09:14                     | DOSED         | ++                   |
|               |            | 0 / 10:00                     | DISORIENT     | MODERATE             |
|               |            |                               | TREMORS       | SLIGHT               |
|               |            | 0 / 11:15                     | DISORIENT     | SLIGHT               |
|               |            |                               | TREMORS       | SLIGHT               |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN        | SEVERITY OR LOCATION |
|---------------|------------|-------------------------------|----------------------|----------------------|
| 88F00279      | M/HSD      | 0 / 13:15                     | DISORIENT<br>TREMORS | SLIGHT               |
|               |            | 1 / 11:21                     | NORMAL               | SLIGHT               |
|               |            | 2 / 09:30                     | NORMAL               |                      |
|               |            | 3 / 10:17                     | NORMAL               |                      |
|               |            | 4 / 14:00                     | NORMAL               |                      |
|               |            | 5 / 11:00                     | NORMAL               |                      |
|               |            | 6 / 10:08                     | NORMAL               |                      |
|               |            | 7 / 10:48                     | NORMAL               |                      |
|               |            | 8 / 13:39                     | INACTIVE             | SLIGHT               |
|               |            | 9 / 15:30                     | NORMAL               |                      |
|               |            | 10 / 13:52                    | NORMAL               |                      |
|               |            | 11 / 09:30                    | NORMAL               |                      |
|               |            | 12 / 08:50                    | NORMAL               |                      |
| 88F00263      | M/HSD      | 13 / 14:38                    | NORMAL               |                      |
|               |            | 14 / 07:00                    | N/EUTH               | ++                   |
|               |            | 0 / 09:14                     | DOSED                | ++                   |
|               |            | 0 / 10:00                     | HUNCHEDE             | MODERATE             |
|               |            | 0 / 11:14                     | HUNCHEDE             | MODERATE             |
|               |            | 0 / 13:15                     | HUNCHEDE             | SLIGHT               |
|               |            | 1 / 11:22                     | NORMAL               |                      |
|               |            | 2 / 09:31                     | NORMAL               |                      |
|               |            | 3 / 10:18                     | NORMAL               |                      |
|               |            | 4 / 14:00                     | NORMAL               |                      |
|               |            | 5 / 11:00                     | NORMAL               |                      |
|               |            | 6 / 10:09                     | NORMAL               |                      |
|               |            | 7 / 10:46                     | NORMAL               |                      |
| 88F00273      | M/D70      | 8 / 13:40                     | NORMAL               |                      |
|               |            | 9 / 15:30                     | NORMAL               |                      |
|               |            | 10 / 13:50                    | NORMAL               |                      |
|               |            | 11 / 09:30                    | NORMAL               |                      |
|               |            | 12 / 08:50                    | NORMAL               |                      |
|               |            | 13 / 14:36                    | NORMAL               |                      |
|               |            | 14 / 07:00                    | N/EUTH               | ++                   |
|               |            | 0 / 11:14                     | DOSED                | ++                   |
|               |            | 0 / 12:15                     | INC RESP RATE        | SLIGHT               |
|               |            | 0 / 13:17                     | INC RESP RATE        | SLIGHT               |
|               |            | 0 / 16:06                     | NORMAL               |                      |
|               |            | 1 / 11:03                     | NORMAL               |                      |
|               |            | 2 / 09:34                     | NORMAL               |                      |
|               |            | 3 / 07:00                     | N/EUTH               | ++                   |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN | SEVERITY OR LOCATION |
|---------------|------------|-------------------------------|---------------|----------------------|
| 88F00294      | M/D70      | 0 / 11:06                     | DOSED         | ++                   |
|               |            | 0 / 12:10                     | NORMAL        |                      |
|               |            | 0 / 13:06                     | NORMAL        |                      |
|               |            | 0 / 16:03                     | NORMAL        |                      |
|               |            | 1 / 11:28                     | NORMAL        |                      |
|               |            | 2 / 09:32                     | NORMAL        |                      |
|               |            | 3 / 07:00                     | N/EUTH        | ++                   |
| 88F00265      | M/D70      | 0 / 11:12                     | DOSED         | ++                   |
|               |            | 0 / 12:12                     | NORMAL        |                      |
|               |            | 0 / 13:10                     | NORMAL        |                      |
|               |            | 0 / 16:06                     | NORMAL        |                      |
|               |            | 1 / 11:29                     | NORMAL        |                      |
|               |            | 2 / 09:33                     | NORMAL        |                      |
|               |            | 3 / 07:00                     | N/EUTH        | ++                   |
| 88F00266      | M/D70      | 0 / 11:26                     | DOSED         | ++                   |
|               |            | 0 / 12:25                     | NORMAL        |                      |
|               |            | 0 / 13:29                     | NORMAL        |                      |
|               |            | 0 / 16:07                     | NORMAL        |                      |
|               |            | 1 / 11:31                     | NORMAL        |                      |
|               |            | 2 / 12:40                     | NORMAL        |                      |
|               |            | 3 / 07:00                     | N/EUTH        | ++                   |
| 88F00267      | M/D70      | 0 / 11:26                     | DOSED         | ++                   |
|               |            | 0 / 12:26                     | NORMAL        |                      |
|               |            | 0 / 13:29                     | NORMAL        |                      |
|               |            | 0 / 16:08                     | NORMAL        |                      |
|               |            | 1 / 11:31                     | NORMAL        |                      |
|               |            | 2 / 09:35                     | NORMAL        |                      |
|               |            | 3 / 07:00                     | N/EUTH        | ++                   |
| 88F00300      | M/D70      | 0 / 11:33                     | DOSED         | ++                   |
|               |            | 0 / 12:30                     | NORMAL        |                      |
|               |            | 0 / 13:32                     | NORMAL        |                      |
|               |            | 0 / 16:08                     | NORMAL        |                      |
|               |            | 1 / 11:10                     | NORMAL        |                      |
|               |            | 2 / 09:51                     | NORMAL        |                      |
|               |            | 3 / 10:32                     | NORMAL        |                      |
|               |            | 4 / 14:00                     | NORMAL        |                      |
|               |            | 5 / 11:00                     | NORMAL        |                      |
|               |            | 6 / 10:14                     | NORMAL        |                      |
|               |            | 7 / 10:53                     | INACTIVE      | SLIGHT               |
|               |            | 8 / 13:46                     | INACTIVE      | SLIGHT               |
|               |            | 9 / 15:30                     | INACTIVE      | SLIGHT               |
|               |            | 10 / 14:00                    | NORMAL        |                      |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN   | CLINICAL SIGN   | SEVERITY OR LOCATION |
|---------------|------------|---|---|----------------------|
| 88F00300      | M/D70      | 11 / 09:30<br>12 / 08:50<br>13 / 14:42<br>14 / 07:00  | NORMAL<br>NORMAL<br>NORMAL<br>N/EUTH  | ++                   |
| 88F00259      | M/D70      | 0 / 11:34<br>0 / 12:30<br>0 / 13:33<br>0 / 14:09<br>1 / 11:31<br>2 / 09:35<br>3 / 10:20<br>4 / 14:00<br>5 / 11:00<br>6 / 10:03<br>7 / 10:47<br>8 / 13:40<br>9 / 15:30<br>10 / 13:50<br>11 / 09:30<br>12 / 08:50<br>13 / 14:36<br>14 / 07:00 | DOSED<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>N/EUTH | ++<br>++             |
| 88F00292      | M/D70      | 0 / 11:41<br>0 / 12:39<br>0 / 13:44<br>0 / 16:10<br>1 / 11:32<br>2 / 09:36<br>3 / 10:21<br>4 / 14:00<br>5 / 11:00<br>6 / 10:03<br>7 / 10:47<br>8 / 13:42<br>9 / 15:30<br>10 / 13:56<br>11 / 09:30<br>12 / 08:50<br>13 / 14:40<br>14 / 07:00 | DOSED<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>N/EUTH | ++<br>++             |
| 88F00286      | M/D70      | 0 / 11:45<br>0 / 12:45  | DOSED<br>NORMAL   | ++<br>++             |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN | SEVERITY OR LOCATION |
|---------------|------------|-------------------------------|---------------|----------------------|
| 88F00286      | M/D70      | 0 / 13:45                     | NORMAL        |                      |
|               |            | 0 / 16:11                     | NORMAL        |                      |
|               |            | 1 / 11:32                     | NORMAL        |                      |
|               |            | 2 / 09:37                     | NORMAL        |                      |
|               |            | 3 / 10:27                     | NORMAL        |                      |
|               |            | 4 / 14:00                     | NORMAL        |                      |
|               |            | 5 / 11:00                     | NORMAL        |                      |
|               |            | 6 / 10:02                     | NORMAL        |                      |
|               |            | 7 / 10:47                     | NORMAL        |                      |
|               |            | 8 / 13:41                     | NORMAL        |                      |
|               |            | 9 / 15:30                     | NORMAL        |                      |
|               |            | 10 / 13:54                    | NORMAL        |                      |
|               |            | 11 / 09:30                    | NORMAL        |                      |
| 88F00276      | M/D70      | 12 / 08:50                    | NORMAL        |                      |
|               |            | 13 / 14:39                    | NORMAL        |                      |
|               |            | 14 / 07:00                    | N/EUTH        | ++                   |
|               |            | 0 / 11:49                     | DOSED         | ++                   |
|               |            | 0 / 12:47                     | INC RESP RATE | MODERATE             |
|               |            | 0 / 13:48                     | INC RESP RATE | SLIGHT               |
|               |            | 0 / 16:11                     | NORMAL        |                      |
|               |            | 1 / 11:35                     | NORMAL        |                      |
|               |            | 2 / 09:37                     | NORMAL        |                      |
|               |            | 3 / 10:23                     | INACTIVE      | SLIGHT               |
|               |            | 4 / 14:00                     | NORMAL        |                      |
|               |            | 5 / 11:00                     | NORMAL        |                      |
|               |            | 6 / 10:01                     | NORMAL        |                      |
| 88F00261      | M/RL       | 7 / 10:49                     | NORMAL        |                      |
|               |            | 8 / 13:41                     | NORMAL        |                      |
|               |            | 9 / 15:30                     | NORMAL        |                      |
|               |            | 10 / 13:52                    | NORMAL        |                      |
|               |            | 11 / 09:30                    | NORMAL        |                      |
|               |            | 12 / 08:50                    | NORMAL        |                      |
|               |            | 13 / 14:32                    | NORMAL        |                      |
|               |            | 14 / 07:00                    | N/EUTH        | ++                   |
|               |            | 0 / 11:54                     | DOSED         | ++                   |
|               |            | 0 / 12:55                     | NORMAL        |                      |
|               |            | 0 / 13:55                     | NORMAL        |                      |
|               |            | 0 / 16:30                     | NORMAL        |                      |
|               |            | 1 / 11:09                     | NORMAL        |                      |
|               |            | 2 / 09:42                     | NORMAL        |                      |
|               |            | 3 / 07:00                     | N/EUTH        | ++                   |

## Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN | SEVERITY OR LOCATION |
|---------------|------------|-------------------------------|---------------|----------------------|
| 88F00296      | M/RL       | 0 / 12:02                     | DOSED         | ++                   |
|               |            | 0 / 13:01                     | NORMAL        |                      |
|               |            | 0 / 14:01                     | NORMAL        |                      |
|               |            | 0 / 16:31                     | NORMAL        |                      |
|               |            | 1 / 11:10                     | NORMAL        |                      |
|               |            | 2 / 09:48                     | NORMAL        |                      |
|               |            | 3 / 07:00                     | N/EUTH        |                      |
|               |            | 0 / 12:05                     | DOSED         |                      |
|               |            | 0 / 12:59                     | NORMAL        |                      |
|               |            | 0 / 14:05                     | NORMAL        |                      |
| 88F00277      | M/RL       | 0 / 16:35                     | NORMAL        | ++                   |
|               |            | 1 / 11:10                     | NORMAL        |                      |
|               |            | 2 / 09:20                     | NORMAL        |                      |
|               |            | 3 / 07:00                     | N/EUTH        |                      |
|               |            | 0 / 12:10                     | DOSED         |                      |
|               |            | 0 / 13:09                     | NORMAL        |                      |
|               |            | 0 / 14:14                     | NORMAL        |                      |
|               |            | 0 / 16:34                     | NORMAL        |                      |
|               |            | 1 / 11:11                     | NORMAL        |                      |
|               |            | 2 / 09:43                     | NORMAL        |                      |
| 88F00287      | M/RL       | 3 / 07:00                     | N/EUTH        | ++                   |
|               |            | 0 / 12:14                     | DOSED         |                      |
|               |            | 0 / 13:14                     | NORMAL        |                      |
|               |            | 0 / 14:14                     | NORMAL        |                      |
|               |            | 0 / 16:36                     | NORMAL        |                      |
|               |            | 1 / 11:12                     | NORMAL        |                      |
|               |            | 2 / 09:43                     | NORMAL        |                      |
|               |            | 3 / 07:00                     | N/EUTH        |                      |
|               |            | 0 / 12:19                     | DOSED         |                      |
|               |            | 0 / 13:19                     | NORMAL        |                      |
| 88F00281      | M/RL       | 0 / 14:18                     | NORMAL        | ++                   |
|               |            | 0 / 16:32                     | NORMAL        |                      |
|               |            | 1 / 11:10                     | NORMAL        |                      |
|               |            | 2 / 09:48                     | NORMAL        |                      |
|               |            | 3 / 10:32                     | NORMAL        |                      |
|               |            | 4 / 14:00                     | NORMAL        |                      |
|               |            | 5 / 11:00                     | NORMAL        |                      |
|               |            | 6 / 10:18                     | INACTIVE      | SLIGHT               |
|               |            | 7 / 10:55                     | INACTIVE      |                      |
|               |            | 8 / 13:47                     | INACTIVE      |                      |
|               |            | 9 / 15:30                     | INACTIVE      |                      |
| 88F00302      | M/RL       | 10 / 14:01                    | INACTIVE      | SLIGHT               |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN | SEVERITY OR LOCATION |
|---------------|------------|-------------------------------|---------------|----------------------|
| 88F00302      | M/RL       | 11 / 09:30                    | INACTIVE      | SLIGHT               |
|               |            | 12 / 08:50                    | INACTIVE      | SLIGHT               |
|               |            | 13 / 14:42                    | INACTIVE      | SLIGHT               |
|               |            | 14 / 07:00                    | INACTIVE      | SLIGHT               |
|               |            |                               | EUTHAN        | ++                   |
| 88F00283      | M/RL       | 0 / 12:20                     | DOSED         | ++                   |
|               |            | 0 / 13:21                     | NORMAL        |                      |
|               |            | 0 / 14:19                     | NORMAL        |                      |
|               |            | 0 / 14:36                     | NORMAL        |                      |
|               |            | 1 / 11:13                     | NORMAL        |                      |
|               |            | 2 / 09:44                     | NORMAL        |                      |
|               |            | 3 / 10:25                     | NORMAL        |                      |
|               |            | 4 / 14:00                     | NORMAL        |                      |
|               |            | 5 / 11:00                     | NORMAL        |                      |
|               |            | 6 / 10:11                     | NORMAL        |                      |
|               |            | 7 / 10:51                     | NORMAL        |                      |
|               |            | 8 / 13:43                     | NORMAL        |                      |
|               |            | 9 / 15:30                     | NORMAL        |                      |
|               |            | 10 / 13:54                    | NORMAL        |                      |
|               |            | 11 / 09:30                    | NORMAL        |                      |
|               |            | 12 / 08:50                    | NORMAL        |                      |
|               |            | 13 / 14:38                    | NORMAL        |                      |
|               |            | 14 / 07:00                    | N/EUTH        | ++                   |
| 88F00284      | M/RL       | 0 / 12:25                     | DOSED         | ++                   |
|               |            | 0 / 13:24                     | NORMAL        |                      |
|               |            | 0 / 14:24                     | NORMAL        |                      |
|               |            | 0 / 14:37                     | NORMAL        |                      |
|               |            | 1 / 11:13                     | NORMAL        |                      |
|               |            | 2 / 09:44                     | NORMAL        |                      |
|               |            | 3 / 10:26                     | NORMAL        |                      |
|               |            | 4 / 14:00                     | NORMAL        |                      |
|               |            | 5 / 11:00                     | NORMAL        |                      |
|               |            | 6 / 10:11                     | NORMAL        |                      |
|               |            | 7 / 10:51                     | NORMAL        |                      |
|               |            | 8 / 13:43                     | NORMAL        |                      |
|               |            | 9 / 15:30                     | NORMAL        |                      |
|               |            | 10 / 13:53                    | INACTIVE      | SLIGHT               |
|               |            | 11 / 09:30                    | NORMAL        |                      |
|               |            | 12 / 08:50                    | INACTIVE      | SLIGHT               |
|               |            | 13 / 14:39                    | INACTIVE      | SLIGHT               |
|               |            | 14 / 07:00                    | INACTIVE      | SLIGHT               |
|               |            |                               | EUTHAN        | ++                   |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN | SEVERITY OR LOCATION |
|---------------|------------|-------------------------------|---------------|----------------------|
| 88F00268      | M/RL       | 0 / 12:29                     | DOSED         | ++                   |
|               |            | 0 / 13:29                     | NORMAL        |                      |
|               |            | 0 / 14:29                     | NORMAL        |                      |
|               |            | 0 / 16:28                     | NORMAL        |                      |
|               |            | 1 / 11:07                     | NORMAL        |                      |
|               |            | 2 / 09:40                     | NORMAL        |                      |
|               |            | 3 / 10:23                     | NORMAL        |                      |
|               |            | 4 / 14:00                     | NORMAL        |                      |
|               |            | 5 / 11:00                     | NORMAL        |                      |
|               |            | 6 / 10:09                     | NORMAL        |                      |
|               |            | 7 / 10:49                     | NORMAL        |                      |
|               |            | 8 / 13:44                     | NORMAL        |                      |
|               |            | 9 / 15:30                     | NORMAL        |                      |
|               |            | 10 / 13:51                    | INACTIVE      | SLIGHT               |
| 88F00269      | M/RL       | 11 / 09:30                    | NORMAL        |                      |
|               |            | 12 / 08:50                    | INACTIVE      | SLIGHT               |
|               |            | 13 / 14:36                    | NORMAL        |                      |
|               |            | 14 / 07:00                    | N/EUTH        | ++                   |
|               |            | 0 / 12:32                     | DOSED         | ++                   |
|               |            | 0 / 13:32                     | NORMAL        |                      |
|               |            | 0 / 14:32                     | NORMAL        |                      |
|               |            | 0 / 16:29                     | NORMAL        |                      |
|               |            | 1 / 11:08                     | NORMAL        |                      |
|               |            | 2 / 09:41                     | NORMAL        |                      |
|               |            | 3 / 10:24                     | NORMAL        |                      |
|               |            | 4 / 14:00                     | NORMAL        |                      |
|               |            | 5 / 11:00                     | NORMAL        |                      |
|               |            | 6 / 10:10                     | NORMAL        |                      |
| 88F00315      | F/HS       | 7 / 10:50                     | NORMAL        |                      |
|               |            | 8 / 13:44                     | NORMAL        |                      |
|               |            | 9 / 15:30                     | NORMAL        |                      |
|               |            | 10 / 13:51                    | NORMAL        |                      |
|               |            | 11 / 09:30                    | NORMAL        |                      |
|               |            | 12 / 08:50                    | NORMAL        |                      |
|               |            | 13 / 14:32                    | NORMAL        |                      |
|               |            | 14 / 07:00                    | N/EUTH        | ++                   |
|               |            | 0 / 08:35                     | DOSED         | ++                   |
|               |            | 0 / 08:38                     | FND DEAD      | ++                   |
|               |            | 0 / 08:40                     | DOSED         | ++                   |
|               |            | 0 / 08:52                     | FND DEAD      | ++                   |
|               |            | 0 / 08:45                     | DOSED         | ++                   |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN                         | SEVERITY OR LOCATION             |
|---------------|------------|-------------------------------|---------------------------------------|----------------------------------|
| 88F00345      | F/HS       | 0 / 09:45                     | INC RESP RATE<br>INACTIVE<br>HUNCHE   | MODERATE<br>MODERATE<br>MODERATE |
|               |            | 0 / 10:45                     | INC RESP RATE<br>INACTIVE<br>HUNCHE   | MODERATE<br>SEVERE<br>MODERATE   |
|               |            | 0 / 12:45                     | INC RESP RATE<br>INACTIVE<br>HUNCHE   | SLIGHT<br>MODERATE<br>MODERATE   |
|               |            | 1 / 13:30                     | INACTIVE                              | SLIGHT                           |
|               |            | 2 / 14:15                     | INACTIVE                              | SLIGHT                           |
|               |            | 3 / 07:33                     | N/EUTH                                | ++                               |
|               |            | 0 / 09:00                     | DOSED                                 | ++                               |
|               |            | 0 / 10:00                     | DISORIENT<br>TREMORS                  | MODERATE<br>MODERATE             |
|               |            | 0 / 11:00                     | INC RESP RATE<br>DISORIENT<br>TREMORS | MODERATE<br>MODERATE<br>MODERATE |
|               |            | 0 / 13:00                     | INC RESP RATE<br>HUNCHE               | MODERATE<br>SLIGHT               |
| 88F00348      | F/HS       | 1 / 13:30                     | NORMAL                                |                                  |
|               |            | 2 / 14:15                     | NORMAL                                |                                  |
|               |            | 3 / 07:39                     | DRYBLOOD                              | MODERATE EAR                     |
|               |            |                               | EUTHAN                                | ++                               |
|               |            | 0 / 09:08                     | DOSED                                 | ++                               |
|               |            | 0 / 09:12                     | FND DEAD                              | ++                               |
|               |            | 0 / 09:12                     | DOSED                                 | ++                               |
|               |            | 0 / 10:12                     | INC RESP RATE<br>INACTIVE             | SEVERE<br>SEVERE                 |
|               |            |                               | HUNCHE                                | MODERATE                         |
|               |            |                               | DISORIENT                             | MODERATE                         |
| 88F00332      | F/HS       |                               | TREMORS                               | MODERATE                         |
|               |            | 0 / 11:12                     | INC RESP RATE<br>INACTIVE             | SEVERE<br>SEVERE                 |
|               |            |                               | HUNCHE                                | MODERATE                         |
|               |            |                               | TREMORS                               | SLIGHT                           |
|               |            | 0 / 11:45                     | INC RESP RATE<br>INACTIVE             | MODERATE<br>MODERATE             |
|               |            |                               | HUNCHE                                | MODERATE                         |
|               |            | 1 / 13:30                     | INACTIVE                              | SLIGHT                           |
|               |            |                               |                                       |                                  |
|               |            |                               |                                       |                                  |
|               |            |                               |                                       |                                  |
| 88F00310      | F/HS       |                               |                                       |                                  |
|               |            |                               |                                       |                                  |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/GROUP | STUDY DAY/TIME DATA WAS TAKEN   | CLINICAL SIGN  | SEVERITY OR LOCATION   |
|---------------|-----------|---|--|--|
| 88F00310      | F/HS      | 2 / 14:15<br>3 / 06:52  | INACTIVE<br>INACTIVE<br>DRYBLOOD<br>EUTHAN   | SLIGHT<br>SLIGHT<br>MODERATE RT EAR<br>++  |
| 88F00331      | F/HS      | 0 / 09:23<br>0 / 10:23<br>0 / 11:21<br>0 / 13:22<br>1 / 13:30<br>2 / 14:15<br>3 / 13:31<br>4 / 09:30<br>5 / 09:06<br>6 / 14:52<br>7 / 15:30<br>8 / 09:57<br>9 / 14:00<br>10 / 14:00<br>11 / 10:30<br>12 / 09:30<br>13 / 14:30<br>14 / 07:00 | DOSED<br>HUNCCHED<br>INC RESP RATE<br>AGGRESIVE<br>HUNCCHED<br>INC RESP RATE<br>AGGRESIVE<br>HUNCCHED<br>INC RESP RATE<br>AGGRESIVE<br>AGGRESIVE<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>NORMAL<br>N/EUTH | MODERATE<br>MODERATE<br>MODERATE<br>MODERATE<br>MODERATE<br>MODERATE<br>MODERATE<br>SLIGHT<br>MODERATE<br>MODERATE<br>SLIGHT<br>SLIGHT<br>SLIGHT<br>SLIGHT<br>SLIGHT<br>++ |
| 88F00327      | F/HS      | 0 / 09:24<br>0 / 10:24<br>0 / 11:23<br>0 / 13:23<br>1 / 13:30<br>2 / 14:15  | DOSED<br>INC RESP RATE<br>DISORIENT<br>TREMORS<br>HUNCCHED<br>INC RESP RATE<br>DISORIENT<br>HUNCCHED<br>INC RESP RATE<br>HUNCCHED<br>NORMAL<br>INACTIVE  | MODERATE<br>MODERATE<br>MODERATE<br>MODERATE<br>MODERATE<br>MODERATE<br>MODERATE<br>SLIGHT<br>SLIGHT<br>SLIGHT   |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN | SEVERITY OR LOCATION |
|---------------|------------|-------------------------------|---------------|----------------------|
| 88F00327      | F/HS       | 3 / 13:29                     | NORMAL        |                      |
|               |            | 4 / 09:30                     | NORMAL        |                      |
|               |            | 5 / 09:05                     | INACTIVE      | SLIGHT               |
|               |            | 6 / 14:51                     | INACTIVE      | SLIGHT               |
|               |            | 7 / 15:30                     | NORMAL        |                      |
|               |            | 8 / 09:56                     | NORMAL        |                      |
|               |            | 9 / 14:00                     | NORMAL        |                      |
|               |            | 10 / 14:00                    | NORMAL        |                      |
|               |            | 11 / 10:30                    | NORMAL        |                      |
|               |            | 12 / 09:30                    | NORMAL        |                      |
|               |            | 13 / 14:58                    | NORMAL        |                      |
|               |            | 14 / 07:00                    | N/EUTH        | ++                   |
|               |            | 0 / 09:31                     | DOSED         | ++                   |
| 88F00341      | F/HS       | 0 / 10:31                     | INC RESP RATE | SEVERE               |
|               |            |                               | INACTIVE      | SEVERE               |
|               |            | 0 / 11:31                     | INC RESP RATE | MODERATE             |
|               |            |                               | INACTIVE      | MODERATE             |
|               |            |                               | HUNCHE        | MODERATE             |
|               |            | 0 / 13:31                     | HUNCHE        | SLIGHT               |
|               |            |                               | DISORIENT     | MODERATE             |
|               |            | 1 / 13:30                     | NORMAL        |                      |
|               |            | 2 / 14:15                     | NORMAL        |                      |
|               |            | 3 / 13:35                     | NORMAL        |                      |
|               |            | 4 / 09:30                     | NORMAL        |                      |
|               |            | 5 / 09:05                     | NORMAL        |                      |
| 88F00305      | F/HS       | 6 / 14:54                     | NORMAL        |                      |
|               |            | 7 / 15:30                     | NORMAL        |                      |
|               |            | 8 / 10:02                     | NORMAL        |                      |
|               |            | 9 / 14:00                     | NORMAL        |                      |
|               |            | 10 / 14:00                    | NORMAL        |                      |
|               |            | 11 / 10:30                    | NORMAL        |                      |
|               |            | 12 / 09:30                    | NORMAL        |                      |
|               |            | 13 / 15:06                    | NORMAL        |                      |
|               |            | 14 / 07:00                    | N/EUTH        | ++                   |
|               |            | 0 / 09:31                     | DOSED         | ++                   |
|               |            | 0 / 10:30                     | HUNCHE        | MODERATE             |
|               |            |                               | INACTIVE      | SEVERE               |
|               |            | 0 / 11:30                     | INC RESP RATE | SEVERE               |
|               |            |                               | HUNCHE        | MODERATE             |
|               |            |                               | INACTIVE      | SLIGHT               |

## Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN   | SEVERITY OR LOCATION                                 |
|---------------|------------|-------------------------------|---|--|
| 88F00305      | F/HS       | 0 / 11:30                     | INC RESP RATE<br>DISORIENT<br>TREMORS<br>HUNCCHED<br>INACTIVE | SEVERE<br>MODERATE<br>MODERATE<br>MODERATE<br>SLIGHT |
|               |            | 0 / 13:31                     | INACTIVE  | SLIGHT   |
|               |            | 1 / 13:30                     | NORMAL  |  |
|               |            | 2 / 14:15                     | NORMAL  |  |
|               |            | 3 / 13:23                     | NORMAL  |  |
|               |            | 4 / 09:30                     | NORMAL  |  |
|               |            | 5 / 09:05                     | NORMAL  |  |
|               |            | 6 / 14:46                     | NORMAL  |  |
|               |            | 7 / 15:30                     | NORMAL  |  |
|               |            | 8 / 09:49                     | NORMAL  |  |
|               |            | 9 / 14:00                     | NORMAL  |  |
|               |            | 10 / 14:00                    | NORMAL  |  |
|               |            | 11 / 10:30                    | NORMAL  |  |
|               |            | 12 / 09:30                    | NORMAL  |  |
|               |            | 13 / 14:52                    | NORMAL  |  |
|               |            | 14 / 07:00                    | N/EUTH  | ++   |
| 88F00313      | F/HSD      | 0 / 09:38                     | DOSED   | ++   |
|               |            | 0 / 10:30                     | DISORIENT<br>INACTIVE   | MODERATE<br>SEVERE                                   |
|               |            | 0 / 11:38                     | INC RESP RATE<br>INACTIVE                                     | MODERATE<br>MODERATE                                 |
|               |            | 0 / 13:38                     | INC RESP RATE<br>HUNCCHED<br>INACTIVE                         | MODERATE<br>MODERATE<br>SLIGHT                       |
|               |            | 0 / 13:38                     | INC RESP RATE<br>HUNCCHED                                     | SLIGHT<br>MODERATE                                   |
|               |            | 1 / 13:30                     | NORMAL  |  |
|               |            | 2 / 14:15                     | NORMAL  |  |
|               |            | 3 / 06:53                     | N/EUTH  | ++   |
|               |            | 0 / 09:41                     | DOSED   | ++   |
|               |            | 0 / 10:40                     | INC RESP RATE<br>DISORIENT<br>HUNCCHED                        | MODERATE<br>SLIGHT<br>MODERATE                       |
| 88F00308      | F/HSD      | 0 / 11:40                     | INC RESP RATE<br>DISORIENT<br>HUNCCHED<br>INACTIVE            | MODERATE<br>MODERATE<br>MODERATE<br>MODERATE         |
|               |            | 0 / 13:40                     | INC RESP RATE<br>HUNCCHED                                     | SLIGHT<br>MODERATE                                   |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN                 | SEVERITY OR LOCATION |
|---------------|-----------|-------------------------------|-------------------------------|----------------------|
| 88F00308      | F/HSD     | 0 / 13:40                     | INACTIVE                      | MODERATE             |
|               |           |                               | AGGRESIVE                     | SLIGHT               |
|               |           | 1 / 13:30                     | NORMAL                        |                      |
|               |           | 2 / 14:15                     | NORMAL                        |                      |
|               |           | 3 / 06:45                     | N/EUTH                        | ++                   |
|               |           | 0 / 09:50                     | DOSED                         | ++                   |
|               |           | 0 / 10:50                     | TREMORS                       | MODERATE             |
|               |           |                               | HUNCCHED                      | MODERATE             |
|               |           | 0 / 11:50                     | INC RESP RATE                 | MODERATE             |
|               |           |                               | HUNCCHED                      | MODERATE             |
| 88F00335      | F/HSD     | 0 / 11:50                     | INC RESP RATE                 | SLIGHT               |
|               |           |                               | DISORIENT                     | SLIGHT               |
|               |           | 0 / 13:50                     | HUNCCHED                      | SLIGHT               |
|               |           |                               | DISORIENT                     | SLIGHT               |
|               |           | 1 / 13:30                     | NORMAL                        |                      |
|               |           | 2 / 14:15                     | NORMAL                        |                      |
|               |           | 3 / 07:23                     | N/EUTH                        | ++                   |
|               |           | 0 / 09:51                     | DOSED                         | ++                   |
|               |           | 0 / 10:51                     | DISORIENT                     | MODERATE             |
|               |           |                               | TREMORS                       | MODERATE             |
| 88F00337      | F/HSD     |                               | INC RESP RATE                 | MODERATE             |
|               |           | 0 / 11:51                     | HUNCCHED                      | MODERATE             |
|               |           |                               | INC RESP RATE                 | MODERATE             |
|               |           | 0 / 11:51                     | HUNCCHED                      | MODERATE             |
|               |           |                               | INACTIVE                      | MODERATE             |
|               |           | 0 / 13:51                     | INC RESP RATE                 | SLIGHT               |
|               |           |                               | HUNCCHED                      | MODERATE             |
|               |           | 0 / 13:51                     | INACTIVE                      | SLIGHT               |
|               |           | 1 / 13:30                     | NORMAL                        |                      |
|               |           | 2 / 14:15                     | NORMAL                        |                      |
| 88F00349      | F/HSD     | 3 / 07:28                     | DISCOLOR SLIGHT LEFT EAR DARK |                      |
|               |           | EUTHAN                        |                               | ++                   |
|               |           | 0 / 09:58                     | DOSED                         | ++                   |
|               |           | 0 / 10:57                     | HUNCCHED                      | MODERATE             |
|               |           |                               | INC RESP RATE                 | MODERATE             |
|               |           | 0 / 11:55                     | INACTIVE                      | MODERATE             |
|               |           |                               | HUNCCHED                      | MODERATE             |
|               |           | 0 / 11:55                     | INC RESP RATE                 | MODERATE             |
|               |           |                               | INACTIVE                      | MODERATE             |
|               |           | 0 / 13:58                     | HUNCCHED                      | MODERATE             |
|               |           |                               | INC RESP RATE                 | MODERATE             |
|               |           |                               | INACTIVE                      | MODERATE             |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN | SEVERITY OR LOCATION |
|---------------|------------|-------------------------------|---------------|----------------------|
| 88F00349      | F/HSD      | 0 / 13:58                     | BRUISE        | SEVERE               |
|               |            | 1 / 13:30                     | INACTIVE      | SLIGHT               |
|               |            | 2 / 14:15                     | NORMAL        |                      |
|               |            | 3 / 07:48                     | N/EUTH        | ++                   |
| 88F00334      | F/HSD      | 0 / 10:05                     | DOSED         | ++                   |
|               |            | 0 / 11:05                     | INC RESP RATE | SEVERE               |
|               |            |                               | DIARRHEA      | MODERATE             |
|               |            |                               | INACTIVE      | MODERATE             |
|               |            | 0 / 12:05                     | DIARRHEA      | MODERATE             |
|               |            |                               | INACTIVE      | MODERATE             |
|               |            |                               | HUNCCHED      | MODERATE             |
|               |            | 0 / 14:05                     | DIARRHEA      | MODERATE             |
|               |            |                               | HUNCCHED      | MODERATE             |
|               |            |                               | DISORIENT     | MODERATE             |
|               |            | 1 / 13:30                     | INACTIVE      | SLIGHT               |
|               |            | 2 / 14:15                     | INACTIVE      | SLIGHT               |
|               |            | 3 / 13:32                     | INACTIVE      | SLIGHT               |
|               |            | 4 / 09:30                     | NORMAL        |                      |
|               |            | 5 / 09:05                     | NORMAL        |                      |
|               |            | 6 / 14:53                     | NORMAL        |                      |
|               |            | 7 / 15:30                     | NORMAL        |                      |
|               |            | 8 / 10:00                     | NORMAL        |                      |
|               |            | 9 / 14:00                     | NORMAL        |                      |
|               |            | 10 / 14:00                    | NORMAL        |                      |
|               |            | 11 / 10:30                    | NORMAL        |                      |
|               |            | 12 / 09:30                    | NORMAL        |                      |
|               |            | 13 / 14:59                    | NORMAL        |                      |
|               |            | 14 / 07:00                    | N/EUTH        | ++                   |
| 88F00322      | F/HSD      | 0 / 10:07                     | DOSED         | ++                   |
|               |            | 0 / 11:06                     | INC RESP RATE | MODERATE             |
|               |            |                               | INACTIVE      | MODERATE             |
|               |            | 0 / 12:05                     | INC RESP RATE | SLIGHT               |
|               |            |                               | INACTIVE      | SLIGHT               |
|               |            |                               | HUNCCHED      | SLIGHT               |
|               |            | 0 / 14:06                     | INACTIVE      | MODERATE             |
|               |            |                               | HUNCCHED      | SLIGHT               |
|               |            | 1 / 13:30                     | NORMAL        |                      |
|               |            | 2 / 14:15                     | NORMAL        |                      |
|               |            | 3 / 13:28                     | BRUISE        | MODERATE             |
|               |            | 4 / 09:30                     | BRUISE        | SLIGHT               |
|               |            | 5 / 09:05                     | BRUISE        | SLIGHT               |
|               |            | 6 / 14:50                     | BRUISE        | SLIGHT               |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN   | CLINICAL SIGN   | SEVERITY OR LOCATION   |
|---------------|------------|---|---|--|
| 88F00322      | F/HSD      | 7 / 15:30<br>8 / 09:55<br>9 / 14:00<br>10 / 14:00<br>11 / 10:30<br>12 / 09:30<br>13 / 14:56<br>14 / 07:00 | BRUISE<br>BRUISE<br>NECROSIS<br>NECROSIS<br>NECROSIS<br>NECROSIS<br>NECROSIS<br>NECROSIS<br>EUTHAN  | SLIGHT LEFT EAR<br>SLIGHT LEFT EAR<br>++ |
| 88F00353      | F/HSD      | 0 / 10:14<br>0 / 11:14<br>0 / 12:14<br>0 / 14:17  | HUNCHEDE<br>INC RESP RATE<br>HUNCHEDE<br>INC RESP RATE<br>HUNCHEDE<br>INC RESP RATE<br>HUNCHEDE<br>INC RESP RATE<br>1 / 13:30<br>2 / 14:15<br>3 / 13:37<br>4 / 09:30<br>5 / 09:05<br>6 / 14:56<br>7 / 15:30<br>8 / 10:04<br>9 / 14:00<br>10 / 14:00<br>11 / 10:30<br>12 / 09:30<br>13 / 15:08<br>14 / 07:00 | MODERATE<br>MODERATE<br>MODERATE<br>MODERATE<br>SLIGHT<br>MODERATE<br>MODERATE<br>SLIGHT LEFT EAR  |
| 88F00333      | F/HSD      | 0 / 10:15<br>0 / 11:15<br>0 / 12:15<br>0 / 14:14<br>1 / 13:30   | DOSED<br>INC RESP RATE<br>HUNCHEDE<br>INACTIVE<br>INC RESP RATE<br>HUNCHEDE<br>INC RESP RATE<br>HUNCHEDE<br>BRUISE<br>DISORIENT<br>INACTIVE   | ++<br>MODERATE<br>MODERATE<br>SLIGHT<br>MODERATE<br>MODERATE<br>SLIGHT<br>MODERATE LEFT EAR<br>SLIGHT<br>SLIGHT  |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN | SEVERITY OR LOCATION |
|---------------|------------|-------------------------------|---------------|----------------------|
| 88F00333      | F/HSD      | 2 / 14:15                     | INACTIVE      | SLIGHT               |
|               |            | 3 / 13:32                     | INACTIVE      | SLIGHT               |
|               |            |                               | HUNCCHED      | SLIGHT               |
|               |            | 4 / 09:30                     | BRUISE        | SLIGHT LEFT EAR      |
|               |            | 5 / 09:05                     | BRUISE        | SLIGHT LEFT EAR      |
|               |            | 6 / 14:52                     | BRUISE        | SLIGHT LEFT EAR      |
|               |            | 7 / 15:30                     | BRUISE        | SLIGHT LEFT EAR      |
|               |            | 8 / 09:58                     | BRUISE        | SLIGHT LEFT EAR      |
|               |            | 9 / 14:00                     | NECROSIS      | MODERATE LEFT EAR    |
|               |            |                               | NECROSIS      | SLIGHT RT EAR        |
|               |            | 10 / 14:00                    | NECROSIS      | MODERATE LEFT EAR    |
|               |            | 11 / 10:30                    | NECROSIS      | MODERATE LEFT EAR    |
|               |            | 12 / 09:30                    | NECROSIS      | MODERATE LEFT EAR    |
| 88F00318      | F/HSD      | 13 / 14:58                    | NECROSIS      | MODERATE LEFT EAR    |
|               |            | 14 / 07:00                    | NECROSIS      | MODERATE LEFT EAR    |
|               |            |                               | EUTHAN        | ++                   |
|               |            | 0 / 10:26                     | DOSED         | ++                   |
|               |            | 0 / 11:26                     | DISORIENT     | MODERATE             |
|               |            |                               | HUNCCHED      | MODERATE             |
|               |            | 0 / 12:26                     | INC RESP RATE | MODERATE             |
|               |            |                               | DISORIENT     | MODERATE             |
|               |            |                               | HUNCCHED      | MODERATE             |
|               |            | 0 / 14:26                     | INC RESP RATE | MODERATE             |
|               |            |                               | DISORIENT     | MODERATE             |
|               |            |                               | HUNCCHED      | SLIGHT               |
|               |            | 1 / 13:30                     | NORMAL        |                      |
| 88F00311      | F/D70      | 2 / 14:15                     | NORMAL        |                      |
|               |            | 3 / 13:25                     | NORMAL        |                      |
|               |            | 4 / 09:30                     | NORMAL        |                      |
|               |            | 5 / 09:05                     | NORMAL        |                      |
|               |            | 6 / 14:47                     | NORMAL        |                      |
|               |            | 7 / 15:30                     | NORMAL        |                      |
|               |            | 8 / 09:50                     | NORMAL        |                      |
|               |            | 9 / 14:00                     | NORMAL        |                      |
|               |            | 10 / 14:00                    | NORMAL        |                      |
|               |            | 11 / 10:30                    | NORMAL        |                      |
|               |            | 12 / 09:30                    | NORMAL        |                      |
|               |            | 13 / 14:55                    | NORMAL        |                      |
|               |            | 14 / 07:00                    | N/EUTH        | ++                   |
|               |            | 0 / 10:28                     | DOSED         | ++                   |
|               |            | 0 / 11:17                     | HUNCCHED      | SEVERE               |
|               |            |                               | INC RESP RATE | MODERATE             |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN | SEVERITY OR LOCATION |
|---------------|------------|-------------------------------|---------------|----------------------|
| 88F00311      | F/D70      | 0 / 11:27                     | DISORIENT     | SEVERE               |
|               |            | 0 / 12:27                     | HUNCCHED      | SEVERE               |
|               |            |                               | INC RESP RATE | MODERATE             |
|               |            |                               | DISORIENT     | SEVERE               |
|               |            | 0 / 14:28                     | HUNCCHED      | SLIGHT               |
|               |            |                               | DISORIENT     | SEVERE               |
|               |            | 1 / 13:30                     | NORMAL        |                      |
|               |            | 2 / 14:15                     | NORMAL        |                      |
|               |            | 3 / 06:52                     | N/EUTH        | ++                   |
|               |            | 0 / 10:41                     | DOSED         | ++                   |
| 88F00314      | F/D70      | 0 / 11:41                     | AGGRESIVE     | MODERATE             |
|               |            |                               | INC RESP RATE | MODERATE             |
|               |            |                               | HUNCCHED      | SLIGHT               |
|               |            | 0 / 12:41                     | AGGRESIVE     | MODERATE             |
|               |            |                               | INC RESP RATE | MODERATE             |
|               |            |                               | HUNCCHED      | SLIGHT               |
|               |            | 0 / 14:41                     | HUNCCHED      | SLIGHT               |
|               |            | 1 / 13:30                     | NORMAL        |                      |
|               |            | 2 / 14:15                     | NORMAL        |                      |
|               |            | 3 / 06:55                     | N/EUTH        | ++                   |
| 88F00338      | F/D70      | 0 / 10:42                     | DOSED         | ++                   |
|               |            | 0 / 11:42                     | HUNCCHED      | MODERATE             |
|               |            |                               | DISORIENT     | SLIGHT               |
|               |            | 0 / 12:42                     | HUNCCHED      | MODERATE             |
|               |            | 0 / 14:42                     | HUNCCHED      | SLIGHT               |
|               |            |                               | HYPERACT      | MODERATE             |
|               |            | 1 / 13:30                     | NORMAL        |                      |
|               |            | 2 / 14:15                     | INACTIVE      | SLIGHT               |
|               |            | 3 / 07:28                     | N/EUTH        | ++                   |
|               |            | 0 / 10:58                     | DOSED         | ++                   |
| 88F00344      | F/D70      | 0 / 11:58                     | NORMAL        |                      |
|               |            | 0 / 12:58                     | NORMAL        |                      |
|               |            | 0 / 14:57                     | NORMAL        |                      |
|               |            | 1 / 13:30                     | NORMAL        |                      |
|               |            | 2 / 14:15                     | NORMAL        |                      |
|               |            | 3 / 07:31                     | DISCOLOR      | MODERATE EAR DARK    |
|               |            |                               | EUTHAN        | ++                   |
|               |            | 0 / 10:49                     | DOSED         | ++                   |
|               |            | 0 / 11:49                     | HUNCCHED      | SLIGHT               |
|               |            | 0 / 12:49                     | INC RESP RATE | SLIGHT               |
| 88F00347      | F/D70      |                               | HUNCCHED      | MODERATE             |
|               |            |                               | INC RESP RATE | MODERATE             |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN                          | SEVERITY OR LOCATION           |
|---------------|------------|-------------------------------|--|--------------------------------|
| 88F00347      | F/D70      | 0 / 14:49                     | HUNCCHED<br>INC RESP RATE              | MODERATE<br>SLIGHT             |
|               |            | 1 / 13:30                     | NORMAL                                 |                                |
|               |            | 2 / 14:15                     | NORMAL                                 |                                |
|               |            | 3 / 07:07                     | N/EUTH                                 | ++                             |
| 88F00319      | F/D70      | 0 / 11:09                     | DOSED                                  | ++                             |
|               |            | 0 / 12:09                     | HUNCCHED<br>TREMORS                    | SLIGHT<br>SLIGHT               |
|               |            | 0 / 13:11                     | HUNCCHED                               | SLIGHT                         |
|               |            | 0 / 15:09                     | HUNCCHED                               | SLIGHT                         |
|               |            | 1 / 13:30                     | NORMAL                                 |                                |
|               |            | 2 / 14:15                     | NORMAL                                 |                                |
|               |            | 3 / 13:26                     | NORMAL                                 |                                |
|               |            | 4 / 09:30                     | NORMAL                                 |                                |
|               |            | 5 / 09:05                     | NORMAL                                 |                                |
|               |            | 6 / 14:49                     | NORMAL                                 |                                |
|               |            | 7 / 15:30                     | NORMAL                                 |                                |
|               |            | 8 / 09:54                     | NORMAL                                 |                                |
|               |            | 9 / 14:00                     | NORMAL                                 |                                |
|               |            | 10 / 14:00                    | NORMAL                                 |                                |
|               |            | 11 / 10:30                    | NORMAL                                 |                                |
|               |            | 12 / 09:30                    | NORMAL                                 |                                |
|               |            | 13 / 14:56                    | NORMAL                                 |                                |
|               |            | 14 / 07:00                    | N/EUTH                                 | ++                             |
| 88F00304      | F/D70      | 0 / 11:06                     | DOSED                                  | ++                             |
|               |            | 0 / 12:06                     | HUNCCHED<br>INC RESP RATE              | MODERATE<br>MODERATE           |
|               |            | 0 / 13:06                     | DISORIENT<br>HUNCCHED<br>INC RESP RATE | MODERATE<br>MODERATE<br>SLIGHT |
|               |            | 1 / 13:30                     | DISORIENT<br>NORMAL                    | MODERATE                       |
|               |            | 2 / 14:15                     | NORMAL                                 |                                |
|               |            | 3 / 13:37                     | NORMAL                                 |                                |
|               |            | 4 / 09:30                     | NORMAL                                 |                                |
|               |            | 5 / 09:05                     | NORMAL                                 |                                |
|               |            | 6 / 14:56                     | NORMAL                                 |                                |
|               |            | 7 / 15:30                     | NORMAL                                 |                                |
|               |            | 8 / 10:05                     | NORMAL                                 |                                |
|               |            | 9 / 14:00                     | NORMAL                                 |                                |
|               |            | 10 / 14:00                    | NORMAL                                 |                                |
|               |            | 11 / 10:30                    | NORMAL                                 |                                |

**APPENDIX D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN | SEVERITY OR LOCATION |
|---------------|------------|-------------------------------|---------------|----------------------|
| 88F00304      | F/D70      | 12 / 09:30                    | NORMAL        |                      |
|               |            | 13 / 15:07                    | NORMAL        |                      |
|               |            | 14 / 07:00                    | N/EUTH        | ++                   |
| 88F00326      | F/D70      | 0 / 11:16                     | DOSED         | ++                   |
|               |            | 0 / 12:16                     | HUNCED        | SLIGHT               |
|               |            |                               | INC RESP RATE | SLIGHT               |
|               |            | 0 / 13:14                     | HUNCED        | SLIGHT               |
|               |            |                               | INC RESP RATE | SLIGHT               |
|               |            | 0 / 15:16                     | NORMAL        |                      |
|               |            | 1 / 13:30                     | NORMAL        |                      |
|               |            | 2 / 14:15                     | INACTIVE      | SLIGHT               |
|               |            | 3 / 13:29                     | INACTIVE      | SLIGHT               |
|               |            | 4 / 09:30                     | NORMAL        |                      |
|               |            | 5 / 09:05                     | NORMAL        |                      |
|               |            | 6 / 14:51                     | NORMAL        |                      |
|               |            | 7 / 15:30                     | NORMAL        |                      |
|               |            | 8 / 09:56                     | NORMAL        |                      |
|               |            | 9 / 14:00                     | NORMAL        |                      |
|               |            | 10 / 14:00                    | NORMAL        |                      |
|               |            | 11 / 10:30                    | NORMAL        |                      |
|               |            | 12 / 09:30                    | NORMAL        |                      |
|               |            | 13 / 14:57                    | NORMAL        |                      |
|               |            | 14 / 07:00                    | N/EUTH        | ++                   |
| 88F00312      | F/D70      | 0 / 11:17                     | DOSED         | ++                   |
|               |            | 0 / 12:17                     | HUNCED        | MODERATE             |
|               |            |                               | INC RESP RATE | SLIGHT               |
|               |            | 0 / 13:15                     | HUNCED        | SLIGHT               |
|               |            |                               | INC RESP RATE | SLIGHT               |
|               |            | 0 / 15:17                     | HUNCED        | SLIGHT               |
|               |            |                               | INC RESP RATE | SLIGHT               |
|               |            | 1 / 13:30                     | NORMAL        |                      |
|               |            | 2 / 14:15                     | NORMAL        |                      |
|               |            | 3 / 13:24                     | NORMAL        |                      |
|               |            | 4 / 09:30                     | NORMAL        |                      |
|               |            | 5 / 09:05                     | NORMAL        |                      |
|               |            | 6 / 14:47                     | INACTIVE      | SLIGHT               |
|               |            | 7 / 15:30                     | NORMAL        |                      |
|               |            | 8 / 09:49                     | NORMAL        |                      |
|               |            | 9 / 14:00                     | NORMAL        |                      |
|               |            | 10 / 14:00                    | NORMAL        |                      |
|               |            | 11 / 10:30                    | NORMAL        |                      |
|               |            | 12 / 09:30                    | NORMAL        |                      |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN                 | SEVERITY OR LOCATION |
|---------------|------------|-------------------------------|-------------------------------|----------------------|
| 88F00312      | F/D70      | 13 / 14:54                    | NORMAL                        |                      |
|               |            | 14 / 07:00                    | N/EUTH                        | ++                   |
| 88F00321      | F/D70      | 0 / 11:24                     | DOSED                         | ++                   |
|               |            | 0 / 12:24                     | INC RESP RATE                 | SLIGHT               |
|               |            | 0 / 13:23                     | AGGRESSIVE                    | MODERATE             |
|               |            | 0 / 15:24                     | INC RESP RATE                 | SLIGHT               |
|               |            | 1 / 13:30                     | NORMAL                        |                      |
|               |            | 2 / 14:15                     | NORMAL                        |                      |
|               |            | 3 / 13:27                     | NORMAL                        |                      |
|               |            | 4 / 09:30                     | NORMAL                        |                      |
|               |            | 5 / 09:05                     | NORMAL                        |                      |
|               |            | 6 / 14:49                     | NORMAL                        |                      |
|               |            | 7 / 15:30                     | NORMAL                        |                      |
|               |            | 8 / 09:55                     | NORMAL                        |                      |
|               |            | 9 / 14:00                     | NORMAL                        |                      |
|               |            | 10 / 14:00                    | NORMAL                        |                      |
|               |            | 11 / 10:30                    | NORMAL                        |                      |
|               |            | 12 / 09:30                    | NORMAL                        |                      |
|               |            | 13 / 14:56                    | NORMAL                        |                      |
|               |            | 14 / 07:00                    | N/EUTH                        | ++                   |
| 88F00323      | F/RL       | 0 / 11:24                     | DOSED                         | ++                   |
|               |            | 0 / 11:24                     | DISORIENT                     | MODERATE             |
|               |            | 0 / 13:25                     | DISORIENT                     | MODERATE             |
|               |            | 0 / 15:25                     | NORMAL                        |                      |
|               |            | 1 / 13:30                     | NORMAL                        |                      |
|               |            | 2 / 14:15                     | NORMAL                        |                      |
|               |            | 3 / 06:59                     | N/EUTH                        | ++                   |
| 88F00336      | F/RL       | 0 / 11:31                     | DOSED                         | ++                   |
|               |            | 0 / 12:31                     | HUNCCHED                      | MODERATE             |
|               |            | 0 / 13:30                     | INC RESP RATE                 | MODERATE             |
|               |            | 1 / 13:30                     | HUNCCHED                      | MODERATE             |
|               |            | 2 / 14:14                     | HUNCCHED                      | MODERATE             |
|               |            | 3 / 07:27                     | NORMAL                        |                      |
|               |            |                               | DISCOLOR SLIGHT LEFT EAR DARK |                      |
|               |            |                               | DRY BLOOD SLIGHT LEFT FOOT    |                      |
|               |            |                               | INC START                     | SLIGHT               |
|               |            |                               | EUTHAN                        | ++                   |
| 88F00330      | F/RL       | 0 / 11:37                     | DOSED                         | ++                   |
|               |            | 0 / 12:35                     | HUNCCHED                      | SLIGHT               |
|               |            | 0 / 13:37                     | INC RESP RATE                 | SLIGHT               |
|               |            |                               | HUNCCHED                      | SLIGHT               |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN | SEVERITY OR LOCATION |
|---------------|------------|-------------------------------|---------------|----------------------|
| 88F00330      | F/RL       | 0 / 13:37                     | INC RESP RATE | SLIGHT               |
|               |            | 0 / 15:55                     | NORMAL        |                      |
|               |            | 1 / 13:30                     | NORMAL        |                      |
|               |            | 2 / 14:15                     | NORMAL        |                      |
|               |            | 3 / 07:04                     | N/EUTH        | ++                   |
| 88F00324      | F/RL       | 0 / 11:38                     | DOSED         | ++                   |
|               |            | 0 / 12:36                     | HUNCHED       | SLIGHT               |
|               |            |                               | INC RESP RATE | MODERATE             |
|               |            | 0 / 13:37                     | HUNCHED       | SLIGHT               |
|               |            |                               | INC RESP RATE | MODERATE             |
|               |            | 0 / 15:55                     | NORMAL        |                      |
|               |            | 1 / 13:30                     | NORMAL        |                      |
|               |            | 2 / 14:15                     | NORMAL        |                      |
|               |            | 3 / 07:01                     | N/EUTH        | ++                   |
| 88F00352      | F/RL       | 0 / 11:44                     | DOSED         | ++                   |
|               |            | 0 / 12:44                     | NORMAL        |                      |
|               |            | 0 / 13:44                     | NORMAL        |                      |
|               |            | 0 / 15:55                     | NORMAL        |                      |
|               |            | 1 / 13:30                     | NORMAL        |                      |
|               |            | 2 / 14:15                     | NORMAL        |                      |
|               |            | 3 / 07:43                     | N/EUTH        | ++                   |
| 88F00346      | F/RL       | 0 / 11:45                     | DOSED         | ++                   |
|               |            | 0 / 12:44                     | NORMAL        |                      |
|               |            | 0 / 13:45                     | NORMAL        |                      |
|               |            | 0 / 15:55                     | NORMAL        |                      |
|               |            | 1 / 13:30                     | NORMAL        |                      |
|               |            | 2 / 14:15                     | NORMAL        |                      |
|               |            | 3 / 13:36                     | NORMAL        |                      |
|               |            | 4 / 09:30                     | NORMAL        |                      |
|               |            | 5 / 09:05                     | NORMAL        |                      |
|               |            | 6 / 14:55                     | NORMAL        |                      |
|               |            | 7 / 15:30                     | NORMAL        |                      |
|               |            | 8 / 10:03                     | NORMAL        |                      |
|               |            | 9 / 14:00                     | NORMAL        |                      |
|               |            | 10 / 14:00                    | NORMAL        |                      |
|               |            | 11 / 10:30                    | NORMAL        |                      |
|               |            | 12 / 09:30                    | NORMAL        |                      |
|               |            | 13 / 15:06                    | NORMAL        |                      |
|               |            | 14 / 07:00                    | N/EUTH        | ++                   |
| 88F00351      | F/RL       | 0 / 11:50                     | DOSED         | ++                   |
|               |            | 0 / 12:50                     | NORMAL        |                      |
|               |            | 0 / 13:48                     | NORMAL        |                      |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN | SEVERITY OR LOCATION |
|---------------|------------|-------------------------------|---------------|----------------------|
| 88F00351      | F/RL       | 0 / 15:55                     | NORMAL        |                      |
|               |            | 1 / 13:30                     | NORMAL        |                      |
|               |            | 2 / 14:15                     | NORMAL        |                      |
|               |            | 3 / 13:36                     | NORMAL        |                      |
|               |            | 4 / 09:30                     | NORMAL        |                      |
|               |            | 5 / 09:05                     | NORMAL        |                      |
|               |            | 6 / 14:55                     | NORMAL        |                      |
|               |            | 7 / 15:30                     | NORMAL        |                      |
|               |            | 8 / 10:03                     | NORMAL        |                      |
|               |            | 9 / 14:00                     | NORMAL        |                      |
|               |            | 10 / 14:00                    | NORMAL        |                      |
|               |            | 11 / 10:30                    | NORMAL        |                      |
|               |            | 12 / 09:30                    | NORMAL        |                      |
| 88F00325      | F/RL       | 13 / 15:08                    | NORMAL        |                      |
|               |            | 14 / 07:00                    | N/EUTH        | ++                   |
|               |            | 0 / 11:53                     | DOSED         | ++                   |
|               |            | 0 / 12:51                     | INC RESP RATE | MODERATE             |
|               |            | 0 / 13:52                     | NORMAL        |                      |
|               |            | 0 / 15:55                     | NORMAL        |                      |
|               |            | 1 / 13:30                     | NORMAL        |                      |
|               |            | 2 / 14:15                     | NORMAL        |                      |
|               |            | 3 / 13:28                     | NORMAL        |                      |
|               |            | 4 / 09:30                     | NORMAL        |                      |
|               |            | 5 / 09:05                     | NORMAL        |                      |
|               |            | 6 / 14:50                     | NORMAL        |                      |
|               |            | 7 / 15:30                     | NORMAL        |                      |
| 88F00307      | F/RL       | 8 / 09:56                     | NORMAL        |                      |
|               |            | 9 / 14:00                     | NORMAL        |                      |
|               |            | 10 / 14:00                    | NORMAL        |                      |
|               |            | 11 / 10:30                    | NORMAL        |                      |
|               |            | 12 / 09:30                    | NORMAL        |                      |
|               |            | 13 / 14:57                    | NORMAL        |                      |
|               |            | 14 / 07:00                    | N/EUTH        | ++                   |
|               |            | 0 / 12:00                     | DOSED         | ++                   |
|               |            | 0 / 13:00                     | HUNCCHED      | MODERATE             |
|               |            |                               | INC RESP RATE | MODERATE             |
|               |            | 0 / 15:59                     | HUNCCHED      | SLIGHT               |
|               |            |                               | INC RESP RATE | SLIGHT               |
|               |            | 0 / 15:55                     | INC RESP RATE | SLIGHT               |
|               |            | 1 / 13:30                     | NORMAL        |                      |
|               |            | 2 / 14:15                     | NORMAL        |                      |
|               |            | 3 / 13:23                     | NORMAL        |                      |

**Appendix D (cont.): INDIVIDUAL ANIMAL HISTORIES**

| ANIMAL NUMBER | SEX/ GROUP | STUDY DAY/TIME DATA WAS TAKEN | CLINICAL SIGN | SEVERITY OR LOCATION |
|---------------|------------|-------------------------------|---------------|----------------------|
| 88F00307      | F/RL       | 4 / 09:30                     | NORMAL        |                      |
|               |            | 5 / 09:05                     | NORMAL        |                      |
|               |            | 6 / 14:46                     | NORMAL        |                      |
|               |            | 7 / 15:30                     | NORMAL        |                      |
|               |            | 8 / 09:49                     | NORMAL        |                      |
|               |            | 9 / 14:00                     | NORMAL        |                      |
|               |            | 10 / 14:00                    | NORMAL        |                      |
|               |            | 11 / 10:30                    | NORMAL        |                      |
|               |            | 12 / 09:30                    | NORMAL        |                      |
|               |            | 13 / 14:53                    | NORMAL        |                      |
|               |            | 14 / 07:00                    | N/EUTH        | ++                   |
|               |            | 0 / 12:01                     | DOSED         | ++                   |
|               |            | 0 / 13:01                     | NORMAL        |                      |
| 88F00340      | F/RL       | 0 / 14:00                     | NORMAL        |                      |
|               |            | 0 / 15:55                     | NORMAL        |                      |
|               |            | 1 / 13:30                     | NORMAL        |                      |
|               |            | 2 / 14:15                     | NORMAL        |                      |
|               |            | 3 / 13:35                     | NORMAL        |                      |
|               |            | 4 / 09:30                     | NORMAL        |                      |
|               |            | 5 / 09:05                     | NORMAL        |                      |
|               |            | 6 / 14:54                     | NORMAL        |                      |
|               |            | 7 / 15:30                     | NORMAL        |                      |
|               |            | 8 / 10:00                     | NORMAL        |                      |
|               |            | 9 / 14:00                     | NORMAL        |                      |
|               |            | 10 / 14:00                    | NORMAL        |                      |
|               |            | 11 / 10:30                    | NORMAL        |                      |
|               |            | 12 / 09:30                    | NORMAL        |                      |
|               |            | 13 / 15:05                    | NORMAL        |                      |
|               |            | 14 / 07:00                    | N/EUTH        | ++                   |

**Appendix E: BODY WEIGHTS (kg)**

| Animal    | Day of Study |      |      |      |      |      |      |
|-----------|--------------|------|------|------|------|------|------|
|           | -19          | -13  | -7   | 0    | 3    | 7    | 14   |
| RL Male   |              |      |      |      |      |      |      |
| 88F00261* | 2.95         | 2.98 | 2.92 | 3.33 | 3.35 |      |      |
| 88F00296* | 3.10         | 3.31 | 3.34 | 3.67 | 3.69 |      |      |
| 88F00277* | 3.22         | 3.35 | 3.28 | 3.43 | 3.48 |      |      |
| 88F00287* | 2.81         | 2.90 | 2.99 | 3.09 | 3.19 |      |      |
| 88F00281* | 2.99         | 3.05 | 3.27 | 3.54 | 3.53 |      |      |
| 88F00302  | 2.73         | 2.92 | 3.03 | 3.17 |      | 3.30 | 3.27 |
| 88F00283  | 3.09         | 3.23 | 3.29 | 3.40 |      | 3.40 | 3.56 |
| 88F00284  | 2.47         | 2.73 | 2.81 | 2.98 |      | 3.10 | 3.12 |
| 88F00268  | 2.57         | 2.78 | 2.97 | 3.16 |      | 3.20 | 3.36 |
| 88F00269  | 2.73         | 3.14 | 3.32 | 3.37 |      | 3.37 | 3.48 |
| Mean      | 2.87         | 3.04 | 3.12 | 3.31 | 3.45 | 3.27 | 3.36 |
| Std.Dev   | 0.24         | 0.22 | 0.20 | 0.21 | 0.19 | 0.13 | 0.17 |
| SEM       | 0.08         | 0.07 | 0.06 | 0.07 | 0.08 | 0.06 | 0.08 |

**HSD Male**

|           |      |      |      |      |      |      |      |
|-----------|------|------|------|------|------|------|------|
| 88F00274* | 3.11 | 3.23 | 3.42 | 3.52 | 3.52 |      |      |
| 88F00258* | 2.74 | 3.01 | 3.14 | 3.23 | 3.32 |      |      |
| 88F00285* | 2.74 | 2.93 | 3.03 | 3.15 | 3.19 |      |      |
| 88F00260* | 2.92 | 3.01 | 3.23 | 3.30 | 3.38 |      |      |
| 88F00293* | 3.06 | 3.28 | 3.44 | 3.51 | 3.57 |      |      |
| 88F00295  | 3.29 | 3.63 | 3.64 | 3.77 |      | 3.81 | 3.88 |
| 88F00289  | 2.68 | 2.79 | 3.06 | 3.12 |      | 3.20 | 3.29 |
| 88F00290  | 2.52 | 2.67 | 2.74 | 2.91 |      | 2.95 | 2.99 |
| 88F00279  | 2.84 | 2.91 | 2.96 | 3.15 |      | 3.12 | 3.19 |
| 88F00263  | 2.98 | 3.14 | 3.28 | 3.35 |      | 3.40 | 3.53 |
| Mean      | 2.89 | 3.06 | 3.19 | 3.30 | 3.40 | 3.30 | 3.38 |
| Std.Dev   | 0.23 | 0.27 | 0.26 | 0.25 | 0.15 | 0.33 | 0.34 |
| SEM       | 0.07 | 0.09 | 0.08 | 0.08 | 0.07 | 0.15 | 0.15 |

# Interim sacrifice animal

**Appendix E (cont.): BODY WEIGHTS (kg)**

| Animal    | Day of Study |      |      |      |      |      |      |
|-----------|--------------|------|------|------|------|------|------|
|           | -19          | -13  | -7   | 0    | 3    | 7    | 14   |
| HS Male   |              |      |      |      |      |      |      |
| 88F00262* | 2.74         | 2.77 | 2.92 | 3.03 | died |      |      |
| 88F00301* | 3.00         | 3.25 | 3.32 | 3.41 | 3.41 |      |      |
| 88F00282* | 3.04         | 3.22 | 3.27 | 3.41 | died |      |      |
| 88F00298* | 2.76         | 3.01 | 3.12 | 3.28 | 3.29 |      |      |
| 88F00257* | 2.90         | 3.09 | 3.32 | 3.52 | 3.58 |      |      |
| 88F00272  | 3.12         | 3.35 | 3.35 | 3.47 | died |      |      |
| 88F00280  | 3.24         | 3.38 | 3.52 | 3.56 |      | 3.55 | 3.69 |
| 88F00303  | 2.45         | 2.89 | 3.03 | 3.12 |      | 3.18 | 3.26 |
| 88F00254  | 2.90         | 3.05 | 3.22 | 3.31 |      | 3.37 | 3.50 |
| 88F00297  | 2.66         | 2.96 | 3.07 | 3.17 |      | 3.18 | 3.20 |
| Mean      | 2.88         | 3.10 | 3.21 | 3.33 | 3.42 | 3.32 | 3.41 |
| Std.Dev   | 0.23         | 0.20 | 0.18 | 0.18 | 0.15 | 0.18 | 0.23 |
| SEM       | 0.07         | 0.06 | 0.06 | 0.06 | 0.09 | 0.09 | 0.12 |
| D70 Male  |              |      |      |      |      |      |      |
| 88F00273* | 2.62         | 2.79 | 2.80 | 2.94 | 3.05 |      |      |
| 88F00294* | 2.75         | 2.98 | 3.12 | 3.23 | 3.20 |      |      |
| 88F00265* | 2.99         | 3.10 | 3.27 | 3.31 | 3.35 |      |      |
| 88F00266* | 3.08         | 3.33 | 3.48 | 3.54 | 3.68 |      |      |
| 88F00267* | 3.03         | 3.17 | 3.31 | 3.41 | 3.53 |      |      |
| 88F00300  | 2.79         | 3.02 | 3.13 | 3.29 |      | 3.43 | 3.45 |
| 88F00259  | 2.61         | 2.76 | 2.87 | 3.05 |      | 3.17 | 3.23 |
| 88F00292  | 2.82         | 2.91 | 3.16 | 3.28 |      | 3.48 | 3.47 |
| 88F00286  | 3.16         | 2.96 | 3.05 | 3.19 |      | 3.19 | 3.33 |
| 88F00276  | 2.84         | 3.30 | 3.35 | 3.39 |      | 3.36 | 3.45 |
| Mean      | 2.87         | 3.03 | 3.16 | 3.26 | 3.37 | 3.33 | 3.38 |
| Std.Dev   | 0.19         | 0.19 | 0.21 | 0.17 | 0.25 | 0.14 | 0.10 |
| SEM       | 0.06         | 0.06 | 0.07 | 0.06 | 0.11 | 0.06 | 0.04 |

# Interim sacrifice animal

**Appendix E (cont.): BODY WEIGHTS (kg)**

| Animal     | Day of Study |      |      |      |      |      |      |
|------------|--------------|------|------|------|------|------|------|
|            | -29          | -20  | -14  | -7   | 0    | 3    | 14   |
| RL Female  |              |      |      |      |      |      |      |
| 88F00323*  | 3.35         | 3.75 | 3.87 | 4.16 | 4.28 | 4.34 |      |
| 88F00336*  | 3.58         | 3.85 | 4.07 | 4.23 | 4.41 | 4.38 |      |
| 88F00330*  | 3.15         | 3.53 | 3.68 | 3.93 | 4.12 | 4.10 |      |
| 88F00324*  | 3.23         | 3.38 | 3.56 | 3.71 | 3.81 | 3.89 |      |
| 88F00352*  | 2.96         | 3.20 | 3.28 | 3.44 | 3.52 | 3.54 |      |
| 88F00346   | 3.22         | 3.60 | 3.85 | 4.19 | 4.22 |      | 4.50 |
| 88F00351   | 3.11         | 3.28 | 3.47 | 3.65 | 3.76 |      | 4.01 |
| 88F00325   | 3.04         | 3.30 | 3.57 | 3.80 | 4.01 |      | 4.09 |
| 88F00307   | 3.23         | 3.43 | 3.63 | 3.78 | 3.88 |      | 4.00 |
| 88F00340   | 2.67         | 2.89 | 3.14 | 3.34 | 3.48 |      | 3.51 |
| Mean       | 3.16         | 3.42 | 3.61 | 3.82 | 3.95 | 4.05 | 4.02 |
| Std.Dev    | 0.24         | 0.28 | 0.28 | 0.31 | 0.31 | 0.35 | 0.35 |
| SEM        | 0.08         | 0.09 | 0.09 | 0.10 | 0.10 | 0.16 | 0.16 |
| HSD Female |              |      |      |      |      |      |      |
| 88F00313*  | 3.45         | 3.53 | 3.65 | 3.69 | 3.87 | 3.88 |      |
| 88F00308*  | 3.23         | 3.32 | 3.46 | 3.61 | 3.85 | 3.75 |      |
| 88F00335*  | 3.18         | 2.66 | 3.24 | 3.54 | 3.73 | 3.86 |      |
| 88F00337*  | 3.30         | 3.40 | 3.40 | 3.26 | 3.72 | 3.66 |      |
| 88F00349*  | 3.05         | 3.25 | 3.54 | 3.73 | 3.92 | 3.96 |      |
| 88F00334   | 3.40         | 3.65 | 3.75 | 3.95 | 4.12 |      | 4.11 |
| 88F00322   | 3.23         | 3.31 | 3.56 | 3.70 | 3.75 |      | 3.82 |
| 88F00353   | 3.45         | 3.73 | 3.92 | 4.10 | 4.18 |      | 4.21 |
| 88F00333   | 3.47         | 3.86 | 4.00 | 4.21 | 4.36 |      | 4.34 |
| 88F00318   | 2.86         | 3.24 | 3.46 | 3.72 | 3.87 |      | 3.94 |
| Mean       | 3.26         | 3.40 | 3.60 | 3.75 | 3.94 | 3.82 | 4.08 |
| Std.Dev    | 0.20         | 0.33 | 0.24 | 0.28 | 0.21 | 0.12 | 0.21 |
| SEM        | 0.06         | 0.11 | 0.08 | 0.09 | 0.07 | 0.05 | 0.09 |

# Interim sacrifice animal

**Appendix E (cont.): BODY WEIGHTS (kg)**

| Animal     | Day of Study |      |      |      |      |      |      |
|------------|--------------|------|------|------|------|------|------|
|            | -29          | -20  | -14  | -7   | 0    | 3    | 14   |
| HS Female  |              |      |      |      |      |      |      |
| 88F00315*  | 2.71         | 3.19 | 3.48 | 3.67 | 3.88 | died |      |
| 88F00339*  | 3.57         | 3.81 | 3.98 | 4.24 | 4.21 | died |      |
| 88F00345*  | 3.73         | 3.94 | 4.13 | 4.37 | 4.41 | 4.42 |      |
| 88F00348*  | 3.02         | 3.26 | 3.40 | 3.59 | 3.72 | 3.64 |      |
| 88F00332   | 3.36         | 3.57 | 3.71 | 3.98 | 4.19 | died |      |
| 88F00310*  | 3.17         | 3.35 | 3.42 | 3.70 | 3.77 | 3.74 |      |
| 88F00331   | 2.97         | 3.28 | 3.37 | 3.64 | 3.80 |      | 4.03 |
| 88F00327   | 2.85         | 3.11 | 3.38 | 3.55 | 3.85 |      | 3.98 |
| 88F00341   | 3.15         | 3.40 | 3.57 | 3.71 | 3.88 |      | 3.88 |
| 88F00305   | 3.44         | 3.63 | 3.75 | 3.94 | 4.05 |      | 4.08 |
| Mean       | 3.20         | 3.45 | 3.62 | 3.84 | 3.98 | 3.93 | 3.99 |
| Std.Dev    | 0.33         | 0.27 | 0.27 | 0.28 | 0.23 | 0.42 | 0.08 |
| SEM        | 0.10         | 0.09 | 0.09 | 0.09 | 0.07 | 0.24 | 0.04 |
| D70 Female |              |      |      |      |      |      |      |
| 88F00311*  | 3.00         | 2.95 | 3.06 | 3.23 | 3.41 | 3.44 |      |
| 88F00314*  | 2.98         | 3.31 | 3.42 | 3.76 | 3.86 | 3.84 |      |
| 88F00338*  | 2.80         | 3.16 | 3.22 | 3.53 | 3.60 | 3.64 |      |
| 88F00344*  | 3.28         | 3.53 | 3.66 | 3.76 | 3.98 | 3.98 |      |
| 88F00347*  | 3.22         | 3.57 | 3.74 | 3.96 | 4.05 | 4.13 |      |
| 88F00319   | 3.43         | 3.76 | 3.80 | 3.91 | 4.00 |      | 4.09 |
| 88F00304   | 2.96         | 3.28 | 3.35 | 3.54 | 3.54 |      | 3.68 |
| 88F00326   | 3.59         | 3.89 | 4.05 | 4.05 | 4.22 |      | 4.25 |
| 88F00312   | 3.31         | 3.46 | 3.63 | 3.85 | 4.02 |      | 4.07 |
| 88F00321   | 3.25         | 3.39 | 3.60 | 3.81 | 3.94 |      | 4.07 |
| Mean       | 3.18         | 3.43 | 3.55 | 3.74 | 3.86 | 3.81 | 4.03 |
| Std.Dev    | 0.24         | 0.28 | 0.29 | 0.24 | 0.26 | 0.27 | 0.21 |
| SEM        | 0.08         | 0.09 | 0.09 | 0.08 | 0.08 | 0.12 | 0.09 |

# Interim sacrifice animal

**Appendix F: WATER CONSUMPTION (ml/day)**

| Animal<br><u>88F00-</u> | -7  | 1   | Study Day |     | 4   | 5   | 6   | 7   | 14       |
|-------------------------|-----|-----|-----------|-----|-----|-----|-----|-----|----------|
|                         |     |     | 2         | 3   |     |     |     |     |          |
| RL Male                 |     |     |           |     |     |     |     |     |          |
| 261*                    | SP@ | 307 | 250       | 340 | 209 |     |     |     |          |
| 296*                    | 294 | 286 | 429       | 310 | 279 |     |     |     |          |
| 277*                    | 330 | 308 | 211       | 211 | 178 |     |     |     |          |
| 287*                    | 378 | SP  | 403       | 276 | SP  |     |     |     |          |
| 281*                    | 327 | 348 | 271       | 444 | 256 |     |     |     |          |
| 302                     | 254 | 281 | 182       | 262 | 240 | 247 | 285 | 256 | 235 143  |
| 283                     | 270 | 200 | 222       | 261 | 224 | 209 | 214 | 419 | NR\$ 245 |
| 284                     | 195 | 208 | 182       | 209 | 220 | 195 | 289 | 390 | NR 216   |
| 268                     | 290 | 288 | 230       | 314 | 361 | 317 | 204 | 399 | NR 294   |
| 269                     | 294 | 265 | 199       | 295 | 252 | 275 | 232 | 320 | NR 269   |
| Mean                    | 292 | 277 | 258       | 292 | 247 | 249 | 245 | 357 | 235 233  |
| Std.Dev                 | 52  | 47  | 88        | 68  | 52  | 50  | 40  | 68  | 58       |
| SEM                     | 17  | 16  | 28        | 22  | 17  | 22  | 18  | 30  | 26       |
| HSD Male                |     |     |           |     |     |     |     |     |          |
| 274*                    | 439 | 429 | 417       | 337 | 203 |     |     |     |          |
| 258*                    | 396 | 399 | 273       | 252 | 193 |     |     |     |          |
| 285*                    | 290 | 398 | 307       | 308 | 308 |     |     |     |          |
| 260*                    | 285 | 294 | 296       | 241 | 214 |     |     |     |          |
| 293*                    | 275 | 277 | 247       | 259 | 290 |     |     |     |          |
| 295                     | 335 | 322 | 391       | 248 | 254 | 233 | 247 | 337 | NR 296   |
| 289                     | 271 | 320 | 277       | 263 | 265 | 296 | 294 | 312 | NR 249   |
| 290                     | 260 | 317 | 254       | 241 | 231 | 225 | SP  | 265 | NR 194   |
| 279                     | 402 | 339 | 401       | 379 | 379 | 313 | 435 | 432 | NR 259   |
| 263                     | 243 | 287 | 246       | 236 | 296 | 270 | 223 | 434 | NR 273   |
| Mean                    | 320 | 338 | 311       | 276 | 263 | 267 | 300 | 356 | 254      |
| Std.Dev                 | 69  | 53  | 67        | 49  | 57  | 38  | 95  | 75  | 38       |
| SEM                     | 22  | 17  | 21        | 15  | 18  | 17  | 47  | 34  | 17       |

\* Interim sacrifice animal

@ Spill

\$ Not recorded

**Appendix F (cont.): WATER CONSUMPTION (ml/day)**

| Animal -13<br>88F00- | Study Day |     |      |     |     |     |     |     |      |     |
|----------------------|-----------|-----|------|-----|-----|-----|-----|-----|------|-----|
|                      | -7        | 1   | 2    | 3   | 4   | 5   | 6   | 7   | 14   |     |
| HS Male              |           |     |      |     |     |     |     |     |      |     |
| 262*                 | 297       | 321 | died |     |     |     |     |     |      |     |
| 301*                 | 386       | 189 | 440  | 386 | 241 |     |     |     |      |     |
| 282*                 | 416       | 414 | died |     |     |     |     |     |      |     |
| 298*                 | 219       | 302 | 320  | 139 | 213 |     |     |     |      |     |
| 257*                 | SP@       | 324 | 429  | 267 | 232 |     |     |     |      |     |
| 272                  | 319       | 322 | died |     |     |     |     |     |      |     |
| 280                  | 283       | 343 | 338  | 366 | SP  | 358 | 320 | 414 | NR\$ | 178 |
| 303                  | 206       | 250 | 248  | 156 | 159 | 177 | 206 | 156 | 204  | 183 |
| 254                  | 263       | 256 | 306  | 251 | 257 | 226 | 263 | 329 | NR   | 186 |
| 297                  | 169       | 261 | 44   | 7   | 335 | 268 | 239 | 207 | 196  | 209 |
| Mean                 | 284       | 298 | 304  | 225 | 240 | 257 | 257 | 277 | 200  | 189 |
| Std.Dev              | 82        | 62  | 133  | 134 | 58  | 77  | 48  | 117 | 6    | 14  |
| SEM                  | 27        | 20  | 50   | 51  | 24  | 38  | 24  | 59  | 4    | 7   |
| D70 Male             |           |     |      |     |     |     |     |     |      |     |
| 273*                 | 226       | 250 | 242  | 247 | 198 |     |     |     |      |     |
| 294*                 | 366       | 399 | 278  | 443 | 193 |     |     |     |      |     |
| 265*                 | 295       | 297 | 231  | 242 | 200 |     |     |     |      |     |
| 266*                 | 329       | 400 | 296  | 120 | 303 |     |     |     |      |     |
| 267*                 | 235       | 162 | 200  | 245 | 162 |     |     |     |      |     |
| 300                  | 297       | 306 | 255  | 242 | 296 | 277 | 259 | 277 | 280  | 270 |
| 259                  | 343       | 316 | 253  | 293 | 287 | 336 | 338 | 327 | NR   | 189 |
| 292                  | 293       | 306 | 173  | 287 | 251 | 261 | 435 | 313 | NR   | 179 |
| 286                  | 264       | 264 | 249  | 282 | 203 | 287 | 242 | 440 | NR   | 188 |
| 276                  | 363       | 426 | 366  | 354 | 289 | 375 | 430 | 412 | NR   | 416 |
| Mean                 | 301       | 313 | 254  | 276 | 238 | 307 | 341 | 354 | 280  | 248 |
| Std.Dev              | 50        | 80  | 53   | 84  | 53  | 47  | 91  | 69  | 101  |     |
| SEM                  | 16        | 25  | 17   | 26  | 17  | 21  | 41  | 31  |      | 45  |

\* Interim sacrifice animal

@ Spill

\$ Not recorded

## Appendix F (cont.): WATER CONSUMPTION (ml/day)

| Animal | -14 | Study Day |   |   |   |   |   |   |   |    |  |
|--------|-----|-----------|---|---|---|---|---|---|---|----|--|
|        |     | -6        | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 14 |  |
| 88F00- |     |           |   |   |   |   |   |   |   |    |  |

## RL Female

|         |     |     |     |     |      |     |     |     |     |    |  |
|---------|-----|-----|-----|-----|------|-----|-----|-----|-----|----|--|
| 323*    | 351 | 340 | 387 | 329 | NR\$ |     |     |     |     |    |  |
| 336*    | 391 | 258 | 406 | 435 | NR   |     |     |     |     |    |  |
| 330*    | 332 | 226 | 288 | 317 | NR   |     |     |     |     |    |  |
| 324*    | 331 | NR  | 301 | 360 | NR   |     |     |     |     |    |  |
| 352*    | 240 | 195 | 169 | 204 | NR   |     |     |     |     |    |  |
| 346     | 423 | 456 | 366 | 351 | 362  | 280 | 435 | 453 | 436 | NP |  |
| 351     | 228 | 225 | 229 | 223 | 222  | 216 | 298 | 289 | 225 | NR |  |
| 325     | 302 | 257 | 194 | 226 | 327  | 158 | 428 | 449 | 253 | NR |  |
| 307     | 226 | 228 | 161 | 180 | 180  | 56  | 283 | 365 | 224 | NR |  |
| 340     | 340 | 312 | 193 | 290 | 278  | 211 | 334 | 363 | 231 | NR |  |
| Mean    | 316 | 277 | 269 | 292 | 274  | 184 | 356 | 384 | 274 |    |  |
| Std.Dev | 68  | 81  | 93  | 82  | 74   | 84  | 72  | 69  | 91  |    |  |
| SEM     | 21  | 27  | 29  | 26  | 33   | 37  | 32  | 31  | 41  |    |  |

## HSD Female

|         |     |     |     |     |     |     |     |     |     |    |  |
|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|--|
| 313*    | 155 | 170 | 325 | 202 | NR  |     |     |     |     |    |  |
| 308*    | 333 | 305 | 398 | 247 | NR  |     |     |     |     |    |  |
| 335*    | 350 | 388 | 417 | 427 | NR  |     |     |     |     |    |  |
| 337*    | 278 | 380 | 295 | 395 | NR  |     |     |     |     |    |  |
| 349*    | 370 | 311 | 378 | 288 | NR  |     |     |     |     |    |  |
| 334     | 423 | 311 | 431 | 437 | 400 | 324 | 448 | 408 | 392 | NR |  |
| 322     | 337 | 329 | 348 | 232 | 268 | 169 | 289 | 363 | 207 | NR |  |
| 353     | 306 | 303 | 359 | 254 | 274 | 241 | 342 | 304 | 215 | NR |  |
| 333     | 429 | 349 | 462 | 314 | 280 | 42  | 361 | 433 | 457 | NR |  |
| 318     | 271 | 303 | 260 | 151 | 381 | 163 | 276 | 270 | 291 | NR |  |
| Mean    | 325 | 315 | 367 | 295 | 321 | 188 | 343 | 356 | 312 |    |  |
| Std.Dev | 80  | 60  | 63  | 97  | 64  | 104 | 68  | 69  | 110 |    |  |
| SEM     | 25  | 19  | 20  | 31  | 29  | 47  | 31  | 31  | 49  |    |  |

# Interim sacrifice animal

\$ Not recorded

**Appendix F (cont.): WATER CONSUMPTION (ml/day)**

| Animal -14<br>88F00- | -6  | 1   | Study Day |     |      |     |     |     |     |    |
|----------------------|-----|-----|-----------|-----|------|-----|-----|-----|-----|----|
|                      |     |     | 2         | 3   | 4    | 5   | 6   | 7   | 14  |    |
| HS Female            |     |     |           |     |      |     |     |     |     |    |
| 315                  | 300 | 319 | died      |     |      |     |     |     |     |    |
| 339                  | 363 | 341 | died      |     |      |     |     |     |     |    |
| 345*                 | 330 | 323 | 471       | 354 | NR\$ |     |     |     |     |    |
| 348*                 | 211 | 167 | 172       | 158 | NR   |     |     |     |     |    |
| 332                  | 419 | 345 | died      |     |      |     |     |     |     |    |
| 310*                 | 250 | 321 | 239       | 140 | NR   |     |     |     |     |    |
| 331                  | 431 | 323 | 419       | 468 | 400  | 416 | 464 | 448 | 335 | NR |
| 327                  | 346 | 382 | 333       | 259 | 361  | 254 | 303 | 387 | 360 | NR |
| 341                  | 373 | 446 | 263       | 308 | 283  | 244 | 393 | 369 | 405 | NR |
| 305                  | 311 | 274 | 427       | 268 | 287  | 211 | 315 | 351 | 336 | NR |
| Mean                 | 333 | 324 | 332       | 279 | 333  | 281 | 369 | 389 | 359 |    |
| Std.Dev              | 69  | 72  | 112       | 113 | 57   | 92  | 75  | 42  | 33  |    |
| SEM                  | 22  | 23  | 42        | 43  | 29   | 46  | 37  | 21  | 16  |    |

**D70 Female**

|         |     |     |     |     |     |     |     |     |     |    |
|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| 311*    | 399 | 357 | 386 | 444 | NR  |     |     |     |     |    |
| 314*    | 3.7 | 403 | 392 | 280 | NR  |     |     |     |     |    |
| 318*    | 241 | 262 | 323 | 231 | NR  |     |     |     |     |    |
| 314*    | 293 | 360 | 331 | 265 | NR  |     |     |     |     |    |
| 347*    | 309 | 304 | 340 | 313 | NR  |     |     |     |     |    |
| 319     | 285 | 316 | 276 | 252 | 238 | 178 | 313 | 424 | 323 | NR |
| 304     | 369 | 462 | 349 | 340 | 335 | 237 | 217 | 441 | 356 | NR |
| 326     | 306 | 144 | 326 | 303 | 314 | 224 | 372 | 285 | 324 | NR |
| 312     | 281 | 268 | 245 | 248 | SP  | 259 | 255 | 331 | 282 | NR |
| 321     | 229 | 212 | 268 | 297 | 294 | 100 | 349 | 401 | 296 | NR |
| Mean    | 307 | 309 | 324 | 297 | 295 | 200 | 301 | 376 | 316 |    |
| Std.Dev | 54  | 93  | 48  | 61  | 42  | 63  | 65  | 66  | 29  |    |
| SEM     | 17  | 29  | 15  | 19  | 21  | 28  | 29  | 30  | 13  |    |

\* Interim sacrifice animal

† Not recorded

**Appendix G: SERUM CHEMISTRY**

**List of Serum Chemistry Abbreviations/Units**

|      |                                   |
|------|-----------------------------------|
| AST  | Aspartate Amino-Transferase (U/l) |
| ALT  | Alanine Amino-Transferase (U/l)   |
| GGT  | Gamma Glutamyl Transferase (U/l)  |
| CK   | Creatine Phosphokinase (U/l)      |
| LDHL | Lactate Dehydrogenase (U/l)       |
| ALK  | Alkaline Phosphatase (U/l)        |
| ALB  | Albumin (g/dl)                    |
| BILI | Total Bilirubin (mg/dl)           |
| CL   | Chloride (Meq/l)                  |
| GLU  | Glucose (mg/dl)                   |
| IRON | Iron ( $\mu$ g/dl)                |
| MAG  | Magnesium (mg/dl)                 |
| CAL  | Calcium (mg/dl)                   |
| PHOS | Phosphorus (mg/dl)                |
| CHOL | Cholesterol (mg/dl)               |
| CR   | Creatinine (mg/dl)                |
| TP   | Total Protein (g/dl)              |
| URIC | Uric Acid (mg/dl)                 |
| NA   | Sodium (Meq/l)                    |
| K    | Potassium (Meq/l)                 |
| TRIG | Triglyceride (mg/dl)              |
| BUN  | Blood Urea Nitrogen (mg/dl)       |
| A-G  | Albumin/Globulin Ratio            |

## Appendix G (cont.): SERUM CHEMISTRY

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Expanded Statistical Table for COBAS I  
 Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

| Animal Number        | Sex | Group/<br>Subgroup | Day of<br>Study | AST    | BUN   | CK      | ALB  | BIL  | CL     | GLU    | IRON   | GGT  | ALK    | LDHL   |
|----------------------|-----|--------------------|-----------------|--------|-------|---------|------|------|--------|--------|--------|------|--------|--------|
| 88F00261             | M   | 4/1                | 4               | 35.2   | 19.2  | 1808.6  | 3.9  | 0    | 108.   | 194.8  | 231.   | 4.3  | 75.5   | 343.9  |
| 88F00296             | M   | 4/1                | 4               | 48.5   | 18.2  | 3594.2  | 3.7  | 0    | 108.   | 129.2  | 183.   | 7.1  | 55.0   | 484.5  |
| 88F00277             | M   | 4/1                | 4               | 37.4   | 16.7  | 1169.62 | 3.9  | 0    | 102.   | 233.4  | 237.   | 7.6  | 65.8   | 349.2  |
| 88F00287             | M   | 4/1                | 4               | 43.3   | 27.5  | 2001.5  | 4.3  | 0    | 110.   | 178.9  | 134.   | 9.8  | 140.4  | 160.6  |
| 88F00281             | M   | 4/1                | 4               | 62.7   | 14.1  | 1398.00 | NT   | 0    | 106.   | 118.0  | 182.   | 8.2  | 74.0   | 590.7  |
| Parameter means:     |     |                    |                 | 45.42  | 19.14 | 1994.38 | 3.95 | 0.00 | 106.80 | 170.86 | 193.40 | 7.40 | 82.14  | 385.78 |
| Standard deviations: |     |                    |                 | 10.97  | 5.05  | 952.61  | 0.25 | 0.00 | 3.03   | 47.64  | 42.07  | 2.01 | 33.57  | 162.43 |
| 88F00274             | M   | 2/1                | 4               | 49.2   | 21.5  | 1564.83 | 3.8  | 0    | 110.   | 168.6  | 205.   | 8.4  | 149.5  | 228.6  |
| 88F00258             | M   | 2/1                | 4               | 46.4   | 19.7  | 1487.65 | 4.0  | 0    | 108.   | 158.1  | 216.   | 5.0  | 106.7  | 486.7  |
| 88F00285             | M   | 2/1                | 4               | 31.0   | 17.2  | 1099.45 | 4.6  | 0    | 106.   | 156.9  | 177.   | 7.1  | 133.6  | 277.9  |
| 88F00260             | M   | 2/1                | 4               | 59.5   | 20.5  | 1429.59 | 3.5  | 0    | 108.   | 129.9  | 200.   | 7.2  | 89.5   | 384.7  |
| 88F00293             | M   | 2/1                | 4               | 49.4   | 21.8  | 1485.45 | 4.1  | 0    | 109.   | 174.3  | 161.   | 7.8  | 88.5   | 266.1  |
| Parameter means:     |     |                    |                 | 47.10  | 20.14 | 1413.39 | 4.00 | 0.00 | 108.20 | 157.56 | 191.80 | 7.10 | 113.56 | 328.40 |
| Standard deviations: |     |                    |                 | 10.29  | 1.84  | 187.98  | 0.41 | 0.00 | 1.48   | 17.09  | 22.33  | 1.28 | 27.14  | 104.87 |
| 88F00301             | M   | 1/1                | 4               | 59.8   | 14.9  | 834.84  | 3.7  | 0    | 102.   | 204.2  | 44.    | 11.9 | 47.2   | 360.9  |
| 88F00298             | M   | 1/1                | 4               | 24.5   | 17.6  | 1245.98 | 3.5  | 0    | 103.   | 172.0  | 87.    | 7.0  | 42.9   | 257.0  |
| 88F00257             | M   | 1/1                | 4               | 32.2   | 12.3  | 2791.1  | 3.4  | 0    | 105.   | 169.6  | 66.    | 4.7  | 36.1   | 450.2  |
| Parameter means:     |     |                    |                 | 38.83  | 14.93 | 1623.31 | 3.53 | 0.00 | 103.33 | 181.93 | 65.67  | 7.87 | 42.07  | 356.03 |
| Standard deviations: |     |                    |                 | 18.56  | 2.65  | 1031.82 | 0.15 | 0.00 | 1.53   | 19.32  | 21.50  | 3.68 | 5.60   | 96.69  |
| 88F00273             | M   | 3/1                | 4               | 449.7  | 29.6  | 3196.5  | 4.2  | 0    | 101.   | 135.9  | 237.   | 4.0  | 221.3  | 582.6  |
| 88F00294             | M   | 3/1                | 4               | 65.4   | 16.5  | 2237.1  | NT   | 0    | 108.   | 99.2   | 296.   | 3.9  | 213.2  | 688.7  |
| 88F00265             | M   | 3/1                | 4               | 184.6  | 25.3  | 3116.9  | 4.1  | 0    | 104.   | 357.4  | 229.   | 5.7  | 86.4   | 479.0  |
| 88F00266             | M   | 3/1                | 4               | 69.7   | 16.1  | 1532.21 | 3.6  | 0    | 106.   | 168.3  | 134.   | 4.2  | 81.7   | 286.7  |
| 88F00267             | M   | 3/1                | 4               | 63.7   | 21.5  | 13375.7 | NT   | 0    | 107.   | 124.6  | 232.   | 3.3  | 88.0   | 668.1  |
| Parameter means:     |     |                    |                 | 166.62 | 21.80 | 4691.68 | 3.97 | 0.00 | 105.20 | 177.08 | 225.60 | 4.22 | 138.12 | 541.02 |
| Standard deviations: |     |                    |                 | 166.35 | 5.78  | 4902.42 | 0.32 | 0.00 | 2.78   | 103.81 | 58.16  | 0.89 | 72.33  | 164.48 |

## Appendix G (cont.) : SERUM CHEMISTRY

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Expanded Statistical Table for COBAS I  
 Study Number: 88002

Study Start Date: 13-Sep-88

| Animal Group / Day of Study |     |          | MAG | NA   | CAL    | PHOS  | CHOL | L     |
|-----------------------------|-----|----------|-----|------|--------|-------|------|-------|
| Number                      | Sex | Subgroup |     |      |        |       |      |       |
| 88F00261                    | M   | 4/1      | 4   | 2.10 | 151.1  | 12.5  | 6.5  | 20.0  |
| 88F00296                    | M   | 4/1      | 4   | 2.27 | 151.4  | 13.0  | 5.2  | 21.5  |
| 88F00277                    | M   | 4/1      | 4   | 1.81 | 147.5  | 12.4  | 5.7  | 30.0  |
| 88F00287                    | M   | 4/1      | 4   | 2.28 | 148.4  | 13.3  | 5.3  | 21.6  |
| 88F00281                    | M   | 4/1      | 4   | 2.44 | 148.7  | 12.6  | 4.7  | 13.6  |
| Parameter means:            |     |          |     | 2.18 | 149.42 | 12.76 | 5.48 | 21.34 |
| Standard deviations:        |     |          |     | 0.24 | 1.73   | 0.38  | 0.67 | 5.85  |
| 88F00274                    | M   | 2/1      | 4   | 1.93 | 148.8  | 13.1  | 5.7  | 26.5  |
| 88F00258                    | M   | 2/1      | 4   | 2.43 | 150.9  | 12.9  | 5.1  | 32.8  |
| 88F00285                    | M   | 2/1      | 4   | 2.22 | 149.9  | 13.5  | 6.2  | 26.2  |
| 88F00260                    | M   | 2/1      | 4   | 2.29 | 149.2  | 12.8  | 5.2  | 20.1  |
| 88F00293                    | M   | 2/1      | 4   | 2.39 | 151.3  | 13.2  | 5.3  | 35.6  |
| Parameter means:            |     |          |     | 2.25 | 150.02 | 13.10 | 5.50 | 28.24 |
| Standard deviations:        |     |          |     | 0.20 | 1.07   | 0.27  | 0.45 | 6.09  |
| 88F00301                    | M   | 1/1      | 4   | 2.10 | 148.1  | 12.9  | 4.2  | 25.6  |
| 88F00298                    | M   | 1/1      | 4   | 1.83 | 147.7  | 13.0  | 5.3  | 98.4  |
| 88F00257                    | M   | 1/1      | 4   | 1.94 | 146.6  | 12.6  | 5.7  | 31.4  |
| Parameter means:            |     |          |     | 1.96 | 147.47 | 12.83 | 5.07 | 51.80 |
| Standard deviations:        |     |          |     | 0.14 | 0.78   | 0.21  | 0.78 | 40.46 |
| 88F00273                    | M   | 3/1      | 4   | 2.38 | 148.5  | 12.3  | 5.7  | 13.6  |
| 88F00294                    | M   | 3/1      | 4   | 2.36 | 158.6  | 11.6  | 5.9  | 16.6  |
| 88F00265                    | M   | 3/1      | 4   | 2.36 | 142.0  | 12.4  | 5.8  | 13.3  |
| 88F00266                    | M   | 3/1      | 4   | 2.08 | 148.1  | 13.5  | 3.7  | 38.6  |
| 88F00267                    | M   | 3/1      | 4   | 2.40 | 150.5  | 13.1  | 5.2  | 16.2  |
| Parameter means:            |     |          |     | 2.32 | 149.54 | 12.58 | 5.26 | 19.66 |
| Standard deviations:        |     |          |     | 0.13 | 5.98   | 0.74  | 0.91 | 10.69 |

Appendix G (cont.): SERUM CHEMISTRY

LETTERMAN ARMY INSTITUTE OF RESEARCH  
DIV OF RES SUPP, PATH SERV GP  
PRESTOLO OF SAN FRANCISCO, CA 94129  
RABBIT/NEW ZEALAND WHITE

Expanded Statistical Table for COBAS 11  
Study Number: 88002

Study Start Date: 13-Sep-88

PRINTED: 17-Jan-89  
Page: 1  
ACUTE/ACUTE INTRAVENOUS

| Animal Number        | Group/<br>Sex | Day of<br>Study | CR | ALT  | TG    | URIC | K    | TRIG | A-G         |
|----------------------|---------------|-----------------|----|------|-------|------|------|------|-------------|
| 88F00261             | M             | 4/1             | 6  | 1.0  | 43.8  | 4.9  | .1   | 4.5  | 85. 3.9     |
| 88F00296             | M             | 4/1             | 4  | 1.0  | 50.6  | 4.0  | .1   | 5.0  | 82. 12.1    |
| 88F00277             | M             | 4/1             | 4  | 1.9  | 19.8  | 4.4  | .0   | 5.7  | 74. 8.3     |
| 88F00287             | M             | 4/1             | 4  | 1.2  | 38.7  | 5.5  | .2   | 4.8  | 68. 3.3     |
| 88F00281             | M             | 4/1             | 4  | .7   | 40.7  | NT   | .1   | 5.6  | 74. NT      |
| Parameter means:     |               |                 |    | 0.96 | 38.72 | 4.70 | 0.10 | 5.12 | 76.60 6.90  |
| Standard deviations: |               |                 |    | 0.18 | 11.50 | 0.65 | 0.07 | 0.52 | 6.84 4.12   |
| 88F00274             | M             | 2/1             | 4  | 1.4  | 48.3  | 5.6  | .1   | 4.3  | 86. 2.1     |
| 88F00258             | M             | 2/1             | 4  | 1.0  | 43.7  | 4.8  | .2   | 5.6  | 148. 5.0    |
| 88F00285             | M             | 2/1             | 4  | .9   | 49.0  | 5.4  | .0   | 5.0  | 173. 5.4    |
| 88F00260             | M             | 2/1             | 4  | 1.2  | 52.4  | 4.5  | .2   | 5.8  | 108. 3.6    |
| 88F00293             | M             | 2/1             | 4  | 1.3  | 67.8  | 4.9  | .1   | 5.2  | 108. 4.7    |
| Parameter means:     |               |                 |    | 1.16 | 52.24 | 5.04 | 0.12 | 5.18 | 124.60 4.16 |
| Standard deviations: |               |                 |    | 0.21 | 9.23  | 0.45 | 0.08 | 0.58 | 35.11 1.33  |
| 88F00301             | M             | 1/1             | 4  | .7   | 58.8  | 4.5  | 0    | 4.3  | 117. 4.7    |
| 88F00298             | M             | 1/1             | 4  | 1.1  | 48.1  | 4.6  | 0    | 5.3  | 126. 2.9    |
| 88F00257             | M             | 1/1             | 4  | .9   | 36.9  | 5.0  | .2   | 5.0  | 100. 2.1    |
| Parameter means:     |               |                 |    | 0.90 | 47.93 | 4.70 | 0.07 | 4.87 | 114.33 3.23 |
| Standard deviations: |               |                 |    | 0.20 | 10.95 | 0.26 | 0.12 | 0.51 | 13.20 1.33  |
| 88F00273             | M             | 3/1             | 4  | 1.0  | 141.9 | 5.0  | .1   | 4.4  | 132. 5.0    |
| 88F00294             | M             | 3/1             | 4  | 1.0  | 43.7  | NT   | .1   | 8.4  | 87. NT      |
| 88F00265             | M             | 3/1             | 4  | 1.0  | 80.0  | 5.1  | .3   | 8.8  | 140. 4.1    |
| 88F00266             | M             | 3/1             | 4  | 1.1  | 46.6  | 5.4  | .1   | 4.7  | 209. 1.9    |
| 88F00267             | M             | 3/1             | 4  | 1.0  | 34.4  | NT   | .1   | 4.0  | 123. NT     |
| Parameter means:     |               |                 |    | 1.02 | 69.32 | 5.17 | 0.14 | 6.06 | 138.20 3.67 |
| Standard deviations: |               |                 |    | 0.94 | 44.08 | 0.21 | 0.09 | 2.34 | 44.46 1.59  |

## Appendix G (cont.) : SERUM CHEMISTRY

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Expanded Statistical Table for COBAS I

Study Number: 880002

Study Start Date: 13-Sep-88

## ACUTE/ACUTE INTRAVENOUS

| Animal Number        | Group Sex | Day of Study | AST   | BUN   | CK      | ALB     | BIL  | CL     | GLU    | IRON   | GGT   | ALK   | LDHL   |
|----------------------|-----------|--------------|-------|-------|---------|---------|------|--------|--------|--------|-------|-------|--------|
| 88F00323             | F         | 4/2          | 4     | 20.4  | 19.8    | 1497.01 | 4.2  | 0      | 102.   | 156.2  | 222.  | 4.7   | 91.0   |
| 88F00336             | F         | 4/2          | 4     | 30.2  | 20.0    | 2460.8  | 4.4  | 0      | 105.   | 155.8  | 210.  | 4.8   | 68.0   |
| 88F00330             | F         | 4/2          | 4     | 25.4  | 19.6    | 2093.2  | 4.0  | 0      | 108.   | 129.0  | 160.  | 4.7   | 37.9   |
| 88F00324             | F         | 4/2          | 4     | 50.1  | 19.6    | 2930.3  | NT   | 0      | 110.   | 106.1  | 79.   | 5.8   | 56.1   |
| 88F00352             | F         | 4/2          | 4     | 43.2  | 23.6    | 1085.40 | NT   | 0      | 103.   | 77.0   | 197.  | 2.8   | 26.3   |
| Parameter means:     |           |              | 33.86 | 20.52 | 2013.34 | 4.20    | 0.00 | 105.60 | 124.82 | 173.60 | 4.56  | 55.86 | 558.92 |
| Standard deviations: |           |              | 12.42 | 1.73  | 737.41  | 0.20    | 0.00 | 3.36   | 33.91  | 57.77  | 1.09  | 25.39 | 254.56 |
| 88F00313             | F         | 2/2          | 4     | 35.8  | 17.7    | 1252.04 | 3.7  | 0      | 101.   | 145.1  | 242.  | 17.4  | 84.9   |
| 88F00308             | F         | 2/2          | 4     | 197.6 | 16.4    | 1976.9  | NT   | 0      | 102.   | 149.3  | 251.  | 20.6  | 48.5   |
| 88F00335             | F         | 2/2          | 4     | 23.3  | 20.6    | 1433.78 | 3.9  | 0      | 101.   | 129.8  | 104.  | 5.7   | 60.1   |
| 88F00337             | F         | 2/2          | 4     | 34.7  | 22.3    | 3260.0  | 3.8  | 0      | 98.    | 260.9  | 168.  | 11.8  | 72.8   |
| 88F00349             | F         | 2/2          | 4     | 29.1  | 19.4    | 1581.00 | 3.7  | 0      | 106.   | 111.7  | 221.  | 7.2   | 138.9  |
| Parameter means:     |           |              | 64.10 | 19.28 | 1900.74 | 3.78    | 0.00 | 101.60 | 159.36 | 197.20 | 12.54 | 81.04 | 445.66 |
| Standard deviations: |           |              | 74.79 | 2.33  | 805.37  | 0.10    | 0.00 | 2.88   | 58.65  | 61.25  | 6.41  | 35.10 | 270.41 |
| 88F00345             | F         | 1/2          | 4     | 23.7  | 21.1    | 1217.04 | 4.1  | 0      | 107.   | 196.2  | 192.  | 9.9   | 55.8   |
| 88F00348             | F         | 1/2          | 4     | 29.0  | 15.5    | 2470.5  | 3.5  | 0      | 102.   | 176.4  | 143.  | 5.9   | 26.5   |
| 88F00310             | F         | 1/2          | 4     | 34.4  | 18.1    | 3260.8  | 3.6  | 0      | 105.   | 160.4  | 66.   | 3.6   | 32.9   |
| Parameter means:     |           |              | 29.03 | 18.23 | 2316.11 | 3.73    | 0.00 | 104.67 | 177.67 | 133.67 | 6.47  | 38.40 | 440.50 |
| Standard deviations: |           |              | 5.35  | 2.80  | 1030.59 | 0.32    | 0.00 | 2.52   | 17.93  | 63.52  | 3.19  | 15.40 | 133.30 |
| 88F00311             | F         | 3/2          | 4     | 68.3  | 15.9    | 1469.56 | 3.9  | 0      | 98.    | 129.7  | 162.  | 4.9   | 107.7  |
| 88F00314             | F         | 3/2          | 4     | 32.3  | 16.6    | 741.33  | 4.1  | 0      | 117.   | 88.7   | 170.  | 2.9   | 59.1   |
| 88F00338             | F         | 3/2          | 4     | 34.7  | 18.1    | 908.87  | 3.9  | 0      | 107.   | 100.2  | 197.  | 2.8   | 70.6   |
| 88F00344             | F         | 3/2          | 4     | 27.1  | 16.9    | 1452.39 | 3.3  | 0      | 99.    | 170.9  | 177.  | 6.8   | 88.3   |
| 88F00347             | F         | 3/2          | 4     | 27.8  | 20.0    | 706.60  | 3.8  | 0      | 102.   | 149.4  | 171.  | 6.0   | 70.0   |
| Parameter means:     |           |              | 38.04 | 17.50 | 1055.75 | 3.80    | 0.00 | 104.60 | 127.78 | 175.40 | 4.68  | 79.14 | 344.40 |
| Standard deviations: |           |              | 17.21 | 1.61  | 377.79  | 0.30    | 0.00 | 7.77   | 33.98  | 13.20  | 1.80  | 19.09 | 73.95  |

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Appendix G (cont.) : SERUM CHEMISTRY

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Expanded Statistical Table for COBAS I  
 Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

| Animal Number        | Group/ Sex | Day of Study | MAG  | NA     | CAL   | PHOS | CHOL  | L    |
|----------------------|------------|--------------|------|--------|-------|------|-------|------|
| 88F00323             | F          | 4/2          | 4    | 2.35   | 148.8 | 12.7 | 4.6   | 97.4 |
| 88F00336             | F          | 4/2          | 4    | 2.29   | 145.8 | 12.3 | 5.5   | 88.3 |
| 88F00330             | F          | 4/2          | 4    | 2.62   | 147.9 | 12.4 | 5.3   | 53.7 |
| 88F00324             | F          | 4/2          | 4    | 2.68   | 145.9 | 11.2 | 4.2   | 40.7 |
| 88F00352             | F          | 4/2          | 4    | 2.83   | 151.5 | 10.8 | 4.9   | 46.1 |
| Parameter means:     |            |              | 2.55 | 147.98 | 11.88 | 4.90 | 65.24 |      |
| Standard deviations: |            |              | 0.23 | 2.35   | 0.83  | 0.52 | 25.83 |      |
| 88F00313             | F          | 2/2          | 4    | 2.63   | 146.4 | 11.8 | 4.2   | 59.1 |
| 88F00308             | F          | 2/2          | 4    | 2.28   | 145.9 | 11.3 | 4.4   | 45.8 |
| 88F00335             | F          | 2/2          | 4    | 2.03   | 145.2 | 11.5 | 5.0   | 49.9 |
| 88F00337             | F          | 2/2          | 4    | 2.07   | 144.2 | 12.0 | 4.7   | 38.7 |
| 88F00349             | F          | 2/2          | 4    | 1.92   | 147.0 | 11.5 | 5.4   | 55.7 |
| Parameter means:     |            |              | 2.19 | 145.74 | 11.62 | 4.74 | 49.84 |      |
| Standard deviations: |            |              | 0.28 | 1.08   | 0.28  | 0.48 | 8.07  |      |
| 88F00345             | F          | 1/2          | 4    | 2.15   | 147.4 | 12.0 | 5.0   | 61.5 |
| 88F00348             | F          | 1/2          | 4    | 1.98   | 146.0 | 12.0 | 4.4   | 44.0 |
| 88F00310             | F          | 1/2          | 4    | 1.90   | 147.1 | 11.9 | 4.2   | 68.5 |
| Parameter means:     |            |              | 2.01 | 146.83 | 11.97 | 4.53 | 58.00 |      |
| Standard deviations: |            |              | 0.13 | 0.74   | 0.06  | 0.42 | 12.62 |      |
| 88F00311             | F          | 3/2          | 4    | 2.42   | 147.2 | 11.7 | 3.7   | 30.2 |
| 88F00314             | F          | 3/2          | 4    | 2.22   | 151.8 | 12.1 | 4.6   | 67.1 |
| 88F00338             | F          | 3/2          | 4    | 2.59   | 144.5 | 12.2 | 4.7   | 33.7 |
| 88F00344             | F          | 3/2          | 4    | 2.19   | 145.2 | 12.1 | 4.5   | 20.9 |
| 88F00347             | F          | 3/2          | 4    | 2.10   | 146.5 | 12.0 | 4.7   | 58.3 |
| Parameter means:     |            |              | 2.30 | 145.04 | 12.02 | 4.44 | 42.04 |      |
| Standard deviations: |            |              | 0.20 | 6.37   | 0.19  | 0.42 | 19.68 |      |

## Appendix G (cont.) : SERUM CHEMISTRY

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Expanded Statistical Table for COBAS II  
 Study Number: 880002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

| Animal Number        | Group/<br>Sex | Day of<br>Subgroup | Study | CR   | ALT   | TP   | URIC | K    | TRIG   | A-G  |
|----------------------|---------------|--------------------|-------|------|-------|------|------|------|--------|------|
| 88F00323             | F             | 4/2                | 4     | 1.1  | 31.2  | 6.1  | 0    | 4.8  | 72.    | 2.3  |
| 88F00336             | F             | 4/2                | 4     | .9   | 25.1  | 5.7  | 0    | 4.7  | 48.    | 3.3  |
| 88F00330             | F             | 4/2                | 4     | 1.1  | 46.3  | 5.5  | 0    | 3.4  | 101.   | 2.8  |
| 88F00324             | F             | 4/2                | 4     | 1.0  | 36.6  | NT   | 0    | 6.2  | 32.    | NT   |
| 88F00352             | F             | 4/2                | 4     | 1.4  | 36.5  | NT   | 0    | 8.5  | 75.    | NT   |
| Parameter means:     |               |                    |       | 1.10 | 35.14 | 5.77 | 0.00 | 5.52 | 65.60  | 2.80 |
| Standard deviations: |               |                    |       | 0.19 | 7.82  | 0.31 | 0.00 | 1.94 | 26.56  | 0.50 |
| 88F00313             | F             | 2/2                | 4     | 1.1  | 79.5  | 4.2  | 0    | 5.0  | 52.    | 8.1  |
| 88F00308             | F             | 2/2                | 4     | 1.0  | 87.5  | NT   | 0    | 5.7  | 65.    | NT   |
| 88F00335             | F             | 2/2                | 4     | 1.1  | 38.8  | 5.4  | 0    | 4.9  | 38.    | 2.8  |
| 88F00337             | F             | 2/2                | 4     | 1.2  | 57.1  | 5.1  | 0    | 4.2  | 73.    | 2.8  |
| 88F00349             | F             | 2/2                | 4     | .8   | 37.4  | 4.9  | 0    | 5.4  | 33.    | 3.1  |
| Parameter means:     |               |                    |       | 1.04 | 60.06 | 4.90 | 0.00 | 5.04 | 52.20  | 4.20 |
| Standard deviations: |               |                    |       | 0.15 | 22.94 | 0.51 | 0.00 | 0.57 | 17.08  | 2.60 |
| 88F00345             | F             | 1/2                | 4     | 1.1  | 30.3  | 5.6  | 1    | 4.4  | 55.    | 2.6  |
| 88F00348             | F             | 1/2                | 4     | .9   | 24.5  | 4.9  | 0    | 4.8  | 143.   | 2.4  |
| 88F00310             | F             | 1/2                | 4     | .7   | 28.9  | 4.9  | 0    | 5.2  | 120.   | 2.7  |
| Parameter means:     |               |                    |       | 0.90 | 27.90 | 5.13 | 0.03 | 4.80 | 106.00 | 2.57 |
| Standard deviations: |               |                    |       | 0.20 | 3.03  | 0.40 | 0.06 | 0.40 | 45.64  | 0.15 |
| 88F00311             | F             | 3/2                | 4     | .9   | 35.4  | 5.4  | 0    | 3.9  | 85.    | 2.7  |
| 88F00314             | F             | 3/2                | 4     | .9   | 43.6  | 5.2  | 0    | 18.8 | 64.    | 3.4  |
| 88F00338             | F             | 3/2                | 4     | .9   | 45.7  | 4.7  | 0    | 5.9  | 41.    | 4.5  |
| 88F00344             | F             | 3/2                | 4     | 1.1  | 23.3  | 4.6  | 0    | 4.6  | 41.    | 2.4  |
| 88F00347             | F             | 3/2                | 4     | 1.2  | 42.1  | 5.1  | 0    | 4.5  | 46.    | 2.9  |
| Parameter means:     |               |                    |       | 1.00 | 38.02 | 5.00 | 0.00 | 7.54 | 55.40  | 3.18 |
| Standard deviations: |               |                    |       | 0.14 | 9.09  | 0.34 | 0.00 | 6.34 | 19.06  | 0.82 |

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## Appendix G (cont.): SERUM CHEMISTRY

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Expanded Statistical Table for COBAS I  
 Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

| Animal Number        | Sex | Day of Study | AST   | BUN   | CK     | ALB     | BIL  | CL     | GLU    | IRON   | GGT   | ALK    | LDHL  |
|----------------------|-----|--------------|-------|-------|--------|---------|------|--------|--------|--------|-------|--------|-------|
| 88F00302             | M   | 4/1          | 14    | 13.5  | 20.1   | 550.86  | 5.1  | 0      | 106.   | 105.7  | 135.  | 7.0    | 85.0  |
| 88F00283             | M   | 4/1          | 14    | 15.8  | 16.2   | 1115.19 | 4.7  | 0      | 100.   | 101.8  | 115.  | 9.2    | 71.6  |
| 88F00284             | M   | 4/1          | 14    | 13.7  | 18.9   | 441.73  | 4.7  | 0      | 109.   | 111.9  | 203.  | 7.6    | 162.7 |
| 88F00268             | M   | 4/1          | 14    | 10.1  | 15.9   | 429.34  | 4.7  | 0      | 101.   | 102.9  | 133.  | 8.5    | 105.7 |
| 88F00269             | M   | 4/1          | 14    | 11.3  | 17.3   | 648.18  | 4.9  | 0      | 96.    | 139.6  | 140.  | 8.9    | 100.5 |
| Parameter means:     |     |              | 12.88 | 17.68 | 637.06 | 4.82    | 0.00 | 102.40 | 112.38 | 145.20 | 8.24  | 105.10 | 101.2 |
| Standard deviations: |     |              | 2.23  | 1.79  | 281.72 | 0.18    | 0.00 | 5.13   | 15.71  | 33.66  | 0.92  | 34.88  | 53.56 |
| 88F00295             | M   | 2/1          | 14    | 10.4  | 17.2   | 502.75  | 4.7  | 0      | 100.   | 119.7  | 218.  | 5.8    | 66.4  |
| 88F00289             | M   | 2/1          | 14    | 10.1  | 15.9   | 655.66  | 4.7  | 0      | 101.   | 173.0  | 156.  | 6.5    | 106.7 |
| 88F00290             | M   | 2/1          | 14    | 11.2  | 17.0   | 529.74  | 4.5  | 0      | 103.   | 104.0  | 158.  | 8.3    | 58.4  |
| 88F00279             | M   | 2/1          | 14    | 13.2  | 20.6   | 871.17  | 4.4  | 0      | 103.   | 113.3  | 104.  | 8.3    | 71.7  |
| 88F00263             | M   | 2/1          | 14    | 12.5  | 16.7   | 439.03  | 4.3  | 0      | 105.   | 94.3   | 183.  | 12.3   | 101.8 |
| Parameter means:     |     |              | 11.58 | 17.48 | 599.67 | 4.52    | 0.00 | 102.40 | 120.86 | 163.80 | 8.24  | 81.00  | 88.40 |
| Standard deviations: |     |              | 1.25  | 1.81  | 170.98 | 0.18    | 0.00 | 1.95   | 30.69  | 41.76  | 2.52  | 21.81  | 27.56 |
| 88F00280             | M   | 1/1          | 14    | 14.9  | 15.4   | 633.20  | 4.5  | 0      | 104.   | 98.7   | 182.  | 7.2    | 155.1 |
| 88F00303             | M   | 1/1          | 14    | 20.4  | 15.5   | 157.86  | 4.4  | 0      | 105.   | 113.6  | 162.  | 12.5   | 84.4  |
| 88F00254             | M   | 1/1          | 14    | 15.8  | 18.7   | 752.63  | 4.7  | 0      | 102.   | 111.4  | 165.  | 6.9    | 62.7  |
| 88F00297             | M   | 1/1          | 14    | 10.7  | 14.5   | 399.49  | 4.6  | 0      | 104.   | 106.6  | 57.   | 13.4   | 40.9  |
| Parameter means:     |     |              | 15.45 | 16.03 | 485.80 | 4.55    | 0.00 | 103.75 | 107.58 | 141.50 | 10.00 | 85.78  | 96.28 |
| Standard deviations: |     |              | 3.98  | 1.84  | 263.26 | 0.13    | 0.00 | 1.26   | 6.60   | 57.02  | 3.43  | 49.51  | 49.34 |
| 88F00300             | M   | 3/1          | 14    | 11.6  | 17.4   | 413.98  | 5.2  | 0      | 100.   | 116.4  | 107.  | 9.1    | 74.5  |
| 88F00259             | M   | 3/1          | 14    | 13.3  | 14.9   | 654.45  | 4.6  | 0      | 105.   | 92.1   | 133.  | 12.5   | 97.4  |
| 88F00292             | M   | 3/1          | 14    | 13.4  | 15.7   | 604.54  | 5.2  | 0      | 99.    | 144.0  | 120.  | 7.7    | 126.1 |
| 88F00286             | M   | 3/1          | 14    | 23.6  | 16.2   | 1505.33 | 4.8  | 0      | 107.   | 115.1  | 138.  | 7.5    | 79.0  |
| 88F00276             | M   | 3/1          | 14    | 15.8  | 16.8   | 869.01  | 4.9  | 0      | 107.   | 123.2  | 186.  | 9.7    | 105.4 |
| Parameter means:     |     |              | 15.54 | 16.20 | 809.46 | 4.94    | 0.00 | 103.60 | 118.16 | 136.80 | 9.30  | 96.48  | 123.9 |
| Standard deviations: |     |              | 4.75  | 0.97  | 421.37 | 0.26    | 0.00 | 3.85   | 18.61  | 30.03  | 2.01  | 20.90  | 84.89 |

## Appendix G (cont.): SERUM CHEMISTRY

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Expanded Statistical Table for COBAS I  
 Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

| Animal Number        | Group/<br>Subgroup | Day of<br>Study | MAG  | NA     | CAL   | PHOS | CHOL  | L |
|----------------------|--------------------|-----------------|------|--------|-------|------|-------|---|
| 88F00302 M           | 4/1                | 14              | 2.22 | 150.7  | 14.3  | 3.6  | 19.7  |   |
| 88F00283 M           | 4/1                | 14              | 1.92 | 140.9  | 14.2  | 4.2  | 19.4  |   |
| 88F00284 M           | 4/1                | 14              | 1.87 | 150.4  | 14.0  | 3.1  | 28.5  |   |
| 88F00268 M           | 4/1                | 14              | 1.99 | 143.8  | 14.2  | 4.5  | 18.0  |   |
| 88F00269 M           | 4/1                | 14              | 2.25 | 146.1  | 14.2  | 3.6  | 37.4  |   |
| Parameter means:     |                    |                 | 2.05 | 146.38 | 14.18 | 3.80 | 24.60 |   |
| Standard deviations: |                    |                 | 0.17 | 4.23   | 0.11  | 0.55 | 8.27  |   |
| 88F00295 M           | 2/1                | 14              | 1.85 | 144.3  | 14.2  | 3.9  | 30.0  |   |
| 88F00289 M           | 2/1                | 14              | 1.97 | 145.6  | 14.1  | 4.6  | 31.6  |   |
| 88F00290 M           | 2/1                | 14              | 1.85 | 145.3  | 14.3  | 3.8  | 28.0  |   |
| 88F00279 M           | 2/1                | 14              | 1.78 | 144.8  | 13.4  | 4.2  | 30.2  |   |
| 88F00263 M           | 2/1                | 14              | 1.79 | 145.2  | 14.4  | 3.1  | 17.6  |   |
| Parameter means:     |                    |                 | 1.85 | 145.04 | 14.08 | 3.92 | 27.48 |   |
| Standard deviations: |                    |                 | 0.08 | 0.50   | 0.40  | 0.55 | 5.67  |   |
| 88F00280 M           | 1/1                | 14              | 1.78 | 142.7  | 13.8  | 4.5  | 20.7  |   |
| 88F00303 M           | 1/1                | 14              | 1.80 | 147.0  | 14.1  | 3.4  | 15.3  |   |
| 88F00254 M           | 1/1                | 14              | 2.35 | 148.9  | 14.0  | 3.9  | 21.9  |   |
| 88F00297 M           | 1/1                | 14              | 2.01 | 148.8  | 14.5  | 3.7  | 64.1  |   |
| Parameter means:     |                    |                 | 1.99 | 146.85 | 14.10 | 3.88 | 30.50 |   |
| Standard deviations: |                    |                 | 0.26 | 2.90   | 0.29  | 0.46 | 22.58 |   |
| 88F00300 M           | 3/1                | 14              | 2.19 | 149.0  | 14.4  | 3.7  | 28.3  |   |
| 88F00259 M           | 3/1                | 14              | 1.99 | 147.1  | 14.7  | 3.5  | 20.1  |   |
| 88F00292 M           | 3/1                | 14              | 2.22 | 146.6  | 14.6  | 5.1  | 32.4  |   |
| 88F00286 M           | 3/1                | 14              | 2.27 | 152.8  | 14.7  | 3.9  | 18.6  |   |
| 88F00276 M           | 3/1                | 14              | 1.68 | 146.2  | 14.3  | 3.6  | 10.0  |   |
| Parameter means:     |                    |                 | 2.07 | 148.34 | 14.54 | 3.96 | -1.4  |   |
| Standard deviations: |                    |                 | 0.24 | 2.72   | 0.18  | 0.65 | 8.76  |   |

## Appendix G (cont.): SEKUM CHEMISTRY

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Expanded Statistical Table for COBAS II  
 Study Number: 88002

Study Start Date: 13 Sep-88

## ACUTE/ACUTE INTRAVENOUS

| Animal Number        | Day of Sex | Day of Subgr up | Study | CR   | ALT   | TP   | URIC | K    | TRIG   | A.G  |
|----------------------|------------|-----------------|-------|------|-------|------|------|------|--------|------|
| 88F00302 M           | 4/1        | 14              |       | 1.1  | 44.5  | 6.5  | 0    | 5.1  | 148.   | 3.8  |
| 88F00283 M           | 4/1        | 14              |       | 1.0  | 59.1  | 6.3  | 0    | 4.1  | 139.   | 2.9  |
| 88F00284 M           | 4/1        | 14              |       | .8   | 63.0  | 6.9  | .1   | 4.2  | 123.   | 2.1  |
| 88F00268 M           | 4/1        | 14              |       | 1.1  | 40.9  | 6.3  | .1   | 4.2  | 104.   | 3.0  |
| 88F00269 M           | 4/1        | 14              |       | 1.2  | 47.5  | 6.8  | 0    | 4.6  | 381.   | 2.6  |
| Parameter means:     |            |                 |       | 1.04 | 51.00 | 6.56 | 0.04 | 4.44 | 179.00 | 2.88 |
| Standard deviations: |            |                 |       | 0.15 | 9.57  | 0.28 | 0.05 | 0.42 | 114.16 | 0.62 |
| 88F00295 M           | 2/1        | 14              |       | 1.3  | 34.4  | 6.7  | 0    | 4.8  | 111.   | 2.3  |
| 88F00289 M           | 2/1        | 14              |       | 1.1  | 21.8  | 6.3  | 0    | 5.1  | 91.    | 3.0  |
| 88F00290 M           | 2/1        | 14              |       | 1.0  | 24.4  | 6.4  | 0    | 3.9  | 184.   | 2.3  |
| 88F00279 M           | 2/1        | 14              |       | 1.1  | 32.6  | 6.1  | 0    | 3.8  | 73.    | 2.5  |
| 88F00263 M           | 2/1        | 14              |       | 1.1  | 29.5  | 5.9  | 0    | 4.1  | 77.    | 2.7  |
| Parameter means:     |            |                 |       | 1.12 | 28.54 | 6.28 | 0.00 | 4.34 | 107.20 | 2.56 |
| Standard deviations: |            |                 |       | 0.11 | 5.35  | 0.30 | 0.00 | 0.58 | 45.3   | 0.30 |
| 88F00280 M           | 1/1        | 14              |       | 1.1  | 35.9  | 6.5  | .1   | 3.5  | 56.    | 2.3  |
| 88F00303 M           | 1/1        | 14              |       | 1.1  | 34.8  | 6.0  | 0    | 4.4  | 74.    | 2.7  |
| 88F00254 M           | 1/1        | 14              |       | 1.3  | 33.7  | 6.5  | 0    | 4.9  | 93.    | 2.7  |
| 88F00297 M           | 1/1        | 14              |       | 1.1  | 41.0  | 6.9  | 0    | 4.6  | 107.   | 2.0  |
| Parameter means:     |            |                 |       | 1.15 | 36.35 | 6.47 | 0.03 | 4.35 | 82.50  | 2.43 |
| Standard deviations: |            |                 |       | 0.10 | 3.23  | 0.37 | 0.05 | 0.60 | 22.25  | 0.34 |
| 88F00300 M           | 3/1        | 14              |       | 1.1  | 57.6  | 6.9  | 0    | 4.5  | 172.   | 3.1  |
| 88F00259 M           | 3/1        | 14              |       | 1.1  | 36.6  | 6.6  | 0    | 4.4  | 72.    | 2.2  |
| 88F00292 M           | 3/1        | 14              |       | 1.3  | 27.3  | 7.0  | 0    | 4.9  | 172.   | 2.8  |
| 88F00286 M           | 3/1        | 14              |       | 1.4  | 36.3  | 6.4  | 0    | 3.8  | 101.   | 2.9  |
| 88F00276 M           | 3/1        | 14              |       | .9   | 39.7  | 6.4  | 0    | 4.4  | 91.    | 3.2  |
| Parameter means:     |            |                 |       | 1.16 | 39.50 | 6.66 | 0.00 | 4.40 | 121.60 | 2.84 |
| Standard deviations: |            |                 |       | 0.19 | 11.13 | 0.28 | 0.00 | 0.39 | 47.17  | 0.39 |

## Appendix G (cont.): SERUM CHEMISTRY

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Expanded Statistical Table for COBAS I  
 Study Number: 88002

Study Start Date: 13-Sep-88

PRINTED: 17-Jan-89  
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ACUTE/ACUTE INTRAVENOUS

| Animal Number        | Group | Day of Study | AST   | BUN   | CK      | ALB  | BIL  | CL     | GLU    | IRON   | GGT  | ALK   | LDHL   |
|----------------------|-------|--------------|-------|-------|---------|------|------|--------|--------|--------|------|-------|--------|
| 88F00346 F           | 4/2   | 14           | 12.0  | 23.9  | 497.08  | 4.6  | .03  | 107.   | 123.4  | 152.   | 8.2  | 71.8  | 74.9   |
| 88F00351 F           | 4/2   | 14           | 11.4  | 22.7  | 593.37  | 5.2  | 0    | 110.   | 123.6  | 198.   | 8.1  | 92.1  | 148.4  |
| 88F00325 F           | 4/2   | 14           | 9.7   | 17.8  | 413.97  | 4.7  | 0    | 107.   | 110.3  | 228.   | 7.7  | 86.3  | 84.1   |
| 88F00307 F           | 4/2   | 14           | 28.8  | 21.4  | 576.02  | 5.1  | 0    | 118.   | 133.8  | 255.   | 4.0  | 95.2  | 202.4  |
| 88F00340 F           | 4/2   | 14           | 18.3  | 26.8  | 1184.74 | 5.4  | 0    | 111.   | 108.5  | 227.   | 6.9  | 90.8  | 191.0  |
| Parameter means:     |       |              | 16.04 | 22.52 | 653.04  | 5.00 | 0.01 | 110.60 | 119.92 | 212.00 | 6.98 | 87.24 | 140.16 |
| Standard deviations: |       |              | 7.84  | 3.31  | 305.65  | 0.34 | 0.01 | 4.51   | 10.50  | 39.13  | 1.74 | 9.21  | 59.01  |
| 88F00334 F           | 2/2   | 14           | 14.0  | 22.3  | 1240.52 | 4.4  | 0    | 111.   | 99.7   | 182.   | 8.1  | 43.9  | 259.2  |
| 88F00322 F           | 2/2   | 14           | 12.3  | 21.8  | 497.55  | 4.6  | 0    | 105.   | 112.2  | 142.   | 9.3  | 39.7  | 98.3   |
| 88F00353 F           | 2/2   | 14           | 13.6  | 28.0  | 584.07  | 5.0  | 0    | 111.   | 108.4  | 188.   | 8.2  | 36.1  | 152.2  |
| 88F00333 F           | 2/2   | 14           | 11.5  | 25.4  | 943.55  | 4.7  | 0    | 115.   | 103.3  | 164.   | 7.2  | 66.6  | 158.1  |
| 88F00318 F           | 2/2   | 14           | 14.3  | 20.5  | 1092.03 | 4.7  | 0    | 108.   | 114.8  | 179.   | 5.5  | 46.8  | 193.2  |
| Parameter means:     |       |              | 13.14 | 23.60 | 871.54  | 4.68 | 0.00 | 110.00 | 107.68 | 171.00 | 7.66 | 46.62 | 172.20 |
| Standard deviations: |       |              | 1.19  | 3.05  | 321.11  | 0.22 | 0.00 | 3.74   | 6.21   | 18.47  | 1.42 | 11.89 | 59.31  |
| 88F00331 F           | 1/2   | 14           | 16.7  | 14.3  | 733.28  | 4.8  | 0    | 105.   | 107.4  | 124.   | 10.1 | 79.4  | 138.2  |
| 88F00327 F           | 1/2   | 14           | 8.4   | 21.3  | 298.47  | 5.2  | 0    | 103.   | 96.7   | 142.   | 8.5  | 102.6 | 53.0   |
| 88F00341 F           | 1/2   | 14           | 16.3  | 18.8  | 538.60  | 4.5  | 0    | 110.   | 120.9  | 140.   | 9.6  | 55.3  | 93.8   |
| 88F00305 F           | 1/2   | 14           | 14.4  | 27.6  | 639.79  | 4.7  | 0    | 109.   | 114.2  | 188.   | 5.3  | 59.6  | 117.1  |
| Parameter means:     |       |              | 14.45 | 20.50 | 552.53  | 4.80 | 0.00 | 106.75 | 109.80 | 148.50 | 8.38 | 74.22 | 100.53 |
| Standard deviations: |       |              | 4.40  | 5.55  | 187.11  | 0.29 | 0.00 | 3.30   | 10.33  | 27.54  | 2.16 | 21.63 | 36.51  |
| 88F00319 F           | 3/2   | 14           | 40.8  | 22.8  | 1331.46 | NT   | 0    | 116.   | 102.3  | 298.   | 2.3  | 121.7 | 983.7  |
| 88F00304 F           | 3/2   | 14           | 9.1   | 20.1  | 347.10  | 4.6  | 0    | 112.   | 108.6  | 117.   | 4.0  | 40.3  | 39.8   |
| 88F00326 F           | 3/2   | 14           | 6.5   | 19.7  | 294.71  | 4.9  | 0    | 111.   | 115.0  | 153.   | 5.3  | 27.7  | 52.3   |
| 88F00312 F           | 3/2   | 14           | 13.4  | 21.8  | 513.93  | 5.1  | 0    | 108.   | 132.4  | 234.   | 4.1  | 78.8  | 144.7  |
| 88F00321 F           | 3/2   | 14           | 16.2  | 20.0  | 687.08  | 5.3  | 0    | 107.   | 119.1  | 209.   | 6.8  | 142.6 | 145.9  |
| Parameter means:     |       |              | 17.20 | 20.88 | 634.86  | 4.98 | 0.00 | 110.80 | 115.48 | 202.20 | 4.50 | 82.22 | 273.28 |
| Standard deviations: |       |              | 13.72 | 1.35  | 418.66  | 0.30 | 0.00 | 3.56   | 11.41  | 70.56  | 1.67 | 49.86 | 400.25 |

## Appendix G (cont.) : SERUM CHEMISTRY

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Expanded Statistical Table for COBAS I  
 Study Number: 88002

Study Start Date: 13-Sep-88

PRINTED: 17-Jan-89  
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ACUTE/ACUTE INTRAVENOUS

| Animal Number | Group / Sex          | Day of Study | MAG  | NA     | CAL   | PHOS | CHOL  | L    |
|---------------|----------------------|--------------|------|--------|-------|------|-------|------|
| 88F00346      | F                    | 4/2          | 14   | 1.76   | 140.1 | 14.3 | 3.4   | 79.5 |
| 88F00351      | F                    | 4/2          | 14   | 1.87   | 142.8 | 13.9 | 3.6   | 49.4 |
| 88F00325      | F                    | 4/2          | 14   | 2.00   | 141.2 | 13.9 | 3.7   | 51.9 |
| 88F00307      | F                    | 4/2          | 14   | 2.31   | 147.6 | 14.4 | 4.7   | 40.6 |
| 88F00340      | F                    | 4/2          | 14   | 1.81   | 144.7 | 14.3 | 3.9   | 54.2 |
|               | Parameter means:     |              | 1.95 | 143.28 | 14.16 | 3.86 | 55.12 |      |
|               | Standard deviations: |              | 0.22 | 2.97   | 0.24  | 0.50 | 14.57 |      |
| 88F00334      | F                    | 2/2          | 14   | 2.15   | 143.0 | 13.9 | 3.1   | 38.3 |
| 88F00322      | F                    | 2/2          | 14   | 2.16   | 146.5 | 6.9  | 4.1   | 72.4 |
| 88F00353      | F                    | 2/2          | 14   | 1.65   | 145.4 | 13.7 | 2.8   | 56.4 |
| 88F00333      | F                    | 2/2          | 14   | 1.90   | 148.7 | 13.7 | 3.2   | 61.8 |
| 88F00318      | F                    | 2/2          | 14   | 1.94   | 142.0 | 14.0 | 3.1   | 74.9 |
|               | Parameter means:     |              | 1.96 | 145.12 | 12.44 | 3.26 | 60.76 |      |
|               | Standard deviations: |              | 0.21 | 2.69   | 3.10  | 0.49 | 14.66 |      |
| 88F00331      | F                    | 1/2          | 14   | 2.12   | 139.9 | 13.5 | 4.0   | 71.0 |
| 88F00327      | F                    | 1/2          | 14   | 2.01   | 142.9 | 14.8 | 4.2   | 71.9 |
| 88F00341      | F                    | 1/2          | 14   | 1.85   | 147.3 | 13.5 | 3.5   | 84.5 |
| 88F00305      | F                    | 1/2          | 14   | 2.05   | 140.9 | 13.7 | 4.0   | 57.8 |
|               | Parameter means:     |              | 2.01 | 142.75 | 13.88 | 3.92 | 71.30 |      |
|               | Standard deviations: |              | 0.11 | 3.28   | 0.62  | 0.30 | 10.91 |      |
| 88F00319      | F                    | 3/2          | 14   | 2.40   | 144.3 | 14.1 | 3.6   | 77.8 |
| 88F00304      | F                    | 3/2          | 14   | 1.74   | 145.7 | 14.3 | 3.2   | 80.1 |
| 88F00326      | F                    | 3/2          | 14   | 2.04   | 146.7 | 14.3 | 3.7   | 41.3 |
| LJF00312      | F                    | 3/2          | 14   | 2.16   | 147.1 | 14.6 | 3.9   | 38.7 |
| 88F00321      | F                    | 3/2          | 14   | 2.03   | 145.6 | 14.8 | 4.0   | 38.7 |
|               | Parameter means:     |              | 2.07 | 145.88 | 14.42 | 3.68 | 55.32 |      |
|               | Standard deviations: |              | 0.24 | 1.09   | 0.28  | 0.31 | 21.61 |      |

## Appendix G (cont.): SERUM CHEMISTRY

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Expanded Statistical Table for COBAS II

Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

| Animal Number        | Group/ Day of Study | Sex | Subgroup | CR   | ALT   | TP   | URIC | K    | TRIG   | A-G  |
|----------------------|---------------------|-----|----------|------|-------|------|------|------|--------|------|
| 88F00346             | F                   | 4/2 | 14       | 1.1  | 49.0  | 6.7  | .1   | 4.8  | 58.    | 2.1  |
| 88F00351             | F                   | 4/2 | 14       | 1.1  | 36.2  | 6.7  | .1   | 4.6  | 85.    | 3.6  |
| 88F00325             | F                   | 4/2 | 14       | 1.0  | 31.0  | 6.4  | .1   | 3.9  | 33.    | 2.9  |
| 88F00307             | F                   | 4/2 | 14       | 1.2  | 58.2  | 6.7  | .0   | 5.9  | 114.   | 3.2  |
| 88F00340             | F                   | 4/2 | 14       | 1.0  | 53.4  | 7.0  | .0   | 4.2  | 61.    | 3.3  |
| Parameter means:     |                     |     |          | 1.08 | 45.56 | 6.70 | 0.06 | 4.68 | 70.20  | 3.02 |
| Standard deviations: |                     |     |          | 0.08 | 11.54 | 0.21 | 0.05 | 0.77 | 30.64  | 0.57 |
| 88F00334             | F                   | 2/2 | 14       | 1.3  | 28.7  | 6.9  | .0   | 4.7  | 58.    | 1.7  |
| 88F00322             | F                   | 2/2 | 14       | 1.4  | 32.2  | 6.8  | .0   | 4.8  | 78.    | 2.1  |
| 88F00353             | F                   | 2/2 | 14       | 1.2  | 34.1  | 6.9  | .1   | 4.9  | 102.   | 2.6  |
| 88F00333             | F                   | 2/2 | 14       | 1.0  | 29.8  | 6.3  | .1   | 4.4  | 42.    | 3.0  |
| 88F00318             | F                   | 2/2 | 14       | 1.1  | 36.5  | 6.3  | .0   | 4.4  | 58.    | 2.9  |
| Parameter means:     |                     |     |          | 1.20 | 32.26 | 6.64 | 0.04 | 4.64 | 67.60  | 2.46 |
| Standard deviations: |                     |     |          | 0.16 | 3.17  | 0.31 | 0.05 | 0.23 | 23.08  | 0.55 |
| 88F00331             | F                   | 1/2 | 14       | 1.2  | 33.8  | 6.4  | .1   | 3.8  | 49.    | 2.9  |
| 88F00327             | F                   | 1/2 | 14       | 1.0  | 27.0  | 6.8  | .1   | 4.3  | 72.    | 3.3  |
| 88F00361             | F                   | 1/2 | 14       | 1.0  | 66.6  | 7.1  | .1   | 4.5  | 99.    | 1.8  |
| 88F00305             | F                   | 1/2 | 14       | 1.4  | 46.4  | 6.4  | 0    | 4.6  | 79.    | 2.8  |
| Parameter means:     |                     |     |          | 1.15 | 43.45 | 6.68 | 0.08 | 4.30 | 74.75  | 2.70 |
| Standard deviations: |                     |     |          | 0.19 | 17.40 | 3.34 | 0.05 | 0.36 | 20.63  | 0.64 |
| 88F00319             | F                   | 3/2 | 14       | .8   | 34.0  | NT   | .1   | 6.9  | 205.   | NT   |
| 88F00304             | F                   | 3/2 | 14       | 1.4  | 32.7  | 7.4  | 0    | 4.4  | 59.    | 1.6  |
| 88F00326             | F                   | 3/2 | 14       | 1.2  | 32.7  | 7.0  | 0    | 4.5  | 42.    | 2.4  |
| 88F00312             | F                   | 3/2 | 14       | 1.1  | 25.5  | 7.0  | 0    | 4.4  | 91.    | 2.8  |
| 88F00321             | F                   | 3/2 | 14       | 1.0  | 56.5  | 6.5  | 0    | 4.8  | 135.   | 4.5  |
| Parameter means:     |                     |     |          | 1.10 | 36.28 | 6.98 | 0.02 | 5.00 | 106.40 | 2.83 |
| Standard deviations: |                     |     |          | 0.22 | 11.79 | 3.37 | 0.04 | 1.07 | 65.52  | 1.22 |

**Appendix H: HEMATOLOGY****List of Hematology Abbreviations/Units**

|      |   |
|------|---|
| RBC  | Erythrocytes ( $\times 10^6/\mu\text{l}$ )          |
| HGB  | Hemoglobin (g/dl)                                   |
| HCT  | Hematocrit (%)                                      |
| MCV  | Mean Corpuscular Volume (femtoliters)               |
| MCH  | Mean Corpuscular Hemoglobin (picograms)             |
| MCHC | Mean Corpuscular Hemoglobin Concentration (g/dl)    |
| RET  | Reticulocytes (%)                                   |
| WBC  | Total Leukocyte Count ( $\times 10^3/\mu\text{l}$ ) |
| SEG  | Polymorphonuclear Granulocytes (%)                  |
| BAN  | Immature Neutrophils (%)                            |
| EOS  | Eosinophils (%)                                     |
| BAS  | Basophils (%)                                       |
| LYM  | Lymphocytes (%)                                     |
| MON  | Monocytes (%)                                       |
| PLT  | Platelets ( $\times 10^3/\mu\text{l}$ )             |
| NRBC | Nucleated Red Blood Cell (#/100 WBC)                |
| PT   | Prothrombin Time (Seconds)                          |
| APPT | Activated Partial Thromboplastin Time (Seconds)     |

## Appendix H (cont.) : HEMATOLOGY

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

EXPANDED STATISTICAL TABLE FOR BAKER I  
 STUDY NUMBER: 88002

STUDY START DATE: 13 Sep 88

ACUTE/ACUTE INTRAVENOUS

| ANIMAL NUMBER        | SEX | GROUP / SUBGROUP | DAY OF STUDY | WBC  | RBC  | HGB   | HCT   | MCV   | MCH   | MCHC  | PLT    |
|----------------------|-----|------------------|--------------|------|------|-------|-------|-------|-------|-------|--------|
| 88F00261             | M   | 4/1              | 4            | 6.8  | 5.48 | 11.7  | 36.3  | 66.3  | 21.4  | 32.2  | 259.   |
| 88F00296             | M   | 4/1              | 4            | 4.6  | 5.77 | 12.4  | 38.3  | 66.3  | 21.5  | 32.4  | 94.    |
| 88F00277             | M   | 4/1              | 4            | 1.2  | 5.92 | 11.7  | 38.1  | 64.3  | 19.8  | 30.4  | 402.   |
| 88F00287             | M   | 4/1              | 4            | 4.9  | 6.17 | 13.6  | 40.5  | 65.7  | 22.0  | 33.6  | 307.   |
| 88F00281             | M   | 4/1              | 4            | 2.5  | 5.39 | 11.3  | 35.1  | 65.1  | 21.0  | 32.2  | 249.   |
| PARAMETER MEANS:     |     |                  |              | 4.00 | 5.75 | 12.14 | 37.66 | 65.54 | 21.14 | 32.22 | 262.20 |
| STANDARD DEVIATIONS: |     |                  |              | 2.19 | 0.32 | 0.91  | 2.07  | 0.85  | 0.83  | 1.03  | 111.83 |
| 88F00274             | M   | 2/1              | 4            | 4.2  | 5.24 | 11.1  | 34.3  | 65.4  | 21.2  | 32.4  | 358.   |
| 88F00258             | M   | 2/1              | 4            | 5.6  | 5.64 | 12.4  | 38.6  | 68.5  | 22.0  | 32.1  | 308.   |
| 88F00285             | M   | 2/1              | 4            | 5.3  | 5.77 | 12.6  | 40.4  | 70.0  | 21.8  | 31.2  | 439.   |
| 88F00260             | M   | 2/1              | 4            | 5.5  | 4.96 | 11.4  | 34.8  | 70.2  | 23.0  | 32.8  | 423.   |
| 88F00293             | M   | 2/1              | 4            | 4.9  | 5.55 | 11.3  | 35.8  | 64.5  | 20.4  | 31.6  | 151.   |
| PARAMETER MEANS:     |     |                  |              | 5.10 | 5.43 | 11.76 | 36.78 | 67.72 | 21.68 | 32.02 | 335.80 |
| STANDARD DEVIATIONS: |     |                  |              | 0.57 | 0.33 | 0.69  | 2.62  | 2.63  | 0.97  | 0.63  | 115.83 |
| 88F00298             | M   | 1/1              | 4            | 2.9  | 5.17 | 10.8  | 33.5  | 64.8  | 20.9  | 32.2  | 381.   |
| 88F00257             | M   | 1/1              | 4            | 5.6  | 4.63 | 10.7  | 32.8  | 70.8  | 23.1  | 32.6  | 500.   |
| PARAMETER MEANS:     |     |                  |              | 4.25 | 4.90 | 10.75 | 33.15 | 67.80 | 22.00 | 32.40 | 440.50 |
| STANDARD DEVIATIONS: |     |                  |              | 1.91 | 0.38 | 0.07  | 0.49  | 4.24  | 1.56  | 0.28  | 84.15  |
| 88F00273             | M   | 3/1              | 4            | 5.6  | 6.28 | 11.6  | 40.5  | 64.5  | 18.5  | 28.6  | 558.   |
| 88F00294             | M   | 3/1              | 4            | 2.6  | 5.62 | 12.1  | 37.8  | 67.3  | 21.5  | 32.0  | 1030.  |
| 88F00265             | M   | 3/1              | 4            | 6.3  | 6.49 | 13.0  | 43.9  | 67.7  | 20.0  | 29.6  | 446.   |
| 88F00266             | M   | 3/1              | 4            | 3.7  | 5.93 | 12.1  | 40.0  | 67.5  | 20.4  | 30.3  | 353.   |
| 88F00267             | M   | 3/1              | 4            | 4.0  | 6.04 | 13.3  | 40.6  | 67.3  | 22.0  | 32.8  | 293.   |
| PARAMETER MEANS:     |     |                  |              | 4.44 | 6.07 | 12.42 | 40.56 | 66.86 | 20.48 | 30.66 | 536.00 |
| STANDARD DEVIATIONS: |     |                  |              | 1.49 | 0.33 | 0.70  | 2.18  | 1.33  | 1.37  | 1.72  | 293.75 |

PRINTED: 05-Jan-89  
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## **Appendix H (cont.): HEMATOLOGY**

LETTERMAN ARMY INSTITUTE OF RESEARCH  
DIV OF RES SUPP., PATH SERV GP  
PRESIDIO OF SAN FRANCISCO, CA 94129  
RABBIT/NEW ZEALAND WHITE

**EXPANDED STATISTICAL TABLE FOR WBC DIFFERENTIAL COUNTS**

STUDY START DATE: 13-SEP-88

ACUTE/ACUTE INTRAVENOUS

| ANIMAL<br>NUMBER     | GROUP/<br>SEX | DAY OF<br>STUDY | SEG   | BAN  | EOS  | BAS  | LYM   | MON  | ATL  | NRBC | PT   | APPT  | RET  |
|----------------------|---------------|-----------------|-------|------|------|------|-------|------|------|------|------|-------|------|
| 88F00261             | M             | 4/1             | 4     | 40   | 0    | 0    | 0     | 54   | 0    | 6    | 1    | NT    | 1.9  |
| 88F00296             | M             | 4/1             | 4     | 69   | 0    | 2    | 1     | 17   | 6    | 5    | 2    | NT    | 1.5  |
| 88F00277             | M             | 4/1             | 4     | 53   | 0    | 0    | 5     | 37   | 1    | 4    | 1    | NT    | 5.5  |
| 88F00287             | M             | 4/1             | 4     | 53   | 0    | 5    | 6     | 26   | 1    | 7    | 5    | 9.5   | 34.5 |
| 88F00281             | M             | 4/1             | 4     | 63   | 0    | 3    | 0     | 27   | 3    | 4    | 8    | NT    | 4.7  |
| PARAMETER MEANS:     |               |                 | 55.60 | 0.00 | 2.00 | 2.40 | 32.60 | 2.20 | 5.20 | 3.40 | 9.50 | 34.50 | 3.54 |
| STANDARD DEVIATIONS: |               |                 | 11.08 | 0.00 | 2.12 | 2.88 | 13.90 | 2.39 | 1.30 | 3.05 | -    | -     | 1.76 |
| 88F00274             | M             | 2/1             | 4     | 32   | 0    | 2    | 4     | 54   | 3    | 5    | 5    | NT    | 1.5  |
| 88F00258             | M             | 2/1             | 4     | 37   | 0    | 3    | 1     | 51   | 0    | 8    | 5    | NT    | 2.1  |
| 88F00285             | M             | 2/1             | 4     | 28   | 0    | 3    | 4     | 52   | 2    | 11   | 8    | NT    | 1.9  |
| 88F00260             | M             | 2/1             | 4     | 53   | 0    | 4    | 2     | 38   | 0    | 3    | 10   | NT    | 5.8  |
| 88F00293             | M             | 2/1             | 4     | 59   | 0    | 2    | 4     | 29   | 3    | 3    | 2    | NT    | 2.1  |
| PARAMETER MEANS:     |               |                 | 41.80 | 0.00 | 2.80 | 3.00 | 44.80 | 1.60 | 6.00 | 6.00 | -    | -     | 2.68 |
| STANDARD DEVIATIONS: |               |                 | 13.52 | 0.00 | 0.84 | 1.41 | 10.85 | 1.52 | 3.46 | 3.08 | -    | -     | 1.76 |
| 88F00298             | M             | 1/1             | 4     | 32   | 0    | 4    | 0     | 60   | 3    | 1    | 4    | NT    | 1.5  |
| 88F00257             | M             | 1/1             | 4     | 35   | 0    | 3    | 1     | 57   | 1    | 3    | 4    | NT    | 0    |
| PARAMETER MEANS:     |               |                 | 33.50 | 0.00 | 3.50 | 0.50 | 58.50 | 2.00 | 2.00 | 4.00 | -    | -     | 0.75 |
| STANDARD DEVIATIONS: |               |                 | 2.12  | 0.00 | 0.71 | 0.71 | 2.12  | 1.41 | 1.41 | 0.00 | -    | -     | 1.06 |
| 88F00273             | M             | 3/1             | 4     | 75   | 0    | 1    | 2     | 18   | 1    | 3    | 10   | NT    | 3.0  |
| 88F00294             | M             | 3/1             | 4     | 9    | 0    | 0    | 1     | 85   | 3    | 4    | 1    | NT    | 2.6  |
| 88F00265             | M             | 3/1             | 4     | 67   | 0    | 3    | 1     | 14   | 5    | 10   | 8    | NT    | 3.5  |
| 88F00266             | M             | 3/1             | 4     | 52   | 0    | 2    | 8     | 29   | 0    | 9    | 8    | NT    | 4.5  |
| 88F00267             | M             | 3/1             | 4     | 74   | 0    | 1    | 1     | 20   | 3    | 1    | 8    | NT    | 2.1  |
| PARAMETER MEANS:     |               |                 | 55.40 | 0.00 | 1.40 | 2.60 | 33.20 | 2.40 | 5.40 | 7.00 | -    | -     | 3.14 |
| STANDARD DEVIATIONS: |               |                 | 27.52 | 0.00 | 1.14 | 3.05 | 29.47 | 1.95 | 3.91 | 3.46 | -    | -     | 0.92 |



## Appendix H (cont.): HEMATOLOGY

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

EXPANDED STATISTICAL TABLE FOR WBC DIFFERENTIAL COUNTS  
 STUDY NUMBER: 88002

STUDY START DATE: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

| ANIMAL<br>NUMBER     | GROUP/<br>SEX | DAY OF<br>SUBGROUP STUDY | SEG | BAN   | EOS  | BAS  | LYM  | MON   | ATL  | NRBC | PT   | APLT | RET   |
|----------------------|---------------|--------------------------|-----|-------|------|------|------|-------|------|------|------|------|-------|
| 88F00323             | F             | 4/2                      | 4   | 44.   | 0.   | 1.   | 3.   | 46.   | 2.   | 4.   | 0.   | NT   | 4.7   |
| 88F00330             | F             | 4/2                      | 4   | 47.   | 0.   | 2.   | 3.   | 43.   | 1.   | 4.   | 0.   | 7.0  | 4.5   |
| 88F00352             | F             | 4/2                      | 4   | 31.   | 0.   | 3.   | 0.   | 63.   | 2.   | 1.   | 0.   | NT   | 2.7   |
| PARAMETER MEANS:     |               |                          |     | 40.67 | 0.00 | 2.00 | 0.00 | 50.67 | 1.67 | 3.00 | 0.00 | 7.00 | 3.97  |
| STANDARD DEVIATIONS: |               |                          |     | 8.50  | 0.00 | 1.00 | 1.73 | 10.79 | 0.58 | 1.73 | 0.00 | -    | 1.10  |
| 88F00313             | F             | 2/2                      | 4   | 26.   | 0.   | 0.   | 67.  | 2.    | 5.   | 0.   | NT   | NT   | 3.7   |
| 88F00335             | F             | 2/2                      | 4   | 49.   | 0.   | 2.   | 5.   | 42.   | 2.   | 0.   | 0.   | 6.8  | 47.5  |
| 88F00337             | F             | 2/2                      | 4   | 32.   | 0.   | 0.   | 0.   | 67.   | 0.   | 1.   | 0.   | 6.5  | 41.1  |
| 88F00349             | F             | 2/2                      | 4   | 31.   | 0.   | 3.   | 2.   | 61.   | 2.   | 1.   | 0.   | NT   | 4.5   |
| PARAMETER MEANS:     |               |                          |     | 34.50 | 0.00 | 1.25 | 1.75 | 59.25 | 1.50 | 1.75 | 0.00 | 6.65 | 44.30 |
| STANDARD DEVIATIONS: |               |                          |     | 10.02 | 0.00 | 1.50 | 2.36 | 11.84 | 1.00 | 2.22 | 0.00 | 0.21 | 4.53  |
| 88F00345             | F             | 1/2                      | 4   | 20.   | 0.   | 0.   | 4.   | 76.   | 0.   | 0.   | 0.   | NT   | NT    |
| 88F00348             | F             | 1/2                      | 4   | 54.   | 0.   | 0.   | 2.   | 41.   | 1.   | 2.   | 0.   | NT   | 3.4   |
| 88F00310             | F             | 1/2                      | 4   | 22.   | 0.   | 1.   | 0.   | 66.   | 3.   | 8.   | 0.   | NT   | 4.5   |
| PARAMETER MEANS:     |               |                          |     | 32.00 | 0.00 | 0.33 | 2.00 | 61.00 | 1.33 | 3.33 | 0.00 | -    | 4.23  |
| STANDARD DEVIATIONS: |               |                          |     | 19.08 | 0.00 | 0.58 | 2.00 | 18.03 | 1.53 | 4.16 | 0.00 | -    | 0.74  |
| 88F00311             | F             | 3/2                      | 4   | 46.   | 0.   | 2.   | 0.   | 39.   | 2.   | 11.  | 0.   | NT   | 2.0   |
| 88F00314             | F             | 3/2                      | 4   | 49.   | 0.   | 0.   | 0.   | 48.   | 2.   | 1.   | 0.   | NT   | 4.0   |
| 88F00347             | F             | 3/2                      | 4   | 30.   | 0.   | 1.   | 3.   | 58.   | 5.   | 3.   | 0.   | NT   | 2.2   |
| PARAMETER MEANS:     |               |                          |     | 41.67 | 0.00 | 1.00 | 0.00 | 48.33 | 3.00 | 5.00 | 0.00 | -    | 2.73  |
| STANDARD DEVIATIONS: |               |                          |     | 10.21 | 0.00 | 1.00 | 1.73 | 9.50  | 1.73 | 5.29 | 0.00 | -    | 1.10  |

## Appendix H (cont.) : HEMATOLOGY

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

EXPANDED STATISTICAL TABLE FOR BAKER I  
 STUDY NUMBER: 880002

STUDY START DATE: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

| ANIMAL<br>NUMBER     | GROUP /<br>SEX | DAY OF<br>SUBGROUP | STUDY | WBC   | RBC  | HGB   | HCT   | MCV   | MCH   | MCHC  | PLT    |
|----------------------|----------------|--------------------|-------|-------|------|-------|-------|-------|-------|-------|--------|
| 88F00302             | M              | 4/1                | 14    | 5.9   | 6.29 | 13.6  | 41.5  | 66.0  | 21.6  | 33.8  | 417.   |
| 88F00283             | M              | 4/1                | 14    | 9.3   | 6.28 | 14.1  | 41.7  | 66.4  | 22.5  | 33.8  | 368.   |
| 88F00284             | M              | 4/1                | 14    | 5.4   | 5.19 | 11.5  | 35.0  | 67.4  | 22.2  | 32.9  | 191.   |
| 88F00268             | M              | 4/1                | 14    | 8.8   | 6.71 | 14.8  | 43.2  | 64.4  | 22.1  | 34.3  | 313.   |
| 88F00269             | M              | 4/1                | 14    | 8.2   | 5.87 | 13.7  | 41.3  | 70.3  | 23.3  | 33.2  | 260.   |
| PARAMETER MEANS:     |                |                    |       | 7.52  | 6.07 | 13.54 | 40.54 | 66.90 | 22.34 | 33.60 | 309.80 |
| STANDARD DEVIATIONS: |                |                    |       | 1.76  | 0.57 | 1.23  | 3.19  | 2.19  | 0.63  | 0.55  | 88.72  |
| 88F00295             | M              | 2/1                | 14    | 4.2   | 4.27 | 10.2  | 30.2  | 70.7  | 23.9  | 33.8  | 140.   |
| 88F00289             | M              | 2/1                | 14    | 6.4   | 6.40 | 13.3  | 40.3  | 63.0  | 20.8  | 33.0  | 214.   |
| 88F00290             | M              | 2/1                | 14    | 10.0  | 6.17 | 14.0  | 41.4  | 67.1  | 22.7  | 33.8  | 306.   |
| 88F00279             | M              | 2/1                | 14    | 9.1   | 5.33 | 12.4  | 37.1  | 69.6  | 23.3  | 33.4  | 272.   |
| 88F00263             | M              | 2/1                | 14    | 9.3   | 6.09 | 14.0  | 41.7  | 68.4  | 23.0  | 33.6  | 298.   |
| PARAMETER MEANS:     |                |                    |       | 7.80  | 5.65 | 12.78 | 38.14 | 67.76 | 22.74 | 33.52 | 246.00 |
| STANDARD DEVIATIONS: |                |                    |       | 2.43  | 0.87 | 1.58  | 4.80  | 2.98  | 1.17  | 0.33  | 69.35  |
| 88F00280             | M              | 1/1                | 14    | 9.3   | 5.34 | 12.8  | 38.2  | 71.5  | 24.0  | 33.5  | 241.   |
| 88F00303             | M              | 1/1                | 14    | 8.3   | 6.29 | 14.3  | 42.7  | 67.9  | 22.7  | 33.5  | 318.   |
| 88F00254             | M              | 1/1                | 14    | 10.4  | 5.97 | 14.7  | 41.8  | 70.1  | 24.6  | 35.2  | 424.   |
| 88F00297             | M              | 1/1                | 14    | 14.6  | 6.72 | 15.6  | 46.4  | 69.0  | 23.2  | 33.6  | 388.   |
| PARAMETER MEANS:     |                |                    |       | 10.65 | 6.08 | 14.35 | 42.28 | 69.63 | 23.63 | 33.95 | 342.75 |
| STANDARD DEVIATIONS: |                |                    |       | 2.77  | 0.58 | 1.17  | 3.37  | 1.54  | 0.84  | 0.83  | 80.86  |
| 88F00300             | M              | 3/1                | 14    | 8.1   | 6.06 | 13.7  | 41.3  | 68.2  | 22.6  | 33.2  | 321.   |
| 88F00259             | M              | 3/1                | 14    | 7.6   | 5.77 | 13.6  | 40.4  | 70.1  | 23.6  | 33.7  | 195.   |
| 88F00292             | M              | 3/1                | 14    | 7.5   | 6.11 | 13.2  | 39.5  | 64.6  | 21.6  | 33.4  | 293.   |
| 88F00286             | M              | 3/1                | 14    | 7.5   | 6.98 | 14.7  | 44.5  | 63.7  | 21.1  | 33.0  | 409.   |
| 88F00276             | M              | 3/1                | 14    | 11.3  | 5.24 | 12.1  | 36.8  | 70.2  | 23.1  | 32.9  | 395.   |
| PARAMETER MEANS:     |                |                    |       | 8.40  | 6.03 | 13.46 | 40.50 | 67.36 | 22.40 | 33.24 | 322.60 |
| STANDARD DEVIATIONS: |                |                    |       | 1.64  | 0.63 | 0.94  | 2.80  | 3.05  | 1.04  | 0.32  | 86.41  |

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## Appendix H (cont.) : HEMATOLOGY

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP., PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

EXPANDED STATISTICAL TABLE FOR WBC DIFFERENTIAL COUNTS  
 STUDY NUMBER: 88002

STUDY START DATE: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

| ANIMAL<br>NUMBER     | GROUP /<br>SEX | DAY OF<br>SUBGROUP STUDY | SEG  | BAN  | EOS  | BAS   | LYM  | MON  | ATL  | NRBC | PT    | APTT | RET |
|----------------------|----------------|--------------------------|------|------|------|-------|------|------|------|------|-------|------|-----|
| 88F00302 M           | 4/1            | 14                       | 43.  | 0.   | 4.   | 7.    | 40.  | 2.   | 4.   | 5.   | 1.7   | 19.5 | 3.9 |
| 88F00283 M           | 4/1            | 14                       | 43.  | 0.   | 3.   | 0.    | 42.  | 4.   | 8.   | 0.   | NT    | NT   | 3.1 |
| 88F00284 M           | 4/1            | 14                       | 16.  | 1.   | 1.   | 3.    | 75.  | 2.   | 2.   | 0.   | 8.0   | 17.7 | 3.9 |
| 88F00268 M           | 4/1            | 14                       | 19.  | 0.   | 0.   | 2.    | 57.  | 2.   | 3.   | 4.   | NT    | NT   | 4.1 |
| 88F00269 M           | 4/1            | 14                       | 24.  | 0.   | 1.   | 1.    | 70.  | 0.   | 4.   | 0.   | NT    | NT   | 4.4 |
| PARAMETER MEANS:     |                | 29.00                    | 0.20 | 1.80 | 2.60 | 56.80 | 2.00 | 4.20 | 1.80 | 4.85 | 18.60 | 3.88 |     |
| STANDARD DEVIATIONS: |                | 13.10                    | 0.45 | 1.64 | 2.70 | 15.87 | 1.41 | 2.28 | 2.49 | 4.45 | 1.27  | 0.48 |     |
| 88F00295 M           | 2/1            | 14                       | 11.  | 0.   | 0.   | 1.    | 87.  | 0.   | 1.   | 0.   | NT    | NT   | 2.6 |
| 88F00289 M           | 2/1            | 14                       | 19.  | 0.   | 1.   | 2.    | 68.  | 1.   | 9.   | 0.   | NT    | NT   | 1.5 |
| 88F00290 M           | 2/1            | 14                       | 28.  | 0.   | 5.   | 6.    | 56.  | 0.   | 4.   | 0.   | NT    | NT   | 1.4 |
| 88F00279 M           | 2/1            | 14                       | 28.  | 0.   | 0.   | 3.    | 58.  | 4.   | 7.   | 0.   | 6.2   | 40.9 | 1.6 |
| 88F00263 M           | 2/1            | 14                       | 57.  | 0.   | 3.   | 5.    | 32.  | 0.   | 3.   | 0.   | 9.5   | NT   | 3.9 |
| PARAMETER MEANS:     |                | 28.60                    | 0.00 | 1.80 | 3.40 | 60.20 | 1.00 | 4.80 | 0.00 | 7.85 | 40.90 | 2.20 |     |
| STANDARD DEVIATIONS: |                | 17.39                    | 0.00 | 2.17 | 2.07 | 19.98 | 1.73 | 3.19 | 0.00 | 2.33 | .     | 1.07 |     |
| 88F00280 M           | 1/1            | 14                       | 20.  | 0.   | 3.   | 71.   | 3.   | 3.   | 0.   | 7.9  | 35.7  | 3.7  |     |
| 88F00303 M           | 1/1            | 14                       | 25.  | 0.   | 4.   | 2.    | 62.  | 0.   | 6.   | 1.   | NT    | NT   | 1.9 |
| 88F00254 M           | 1/1            | 14                       | 43.  | 0.   | 4.   | 2.    | 32.  | 5.   | 8.   | 0.   | 4.9   | 32.2 | 1.5 |
| 88F00297 M           | 1/1            | 14                       | 65.  | 0.   | 6.   | 2.    | 14.  | 4.   | 9.   | 0.   | 2.4   | 1.7  | 2.2 |
| PARAMETER MEANS:     |                | 38.25                    | 0.00 | 3.50 | 2.25 | 44.75 | 3.00 | 6.50 | 0.25 | 5.07 | 23.20 | 2.33 |     |
| STANDARD DEVIATIONS: |                | 20.39                    | 0.00 | 2.52 | 0.50 | 26.42 | 2.16 | 2.65 | 0.50 | 2.75 | 18.70 | 0.96 |     |
| 88F00300 M           | 3/1            | 14                       | 20.  | 0.   | 4.   | 2.    | 71.  | 1.   | 2.   | 3.   | 6.4   | 15.6 | 4.7 |
| 88F00259 M           | 3/1            | 14                       | 8.   | 0.   | 1.   | 78.   | 5.   | 8.   | 0.   | NT   | NT    | 3.4  |     |
| 88F00292 M           | 3/1            | 14                       | 45.  | 0.   | 4.   | 3.    | 45.  | 1.   | 2.   | 5.   | 7.5   | 18.8 | 2.1 |
| 88F00286 M           | 3/1            | 14                       | 30.  | 0.   | 2.   | 2.    | 60.  | 2.   | 4.   | 5.   | 7.0   | 48.3 | 3.9 |
| 88F00276 M           | 3/1            | 14                       | 35.  | 1.   | 1.   | 0.    | 54.  | 7.   | 2.   | 0.   | 3.3   | 18.7 | 2.2 |
| PARAMETER MEANS:     |                | 27.60                    | 0.20 | 2.20 | 1.60 | 61.60 | 3.20 | 3.60 | 2.60 | 6.05 | 25.35 | 3.26 |     |
| STANDARD DEVIATIONS: |                | 14.19                    | 0.45 | 1.79 | 1.14 | 13.16 | 2.68 | 2.61 | 2.51 | 1.89 | 15.37 | 1.11 |     |

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## Appendix H (cont.): HEMATOLOGY

LETERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

EXPANDED STATISTICAL TABLE FOR BAKER I  
 STUDY NUMBER: 88002

STUDY START DATE: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

| ANIMAL<br>NUMBER     | GROUP/<br>SEX | DAY OF<br>STUDY | WBC  | RBC  | HGB   | HCT   | MCV   | MCH   | MCHC  | PLT    |
|----------------------|---------------|-----------------|------|------|-------|-------|-------|-------|-------|--------|
| 88F00346 F           | 4/2           | 14              | 6.7  | 5.23 | 11.5  | 34.2  | 65.4  | 22.0  | 33.6  | 432    |
| 88F00351 F           | 4/2           | 14              | 6.7  | 6.14 | 13.9  | 41.4  | 67.5  | 22.6  | 33.6  | 296    |
| 88F00325 F           | 4/2           | 14              | 6.1  | 5.37 | 12.1  | 36.6  | 68.2  | 22.5  | 33.1  | 493    |
| 88F00307 F           | 4/2           | 14              | 3.4  | 4.46 | 10.6  | 31.9  | 71.5  | 23.8  | 33.2  | 184    |
| 88F00340 F           | 4/2           | 14              | 8.1  | 6.18 | 13.7  | 41.1  | 66.5  | 22.2  | 33.3  | 560    |
| PARAMETER MEANS:     |               |                 | 6.20 | 5.48 | 12.36 | 37.04 | 67.82 | 22.62 | 33.36 | 393.00 |
| STANDARD DEVIATIONS: |               |                 | 1.73 | 0.71 | 1.42  | 4.19  | 2.31  | 0.70  | 0.23  | 152.07 |
| 88F00334 F           | 2/2           | 14              | 6.1  | 4.62 | 11.0  | 33.3  | 72.1  | 23.8  | 33.0  | 369    |
| 88F00322 F           | 2/2           | 14              | 10.0 | 5.42 | 13.1  | 39.5  | 72.9  | 24.4  | 33.2  | 358    |
| 88F00353 F           | 2/2           | 14              | 6.2  | 5.48 | 12.4  | 36.1  | 65.9  | 22.6  | 34.3  | 259    |
| 88F00333 F           | 2/2           | 14              | 6.4  | 5.45 | 13.2  | 40.0  | 73.4  | 24.2  | 33.0  | 348    |
| 88F00318 F           | 2/2           | 14              | 7.7  | 5.09 | 11.4  | 34.0  | 66.8  | 22.4  | 33.5  | 375    |
| PARAMETER MEANS:     |               |                 | 7.28 | 5.21 | 12.22 | 36.58 | 70.22 | 23.48 | 33.40 | 341.80 |
| STANDARD DEVIATIONS: |               |                 | 1.65 | 0.37 | 0.99  | 3.08  | 3.58  | 0.92  | 0.54  | 47.43  |
| 88F00331 F           | 1/2           | 14              | 6.1  | 5.37 | 12.4  | 37.2  | 69.2  | 23.1  | 33.3  | 255    |
| 88F00327 F           | 1/2           | 14              | 5.7  | 5.69 | 13.5  | 40.1  | 70.5  | 23.7  | 33.7  | 494    |
| 88F00341 F           | 1/2           | 14              | 8.0  | 5.44 | 12.9  | 37.8  | 69.4  | 23.7  | 34.1  | 373    |
| 88F00305 F           | 1/2           | 14              | 8.3  | 5.34 | 12.4  | 36.7  | 68.7  | 23.2  | 33.8  | 172    |
| PARAMETER MEANS:     |               |                 | 7.03 | 5.46 | 12.80 | 37.95 | 69.45 | 23.43 | 33.72 | 323.50 |
| STANDARD DEVIATIONS: |               |                 | 1.31 | 0.16 | 0.52  | 1.50  | 0.76  | 0.32  | 0.33  | 140.43 |
| 88F00319 F           | 3/2           | 14              | 8.2  | 5.23 | 12.3  | 36.2  | 69.3  | 23.5  | 34.0  | 193    |
| 88F00304 F           | 3/2           | 14              | 7.5  | 4.43 | 10.1  | 29.7  | 67.1  | 22.8  | 34.0  | 281    |
| 88F00326 F           | 3/2           | 14              | 5.8  | 6.05 | 13.4  | 40.1  | 66.3  | 22.1  | 33.4  | 349    |
| 88F00312 F           | 3/2           | 14              | 2.5  | 3.82 | 8.9   | 25.1  | 65.8  | 23.3  | 35.5  | 159    |
| 88F00321 F           | 3/2           | 14              | 8.0  | 5.71 | 13.3  | 39.3  | 68.8  | 23.3  | 33.8  | 300    |
| PARAMETER MEANS:     |               |                 | 6.40 | 5.05 | 11.60 | 34.08 | 67.46 | 23.00 | 34.14 | 256.40 |
| STANDARD DEVIATIONS: |               |                 | 2.38 | 0.92 | 2.01  | 6.48  | 1.53  | 0.57  | 0.80  | 78.40  |

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## Appendix H (cont.) : HEMATOLOGY

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

EXPANDED STATISTICAL TABLE FOR WBC DIFFERENTIAL COUNTS  
 STUDY NUMBER: 88002

STUDY START DATE: 13-Sep-88

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 ACUTE/ACUTE INTRAVENOUS

| ANIMAL<br>NUMBER     | GROUP /<br>SEX | DAY /<br>SUBGROUP | STUDY | SEG   | BAN  | EOS  | BAS  | LYM   | MON  | ATL  | NRBC | PT   | APPT  | RET  |
|----------------------|----------------|-------------------|-------|-------|------|------|------|-------|------|------|------|------|-------|------|
| 88F00346 F           | 4/2            | 14                |       | 39    | 0    | 2    | 2    | 45    | 0    | 12   | 0    | NT   | NT    | 3.9  |
| 88F00351 F           | 4/2            | 14                |       | 65    | 0    | 2    | 0    | 25    | 3    | 5    | 0    | 6.2  | 12.7  | 2.5  |
| 88F00325 F           | 4/2            | 14                |       | 44    | 0    | 0    | 1    | 51    | 0    | 4    | 0    | 7.1  | 1.4   | 3.5  |
| 88F00307 F           | 4/2            | 14                |       | 37    | 0    | 7    | 1    | 43    | 6    | 6    | 0    | 5.5  | 5.5   | 3.4  |
| 88F00340 F           | 4/2            | 14                |       | 20    | 0    | 2    | 0    | 29    | 3    | 4    | 0    | 5.5  | 16.5  | 3.9  |
| PARAMETER MEANS:     |                |                   |       | 41.00 | 0.00 | 2.60 | 0.80 | 38.60 | 2.40 | 6.20 | 0.00 | 6.08 | 9.03  | 3.44 |
| STANDARD DEVIATIONS: |                |                   |       | 16.17 | 0.00 | 2.61 | 0.84 | 11.08 | 2.51 | 3.35 | 0.00 | 0.76 | 6.83  | 0.57 |
| 88F00334 F           | 2/2            | 14                |       | 10    | 0    | 0    | 0    | 11    | 1    | 1    | 0    | 8.8  | 14.2  | 4.5  |
| 88F00322 F           | 2/2            | 14                |       | 46    | 0    | 1    | 1    | 45    | 4    | 3    | 0    | NT   | NT    | 6.7  |
| 88F00353 F           | 2/2            | 14                |       | 39    | 0    | 0    | 0    | 58    | 1    | 2    | 0    | NT   | NT    | 5.1  |
| 88F00333 F           | 2/2            | 14                |       | 55    | 0    | 0    | 0    | 40    | 2    | 3    | 0    | 8.8  | 24.7  | 6.5  |
| 88F00318 F           | 2/2            | 14                |       | 51    | 1    | 0    | 0    | 47    | 0    | 1    | 0    | NT   | NT    | 2.4  |
| PARAMETER MEANS:     |                |                   |       | 40.20 | 0.20 | 0.20 | 0.20 | 40.20 | 1.60 | 2.00 | 0.00 | 8.80 | 19.45 | 5.04 |
| STANDARD DEVIATIONS: |                |                   |       | 17.91 | 0.45 | 0.45 | 0.45 | 17.60 | 1.52 | 1.00 | 0.00 | 0.00 | 7.42  | 1.74 |
| 88F00331 F           | 1/2            | 14                |       | 51    | 0    | 3    | 0    | 42    | 1    | 3    | 0    | 6.0  | 1.2   | 2.9  |
| 88F00327 F           | 1/2            | 14                |       | 60    | 0    | 2    | 2    | 31    | 3    | 2    | 0    | 7.0  | 22.0  | 4.4  |
| 88F00341 F           | 1/2            | 14                |       | 54    | 0    | 2    | 0    | 39    | 1    | 4    | 0    | NT   | NT    | 3.1  |
| 88F00305 F           | 1/2            | 14                |       | 40    | 0    | 5    | 0    | 45    | 10   | 0    | 0    | 5.9  | 15.0  | 1.1  |
| PARAMETER MEANS:     |                |                   |       | 51.25 | 0.00 | 3.00 | 0.50 | 39.25 | 3.75 | 2.25 | 0.00 | 6.30 | 12.73 | 2.88 |
| STANDARD DEVIATIONS: |                |                   |       | 8.38  | 0.00 | 1.41 | 1.00 | 6.02  | 4.27 | 1.71 | 0.00 | 0.61 | 10.58 | 1.36 |
| 88F00319 F           | 3/2            | 14                |       | 59    | 0    | 0    | 0    | 34    | 2    | 5    | 0    | NT   | NT    | 5.5  |
| 88F00304 F           | 3/2            | 14                |       | 40    | 0    | 6    | 0    | 52    | 0    | 2    | 0    | 9.5  | 11.5  | 4.3  |
| 88F00326 F           | 3/2            | 14                |       | 57    | 0    | 2    | 1    | 39    | 1    | 0    | 0    | 7.5  | 1.6   | 8.8  |
| 88F00312 F           | 3/2            | 14                |       | 33    | 0    | 5    | 0    | 32    | 0    | 10   | 0    | NT   | NT    | 1.3  |
| 88F00321 F           | 3/2            | 14                |       | 23    | 0    | 0    | 0    | 73    | 1    | 3    | 0    | NT   | NT    | 4.5  |
| PARAMETER MEANS:     |                |                   |       | 42.40 | 0.00 | 2.60 | 0.20 | 50.00 | 0.80 | 4.00 | 0.00 | 8.50 | 6.55  | 4.88 |
| STANDARD DEVIATIONS: |                |                   |       | 15.49 | 0.00 | 2.79 | 0.45 | 15.12 | 0.84 | 3.81 | 0.00 | 1.41 | 7.00  | 2.69 |

**Appendix I: PATHOLOGY REPORT**

TOXICOLOGY STUDY NO. 88002

PRINCIPAL INVESTIGATOR: Gary M. Zaucha, DVM, CPT, VC  
CO-PRINCIPAL INVESTIGATOR: Denzil F. Frost, MS, DVM, CPT, VC  
PATHOLOGIST: Luann McKinney, DVM, MAJ, VC

**I. INTRODUCTION**

Type: Acute Rabbit Intravenous Toxicity Test

Compound: Hypertonic Saline/Dextran 70®

Animal: Oryctolagus cuniculus (New Zealand White)  
Male and Female Juveniles

Dosage groups

|         |           |                               |
|---------|-----------|-------------------------------|
| GROUP 1 | (M&F)     | Hypertonic saline             |
| GROUP 2 | "         | Hypertonic saline/Dextran 70® |
| GROUP 3 | "         | Dextran 70®                   |
| GROUP 4 | (Control) | Lactated Ringer's Solution    |

Dose: 20.00 ml/kg

**II. Summary of post-mortem examination procedures**

Tranquilization: Ketamine and Acepromazine, IM

Clinical Lab values: Hematology and Serology

Euthanasia: Pentobarbital overdose, IV

Fixative: 10% Neutral Buffered Formalin

Histopathology: Routine light microscopy of Brain,  
Heart, Kidney, Liver, Lungs and Spleen.

**III. GROSS FINDINGS:**

**PATHOLOGY TABLE 1 - Incidence Summary of all Gross Observations**

Gross lesions of congestion, hemorrhage, edema, exophthalmus and blood in the nares were limited to dosing deaths in group 1 (hypertonic saline). Pitting of the renal capsule, also noted among these animals, is attributed to parenchymal swelling accentuating pre-existing interstitial lesions.

One gross lesion, disseminated hepatic foci, was observed at scheduled death; in the absence of any microscopic lesions, this mottling is attributed to post-mortem blood pooling.

**Appendix I (cont.): PATHOLOGY REPORT**

**IV. MICROSCOPIC FINDINGS:**

All specified tissues were examined in all groups.

**PATHOLOGY TABLE 2 - Incidence Summary of Microscopic Observations (KOLMOGOROV-SMIRNOV  
2-Tailed test, 0.05 level)**  
2-A - Scheduled deaths  
2-B - Unscheduled deaths

**PATHOLOGY ANNEX - Individual animal reports/ Gross and Microscopic**

Lesions of leptomeningitis, granulomatous encephalitis, and subacute and chronic interstitial nephritis are frequently associated with infection by Encephalitozoon cuniculi, a common condition of domesticated rabbits. Lymphogranulomatous hepatitis, accompanied by some degree of biliary epithelial hyperplasia, is compatible with the recovery stage of hepatic Eimeriosis, another common condition in laboratory rabbits. The mild pulmonary inflammatory responses and splenic and pulmonary lymphoid hyperplasias are attributed to a subclinical infectious process. Glycogen storage is a physiologic change seen in animals on a high plane of nutrition.

Seen in all groups, the acute hemorrhage, congestion and edema, are attributed to hemodynamic changes associated with tranquilization and euthanasia. No microscopic lesions unique to the unscheduled deaths in group 1 were observed.

Based on the results of the Kolmogorov-Smirnov two-tailed analysis (95% confidence level) of the microscopic findings, no lesion was significantly more frequent in a treated group of either sex than in the control group. No microscopic observations are attributed to treatment effect.

**Appendix I (cont.): PATHOLOGY REPORT**

**V. SUMMARY COMMENTS:**

Lesions observed in these rabbits are considered to be either incidental lesions common to the species, or are changes associated with acute hemodynamic alterations. No morphologic evidence of toxicity of Hypertonic Saline/Dextran 70® was observed.



Luann McKinney, DVM  
MAJ, VC  
Diplomate, ACVP  
C, Div Pathology

**Appendix I (cont.): PATHOLOGY REPORT**

**DEFINITION OF MICROSCOPIC TERMS, BY ORGAN**

I. BRAIN:

1. ENCEPHALITIS, LYMPHOGANULOMATOUS - FOCI OF LYMPHOCYTES AND MACROPHAGES (10 TO 50 CELLS) IN THE NEUROPIL EXCLUSIVE OF PRESENCE/SEVERITY OF PARENCHYMAL DAMAGE.
2. LEPTOMENINGITIS, NONSUPURATIVE- LYMPHOCYTES AND MONONUCLEAR CELLS IN THE LEPTOMENINGES, EXTENDING TO THE VIRCHOW-ROBBINS SPACE.

II. HEART:

1. HEMORRHAGE, ACUTE, EPICARDIUM- POOLS, 25 OR MORE MICRONS IN DIAMETER, OF ERYTHROCYTES IN THE EPICARDIAL FAT AND MESENCHYME.
2. MYOCARDITIS, SUBACUTE, INTERSTITIUM- AGGREGATES OF LYMPHOCYTES, 10 OR MORE CELLS, BETWEEN MYOCARDIAL FIBERS OR IN MYOCARDIAL VASCULAR ADVENTITIA. PRESENCE/SEVERITY OF PARENCHYMAL DAMAGE NOT REQUIRED.

III. KIDNEY:

1. INFLAMMATION, SUBACUTE, PERIPELVIC FAT- AGGREGATES OF LYMPHOCYTES AND PLASMA CELLS IN THE PERIPELVIC FAT.
2. NEPHRITIS, CHRONIC, INTERSTITIUM- FOCAL INTERSTITIAL FIBROPLASIA, OFTEN WITH DEFORMATION OF NORMAL LINEAR ARRAYS OF CORTICAL ELEMENTS; USUALLY ACCCOMPANIED BY LOCAL INFILTRATE OF LYMPHOCYTES/PLASMA CELLS/AND MACROPHAGES.
3. NEPHRITIS, SUBACUTE, INTERSTITIUM- AGGREGATES OF LYMPHOCYTES AND PLASMA CELLS, WITH OR WITHOUT MACROPHAGES, IN CORTICAL OR MEDULLARY INTERSTITIUM. USUALLY ACCOMPANIED BY SOME DEGREE OF DAMAGE OR DISARRAY OF THE NEPHRON.
4. VACUOLIZATION, TUBULAR EPITHELIUM- CLEAR CYTOPLASMIC VACUOLES, BOTH MULTIPLE AND SINGULAR, THAT DISPLACE THE NUCLEUS PERIPHERALLY; USUALLY SEEN AS A CLUSTER OF CROSS-SECTIONS OF ONE NEPHRON.

**Appendix I (cont.): PATHOLOGY REPORT**

**IV. LIVER:**

1. HEPATITIS, LYMPHOGRANULOMATOUS, PORTAL TRACKS- INFILTRATES OF LYMPHOCYTES, PLASMA CELLS, AND SOME MACROPHAGES AROUND BILE DUCTS AND DUCTULES, INCLUDING, BUT NOT LIMITED TO THE PORTAL TRIADS. HEPATOCYTES ARE UNAFFECTED BUT THERE ARE VARIABLE DEGREES OF BILIARY EPITHELIAL HYPERPLASIA.
2. NECROSIS, COAGULATIVE, CHRONIC- FOCI OF LOBULES OR PORTIONS OF LOBULES THAT HAVE UNDERGONE COAGULATIVE NECROSIS (CELL OUTLINES INTACT, NUCLEI NOT DISCERNABLE) AND ARE BOUNDED BY A 4-10 CELL THICK RIM OF MACROPHAGES/FIBROBLASTS.
3. MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCYTES- HEPATOCELLULAR CYTOPLASM DISTENDED BY SMALL CLEAR VACUOLES; CYTOPLASM IS REDUCED TO SMALL GRANULES SUSPENDED BETWEEN THE VACUOLES; NUCLEI ARE UNAFFECTED.

**V. LUNGS:**

1. CONGESTION, ACUTE, VASCULATURE- VESSELS, TO INCLUDE CAPILLARIES, ARE DISTENDED BY BLOOD.
2. FREE BLOOD, AIRWAYS- BRONCHI AND/OR PRIMARY BRONCHIOLES ARE FILLED BY ERYTHROCYTES.
3. HYPERPLASIA, BRONCHIAL-ASSOCIATED LYMPHOID TISSUE- INCREASED PROMINENCE OF LYMPHOID ELEMENTS, WITH SECONDARY GERMINAL CENTER FORMATION ABOUT TERMINAL BRONCHI AND PRIMARY BRONCHIOLES.
4. INTRA-ALVEOLAR ERYTHROCYTES- APPROXIMATELY 10 OR MORE ERYTHROCYTES FREE IN THE ALVEOLAR SPACE; NO CELL RESPONSE; NO ARCHITECTURAL ALTERATION.
5. INTRA-ALVEOLAR MACROPHAGES- FOAMY OR PROTEIN-LADEN MACROPHAGES IN ALVEOLI; NUMEROUS ALVEOLI CONTAIN 3 OR MORE CELLS, OR A FOCUS OF CONTIGUOUS ALVEOLI CONTAINING 25 OR MORE.
6. INTRA-ALVEOLAR PROTEIN (EDEMA), ACUTE- ALVEOLAR SPACES FILLED WITH HOMOGENOUS PALE EOSINOPHILIC MATERIAL; NO CELLULAR RESPONSE.

**Appendix I (cont.): PATHOLOGY REPORT**

7. LYMPHORRHEXIS OF BRONCHIAL-ASSOCIATED LYMPHOID TISSUE-KARYORRHEXIS OF INDIVIDUAL LYMPHOCYTES OF THE 'BALT'.
8. PNEUMONIA, PYOGRANULOMATOUS, INTERSTITIUM- EXPANSION OF ALVEOLAR SEPTA AND/OR PERIBRONCHIOLAR ADVENTITIA BY VARIABLE CONCENTRATIONS OF MACROPHAGES AND EOSINOPHILIC NEUTROPHILS.

VI. SPLEEN:

1. HEMATOPOIESIS- PRESENCE OF ERYTHROID, MYELOID AND THROMBOCYTIC COLONIES IN THE RED PULP.
2. HEMOSIDEROSIS- PRESENCE OF MACROPHAGES CONTAINING VARIABLE AMOUNTS OF BROWN HEMOSIDERIN PIGMENT. USUALLY SEEN ALONG THE SINUSOIDS OF THE INTRASPLENIC TRABECULAE; SOMETIMES IN ASSOCIATION WITH ERYTHROPHAGOCYTIC MACROPHAGES.
3. LYMPHOID HYPERPLASIA- MARKED INCREASE IN WHITE PULP ELEMENTS AND RELATIVE DECREASE IN RED PULP; PRESENCE OF IMMATURE LYMPHOCYTES IN SINUSOIDS AND VASCULAR SPACES OF THE RED PULP.

## Appendix I (cont.) : PATHOLOGY REPORT

|                          | Incidence Summary Report for Gross Necropsy Observations |         |      | PRINTED: 23-Mar-89      |
|--------------------------|--|---------|------|-------------------------|
|                          | Study Number: 88002                                      |         |      | Page: 1                 |
|                          | Report includes all dead animals                         |         |      |                         |
|                          | Study Start Date: 13-Sep-88                              |         |      | ACUTE/ACUTE INTRAVENOUS |
|                          | Males  | Females | Ctls |                         |
| PERITONEAL CAV.          |  |         |      |                         |
| FRANK BLOOD PRESENT      | 0  | 0       | 0    | 0                       |
| HEMORRHAGE               | 0  | 0       | 0    | 0                       |
| EYES & OPTIC N.          | 0  | 1       | 0    | 0                       |
| EXOPHTHALMUS             |  |         |      |                         |
| KIDNEY                   |  |         |      |                         |
| PITTED CAPSULE           | 0  | 3       | 0    | 0                       |
| LIVER                    |  |         |      |                         |
| DISSEMINATED FOCI        | 0  | 0       | 1    | 0                       |
| WHITE FOCUS, RED EDGES   | 0  | 1       | 0    | 0                       |
| CONGESTED                | 0  | 0       | 0    | 0                       |
| LUNGS                    |  |         |      |                         |
| HEMORRHAGE(S)            | 0  | 3       | 0    | 0                       |
| CONGESTION               | 0  | 0       | 0    | 0                       |
| EDEMATOUS                | 0  | 0       | 0    | 0                       |
| NOSE/TURBINATES          |  |         |      |                         |
| BLOOD WITHIN NARES       | 0  | 1       | 0    | 0                       |
| SKIN                     |  |         |      |                         |
| HEMORRHAGE, SUBCUTANEOUS | 0  | 0       | 0    | 0                       |
| THYMUS                   |  |         |      |                         |
| HEMORRHAGE(S)            | 0  | 3       | 0    | 0                       |
| TRACHEA                  |  |         |      |                         |
| FLUID FILLED LUMEN       | 0  | 3       | 0    | 0                       |
| WHOLE BODY               |  |         |      |                         |
| NO GROSS LESIONS         | 10   | 7       | 10   | 7                       |
|                          |  |         | 10   | 10                      |

Pathology Table 1



## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

## Incidence Summary of Microscopic Observations

Study Number: 88002

All Diagnoses

Study Start Date: 13-Sep-88

| Notes: Animals = all scheduled sacrificed animal |  | Animal sex:      |               | Animals |         | Affected |      |
|--|--|------------------|---------------|---------|---------|----------|------|
|  |  | Dosage group:    | No. in group: | Males   | Females | Ctls     | Ctls |
| Controls from group(s):                          | 4  | Ctls             | 1             | 2       | 3       | 1        | 2    |
| Tissues with Diagnoses                           |  | 10               | 7             | 10      | 10      | 10       | 10   |
| BRAIN  | LEPTOMENINGITIS, NONSUPPURATIVE<br>ENCEPHALITIS, LYMPHOGANULOMATOUS  | Number examined: | 10            | 7       | 10      | 10       | 10   |
| HEART  | HEMORRHAGE, ACUTE, EPICARDIUM<br>MYOCARDITIS, SUBACUTE, INTERSTITIUM   | Number examined: | 10            | 7       | 10      | 10       | 10   |
| KIDNEY   | NEPHRITIS, CHRONIC, INTERSTITIUM<br>NEPHRITIS, SUBACUTE, INTERSTITIUM<br>INFLAMMATION, SUBACUTE, PERIPELVIC FAT<br>VACUOLIZATION, TUBULAR EPITHELIUM   | Number examined: | 10            | 7       | 10      | 10       | 10   |
| LIVER  | HEPATITIS, LYMPHOGANULOMATOUS, PORTAL TRACKS<br>NECROSIS, COAGULATIVE, CHRONIC<br>MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR   | Number examined: | 10            | 7       | 10      | 10       | 10   |
| LUNGS  | INTRA-ALVEOLAR ERYTHROCYTES<br>LYMPHORRHEXIS OF BRONCHIAL-ASSOCIATED LYMPHOID TISSUE<br>PNEUMONIA, PYOGRANULOMATOUS, INTERSTITIUM<br>FREE BLOOD, AIRWAYS<br>INTRA-ALVEOLAR MACROPHAGES<br>HYPERPLASIA, BRONCHIAL-ASSOCIATED LYMPHOID TISSUE<br>INTRA-ALVEOLAR PROTEIN (EDEMA), ACUTE<br>CONGESTION, ACUTE, VASCULATURE | Number examined: | 10            | 7       | 10      | 10       | 10   |
| SPLEEN   | HEMOSIDEROSIS<br>HEMATOPOIESIS<br>LYMPHOID HYPERPLASIA   | Number examined: | 10            | 7       | 10      | 10       | 10   |

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
DIV OF RES SUPP, PATH SERV GP  
PRESIDIO OF SAN FRANCISCO, CA 94129  
RABBIT/NEW ZEALAND WHITE

## Incidence Summary of Microscopic Observations

Study Number: 88002

## All Diagnoses

Study Start Date: 13-Sep-88

|                               |  | 1 - 22                | ... Animals ... | Affected        |
|-------------------------------|--|-----------------------|-----------------|-----------------|
|                               |  | Animal sex:           | Males           | ... Females ... |
|                               |  | Dosage group:         | Ctls            | Ctls            |
|                               |  | No. in group:         | 1               | 2               |
|                               |  | Number examined:      | 0               | 3               |
|                               |  | .....Number examined: | 0               | 0               |
| <b>Tissues with diagnoses</b> |  |                       |                 |                 |
| <b>BRAIN</b>                  | LEPMONENITIS, NONSUPPURATIVE<br>ENCEPHALITIS, LYMPHOGANULOMATOUS   |                       | 0 3 0           | 0 3 0           |
| <b>HEART</b>                  | HEMORRHAGE, ACUTE, EPICARDIUM<br>MYOCARDITIS, SUBACUTE, INTERSTITIUM   |                       | 0 0 0           | 0 0 0           |
| <b>KIDNEY</b>                 | NEPHRITIS, CHRONIC, INTERSTITIUM<br>NEPHRITIS, SUBACUTE, INTERSTITIUM<br>INFLAMMATION, SUBACUTE, PERIPELVIC FAT<br>VACUOLIZATION, TUBULAR EPITHELIUM   |                       | 0 3 0           | 0 3 0           |
| <b>LIVER</b>                  | HEPATITIS, LYMPHOGANULOMATOUS, PORTAL TRACKS<br>NECROSIS, COAGULATIVE, CHRONIC<br>MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR   |                       | 0 0 0           | 0 0 0           |
| <b>LUNGS</b>                  | INTRA-ALVEOLAR ERYTHROCYTES<br>LYMPHORRHEA OF BRONCHIAL-ASSOCIATED LYMPHOID TISSUE<br>PNEUMONIA, PYOGRANULOMATOUS, INTERSTITIUM<br>FREE BLOOD, AIRWAYS<br>INTRA-ALVEOLAR MACROPHAGES<br>HYPERPLASIA, BRONCHIAL-ASSOCIATED LYMPHOID TISSUE<br>INTRA-ALVEOLAR PROTEIN (EDEMA), ACUTE<br>CONGESTION, ACUTE, VASCULATURE |                       | 0 3 0           | 0 3 0           |
| <b>SPLEEN</b>                 | HEMOSIDEROSIS<br>HEMATOPOIESIS<br>LYMPHOID HYPERPLASIA   |                       | 0 0 0           | 0 0 0           |

PRINTED: 19-Apr-89

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## Appendix I (cont.) : PATHOLOGY REPORT

| LETTERMAN ARMY INSTITUTE OF RESEARCH<br>DIV OF RES SUPP, PATH SERV GP<br>PRESIDIO OF SAN FRANCISCO, CA 94129<br>RABBIT/NEW ZEALAND WHITE |  | Individual Animal Data Dump Table<br>Study Number: 88002  |                          | PRINTED: 19-Apr-89<br>Page: 1    |
|--|--|---|--------------------------|----------------------------------|
|  |  | Study Start Date: 13-Sep-88                               |                          | ACUTE/ACUTE INTRAVENOUS          |
|  |  |   |                          | Dose level: 20.00 ML/KG/day      |
|  |  |   |                          | Terminal body weight (kms): 3.03 |
| Animal: 88F00262   | Sex: Male  | Group: 1  |                          |                                  |
| Day of death: 1  | Status: FOUND DEAD   |   |                          |                                  |
| Tissue   | Finding, severity  | << Gross Observations >>                                  |                          |                                  |
| NOSE/TURBINATES  | BLOOD WITHIN NARES   |   | Gross Free Text Comments |                                  |
| THYMUS   | HEMORRHAGE(S), Trace   |   | PETECHIAE                |                                  |
| LUNGS  | HEMORRHAGE(S), Trace   |   | PETECHIAE                |                                  |
| TRACHEA  | FLUID FILLED LUMEN, Mild   |   | FOAM                     |                                  |
| KIDNEY   | PITTED CAPSULE, Mild   |   | PURPLE, DIFFUSE          |                                  |
| Tissue   | Necropsy memos   | << Necropsy Memos >>                                      |                          |                                  |
| No necropsy memos recorded on animal   |  |   |                          |                                  |
| Tissue   |  | << Pathology Observations >>                              |                          |                                  |
| LIVER  | MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Moderate, Diffuse.   | Histopathologic diagnoses / Special histological comments |                          |                                  |
| LUNGS  | INTRA-ALVEOLAR ERYTHROCYTES, Mild, Multifocal.<br>LYMPHORRHEXIS OF BRONCHIAL-ASSOCIATED LYMPHOID TISSUE, Mild, Multifocal. |   |                          |                                  |

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

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| ACUTE/ACUTE INTRAVENOUS |   |                              |                             |
|-------------------------|---|------------------------------|-----------------------------|
| Animal:                 | Day of death:   | Study Start Date:            |                             |
| 88F00301                | 4   | 13-Sep-88                    |                             |
|                         |   | Sex: Male                    | Group: 1                    |
|                         |   | Status: Interim sacrifice 1  | Dose level:                 |
|                         |   |                              | 20.00 ML/KG/day             |
|                         |   |                              | Terminal body weight (kms): |
|                         |   |                              | 3.41                        |
| Tissue                  | Finding, severity   | << Gross Observations >>     |                             |
| WHOLE BODY              | NO GROSS LESIONS  | Gross Free-Text Comments     |                             |
| Tissue                  | Necropsy memos  | << Necropsy Memos >>         |                             |
|                         | No necropsy memos recorded on animal  |                              |                             |
| Tissue                  | Histopathologic diagnoses / Special histological comments                               | << Pathology Observations >> |                             |
| LIVER                   | MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Moderate, Diffuse.                    |                              |                             |
| LUNGS                   | INTRA-ALVEOLAR ERYTHROCYTES, Slight, Multifocal.<br>FREE BLOOD, AIRWAYS, Marked, Focal. |                              |                             |

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

| Animal: 88F00282                      |   | Sex: Male                | Group: 1 | Dose level:                 |
|---------------------------------------|---|--------------------------|----------|-----------------------------|
| Day of death: 1                       |   | Status: FOUND DEAD       |          | Terminal body weight (kms): |
| Tissue                                | Finding, severity   | << Gross Observations >> |          |                             |
| EYES & OPTIC N.                       | EXOPHTHALMUS, Moderate  | Gross Free-Text Comments |          |                             |
| KIDNEY                                | PITTED CAPSULE, Mild  | CLEAR CORNEA             |          |                             |
| THYMUS                                | HEMORRHAGE(S), Mild   | PURPLE                   |          |                             |
| LUNGS                                 | HEMORRHAGE(S), Moderate   | PETECHIAE                |          |                             |
| TRACHEA                               | FLUID FILLED LUMEN, Mild  | AND PETECHIAE            |          |                             |
| Tissue                                | Necropsy memos  | << Necropsy Memos >>     |          |                             |
| No necropsy memos recorded on animal! |   |                          |          |                             |
| Tissue                                | << Pathologic diagnoses / Special histological comments >>  |                          |          |                             |
| LIVER                                 | MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Moderate, Diffuse.  |                          |          |                             |
| KIDNEY                                | NEPHRITIS, CHRONIC, INTERSTITIUM, Moderate, Multifocal.   |                          |          |                             |
| LUNGS                                 | INTRA-ALVEOLAR ERYTHROCYTES, Mild, Multifocal.<br>LYMPHORRHEXIS OF BRONCHIAL-ASSOCIATED LYMPHOID TISSUE, Mild, Multifocal.<br>PNEUMONIA, PYOGANULOMATOUS, INTERSTITIUM, Slight, Multifocal. |                          |          |                             |
| BRAIN                                 | LEPTONEUROPATHY, NONSUPPURATIVE, Moderate, Diffuse.<br>ENCEPHALITIS, LYMPHOGANULOMATOUS, Slight, Focal.   |                          |          |                             |

**Appendix I (cont.): PATHOLOGY REPORT**

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

**ACUTE/INTRAVENOUS**

| Animal:       | Sex:                                 | Male                     | Group:  | 1 | Dose level:                 | 20.00 ML/KG/day |
|---------------|--------------------------------------|--------------------------|---|---|-----------------------------|-----------------|
| Day of death: | Status:                              | Interim sacrifice        | 1   |   | Terminal body weight (kms): | 3.29            |
|               | Finding, severity                    | << Gross Observations >> |   |   |                             |                 |
| Tissue        | WHOLE BODY                           | NO GROSS LESIONS         |   |   |                             |                 |
|               |                                      |                          | << Necropsy Memos >>  |   |                             |                 |
| Tissue        |                                      | Necropsy memos           |   |   |                             |                 |
|               | No necropsy memos recorded on animal |                          |   |   |                             |                 |
| Tissue        |                                      |                          | << Pathology Observations >>  |   |                             |                 |
|               |                                      |                          | Histopathologic diagnoses / Special histological comments   |   |                             |                 |
| LIVER         |                                      |                          | NECROSIS, COAGULATIVE, CHRONIC, Marked, Multifocal.   |   |                             |                 |
| LUNGS         |                                      |                          | PNEUMONIA, PYOGRANULOMATOUS, INTERSTITIUM, Mild, Focal,<br>INTRA-ALVEOLAR MACROPHAGES, Mild, Diffuse. |   |                             |                 |

## Appendix I (cont.): PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

|  |   |          |                                  |
|--|---|----------|----------------------------------|
| Animal: 88F00257   | Sex: Male   | Group: 1 | Dose level: 20.00 ML/KG/day      |
| Day of death: 4  | Status: Interim sacrifice 1                                 |          | Terminal body weight (kms): 3.58 |
| Finding, severity  | << Gross Observations >>                                    |          |                                  |
| Tissue   | Gross Free-Text Comments                                    |          |                                  |
| WHOLE BODY   | NO GROSS LESIONS  |          |                                  |
| Tissue   | << Necropsy Memos >>  |          |                                  |
| No necropsy memos recorded on animal                             |   |          |                                  |
| Tissue   | << Pathology Observations >>                                |          |                                  |
| LIVER  | Histopathologic diagnoses / Special histological comments   |          |                                  |
| LIVER  | HEPATITIS, LYMPHOGRANULOMATOUS, PORTAL TRACKS, Mild, Focal. |          |                                  |
| MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Mild, Diffuse. |   |          |                                  |
| LUNGS  | INTRALYMPHOEDEMA, Marked, Multifocal.                       |          |                                  |
| PNEUMONIA, PYOGRANULOMATOUS, INTERSTITIUM, Slight, Focal.        |   |          |                                  |

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

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## ACUTE/ACUTE INTRAVENOUS

| Animal:                              | 88F00272  | Sex:                     | Male       | Study Start Date: | 13-Sep-88 | Group: | 1 | Dose level:                 | 20.00 ML/KG/day |
|--------------------------------------|---|--------------------------|------------|-------------------|-----------|--------|---|-----------------------------|-----------------|
| Day of death:                        | 1   | Status:                  | FOUND DEAD |                   |           |        |   | Terminal body weight (kms): | 3.47            |
| Tissue                               | Finding, severity   | << Gross Observations >> |            |                   |           |        |   | Gross Free-Text Comments    |                 |
| TRACHEA                              | FLUID FILLED LUMEN, Mild                                  |                          |            |                   |           |        |   |                             |                 |
| THYMUS                               | HEMORRHAGE(S), Mild                                       | PETECHIAE                |            |                   |           |        |   |                             |                 |
| LUNGS                                | HEMORRHAGE(S), Mild                                       | AND PETECHIAE            |            |                   |           |        |   |                             |                 |
| KIDNEY                               | PITTED CAPSULE, Mild                                      | PURPLE                   |            |                   |           |        |   |                             |                 |
| LIVER                                | WHITE FOCUS, RED EDGES, Trace                             |                          |            |                   |           |        |   |                             |                 |
| Tissue                               | Necropsy memos  | << Necropsy Memos >>     |            |                   |           |        |   |                             |                 |
| No necropsy memos recorded on animal |   |                          |            |                   |           |        |   |                             |                 |
| Tissue                               | << Pathology Observations >>                              |                          |            |                   |           |        |   |                             |                 |
| LUNGS                                | Histopathologic diagnoses / Special histological comments |                          |            |                   |           |        |   |                             |                 |
| BRAIN                                | INTRA-ALVEOLAR ERYTHROCYTES, Mild, Multifocal.            |                          |            |                   |           |        |   |                             |                 |
|                                      | LEPTOMENINGITIS, NONSUPPURATIVE, Slight, Multifocal.      |                          |            |                   |           |        |   |                             |                 |

## Appendix I (cont.) : PATHOLOGY REPORT

|  |   |  |                             |                               |
|--|---|--|-----------------------------|-------------------------------|
| LETTERMAN ARMY INSTITUTE OF RESEARCH<br>DIV OF RES SUPP, PATH SERV GP<br>PRESIDIO OF SAN FRANCISCO, CA 94129<br>RABBIT/NEW ZEALAND WHITE |   | Individual Animal Data Dump Table<br>Study Number: 88002 |                             | PRINTED: 19-Apr-89<br>Page: 7 |
|  |   | Study Start Date: 13-Sep-88                              |                             | ACUTE/ACUTE INTRAVENOUS       |
| Animal: 88F00280   | Sex: Male   | Group: 1   | Dose level:                 | 20.00 ML/KG/day               |
| Day of death: 15   | Status: Final sacrifice   |  | Terminal body weight (kms): | 3.69                          |
|  |   | << G r o s s   O b s e r v a t i o n s >>                |                             |                               |
| Tissue   | Finding, severity   | Gross Free-Text Comments                                 |                             |                               |
| NO GROSS LESIONS   |   |  |                             |                               |
| << N e c r o p s y   M e m o s   >>  |   |  |                             |                               |
| Tissue   | Necropsy memos  |  |                             |                               |
| No necropsy memos recorded on animal   |   |  |                             |                               |
| << P a t h o l o g i c   O b s e r v a t i o n s >>  |   |  |                             |                               |
| Histopathologic diagnoses / Special histological comments  |   |  |                             |                               |
| SPLEEN   | HEMOSIDEROSIS, Slight, Diffuse.                                   |  |                             |                               |
| LIVER  | HEPATITIS, LYMPHOGRANULOMATOUS, PORTAL TRACKS, Moderate, Diffuse. |  |                             |                               |
| KIDNEY   | NEPHRITIS, CHRONIC, INTERSTITIUM, Mild, Multifocal.               |  |                             |                               |
| BRAIN  | LEPTOMENINGITIS, NONSUPPURATIVE, Mild, Multifocal.                |  |                             |                               |

## Appendix I (cont.): PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

PRINTED: 19-Apr-89

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## ACUTE/ACUTE INTRAVENOUS

Study Start Date: 13-Sep-88

Dose level:

20.00 ML/KG/day

Terminal body weight (kms):

3.26

Group: 1

Sex: Male

Status: Final sacrifice

Finding, severity

<< Gross Observations >>

Gross Free-Text Comments

NO GROSS LESIONS

WHOLE BODY

Tissue Necropsy memos

No necropsy memos recorded on animal

Tissue Histopathologic diagnoses / Special histological comments

LIVER MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Mild, Diffuse.

<< Necropsy Memos >>

No necropsy memos recorded on animal

<< Pathology Observations >>

LIVER MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Mild, Diffuse.

## Appendix I (cont.): PATHOLOGY REPORT

|  |  |  |                                  |
|--|--|--|----------------------------------|
| LETTERMAN ARMY INSTITUTE OF RESEARCH<br>DIV OF RES SUPP, PATH SERV GP<br>PRESIDIO OF SAN FRANCISCO, CA 94129<br>RABBIT/NEW ZEALAND WHITE |  | Individual Animal Data Dump Table<br>Study Number: 88002 | PRINTED: 19-Apr-89<br>Page: 9    |
|  |  | Study Start Date: 13-Sep-88                              | ACUTE/ACUTE INTRAVENOUS          |
| Animal: 88F00254   | Sex: Male  | Group: 1   | Dose level: 20.00 ML/KG/day      |
| Day of death: 15   | Status: Final sacrifice  |  | Terminal body weight (kms): 3.50 |
| Tissue   | Finding, severity  | << G r o s s      O b s e r v a t i o n s >>             | Gross Free-Text Comments         |
| WHOLE BODY   | NO GROSS LESIONS   |  |                                  |
| Tissue   | Necropsy memos   | << N e c r o p s y      M e m o s >>                     |                                  |
|  | No necropsy memos recorded on animal                             |  |                                  |
| Tissue   | Histopathologic diagnoses / Special histological comments        | << P a t h o l o g y      O b s e r v a t i o n s >>     |                                  |
| LIVER  | MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Mild, Diffuse. |  |                                  |



## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table

Study Number: 880002

PRINTED: 19-Apr-89

Page: 11

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

|                  |                             |                          |                                  |
|------------------|-----------------------------|--------------------------|----------------------------------|
| Animal: 88F00274 | Sex: Male                   | Group: 2                 | Dose level: 20.00 ML/KG/day      |
| Day of death: 4  | Status: Interim sacrifice 1 |                          | Terminal body weight (kms): 3.52 |
|                  |                             | << Gross observations >> |                                  |
| Tissue           | Finding, severity           | Gross Free-Text Comments |                                  |
| WHOLE BODY       | NO GROSS LESIONS            |                          |                                  |

Tissue                    Necropsy memos  
 No necropsy memos recorded on animal

Tissue                    Histopathologic diagnoses / Special histological comments  
 SPLEEN                    HEMATOPOIESIS, Slight, Multifocal.

LIVER                    HEPATITIS, LYMPHOGRANULOMATOUS, PORTAL TRACKS, Slight, Multifocal.

KIDNEY                    NEPHRITIS, SUBACUTE, INTERSTITIUM, Slight, Focal.

HEART                    HEMORRHAGE, ACUTE, EPICARDIUM, Moderate, Focal.

BRAIN                    LEPTOMENINGITIS, NONSUPPURATIVE, Moderate, Multifocal.

## Appendix I (cont.): PATHOLOGY REPORT

| LETTERMAN ARMY INSTITUTE OF RESEARCH<br>DIV OF RES SUPP, PATH SERV GP<br>PRESIDIO OF SAN FRANCISCO, CA 94129<br>RABBIT/NEW ZEALAND WHITE |  | Individual Animal Data Dump Table<br>Study Number: 88002 |                                  | PRINTED: 19-Apr-89<br>Page: 12 |  |
|--|--|--|----------------------------------|--------------------------------|--|
|  |  | Study Start Date: 13-Sep-88                              |                                  | ACUTE/ACUTE INTRAVENOUS        |  |
| Animal: 88F00258   | Sex: Male  | Group: 2   | Dose level: 20.00 ML/KG/day      |                                |  |
| Day of death: 4  | Status: Interim sacrifice 1                                      |  | Terminal body weight (kms): 3.32 |                                |  |
| Tissue   | Finding, severity  | << Gross Observations >>                                 |                                  |                                |  |
| WHOLE BODY   | NO GROSS LESIONS   | Gross Free-Text Comments                                 |                                  |                                |  |
| Tissue   | Necropsy memos   | << Necropsy Memos >>                                     |                                  |                                |  |
| No necropsy memos recorded on animal   |  |  |                                  |                                |  |
| Tissue   | << Pathologic Observations >>                                    |  |                                  |                                |  |
| LIVER  | Histopathologic diagnoses / Special histological comments        |  |                                  |                                |  |
| KIDNEY   | HEPATITIS, LYMPHOGRANULOMATOUS, PORTAL TRACKS, Mild, Diffuse.    |  |                                  |                                |  |
| LUNGS  | MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Mild, Diffuse. |  |                                  |                                |  |
| BRAIN  | NEPHRITIS, SUBACUTE, INTERSTITIUM, Mild, Focal.                  |  |                                  |                                |  |
|  | INTRA-ALVEOLAR ERYTHROCYTES, Slight, Diffuse.                    |  |                                  |                                |  |
|  | LEPTOMENINGITIS, NONSUPPURATIVE, Moderate, Multifocal.           |  |                                  |                                |  |
|  | ENCEPHALITIS, LYMPHOGANULOMATOUS, Moderate, Focal.               |  |                                  |                                |  |

## Appendix I (cont.): PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

|               |   | Individual Animal Data Dump Table |          | PRINTED: 19-Apr-89               |
|---------------|---|-----------------------------------|----------|----------------------------------|
|               |   | Study Number: 88002               |          | Page: 13                         |
|               |   | Study Start Date: 13-Sep-88       |          | ACUTE/ACUTE INTRAVENOUS          |
| Animal:       | 88F00285  | Sex: Male                         | Group: 2 | Dose level: 20.00 ML/KG/day      |
| Day of death: | 4   | Status: Interim sacrifice 1       |          | Terminal body weight (kms): 3.19 |
| Tissue        | Finding, severity   | << Gross Observations >>          |          | Gross Free-Text Comments         |
| WHOLE BODY    | NO GROSS LESIONS  |                                   |          |                                  |
| Tissue        | Necropsy memos  | << Necropsy Memos >>              |          |                                  |
|               | No necropsy memos recorded on animal  |                                   |          |                                  |
| Tissue        | Histopathologic diagnoses / Special histological comments   | << Pathologic observations >>     |          |                                  |
| LIVER         | MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Slight, Diffuse.  |                                   |          |                                  |
| LUNGS         | PNEUMONIA, PYGRANULOMATOUS, INTERSTITIUM, Mild, Focal.<br>INTRA-ALVEOLAR MACROPHAGES, Mild, Focal.<br>HYPERPLASIA, BRONCHIAL-ASSOCIATED LYMPHOID TISSUE, Mild, Focal. |                                   |          |                                  |
| BRAIN         | LEPTOMENINGITIS, MANSUPPURATIVE, Moderate, Multifocal.<br>ENCEPHALITIS, LYMPHOGANULMATOUS, Mild, Multifocal.  |                                   |          |                                  |

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

PRINTED: 19-Apr-89

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Study Start Date: 13-Sep-88      ACUTE/ACUTE INTRAVENOUS

Animal: 88F00260      Sex: Male      Group: 2      Dose level: 20.00 ML/KG/day

Day of death: 4      Status: Interim sacrifice 1      Terminal body weight (kms): 3.38

Tissue      Finding, severity      << Gross Observations >>  
 WHOLE BODY      NO GROSS LESIONS      Gross Free-Text Comments

Tissue      Necropsy memos      << Necropsy Memos >>

No necropsy memos recorded on animal

Tissue      Histopathologic diagnoses / Special histological comments  
 All protocol required tissues normal.

## Appendix I (cont.): PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

|               |  | Individual Animal Data Dump Table |                     |
|---------------|--|-----------------------------------|---------------------|
|               |  | Study Number:                     | 88002               |
|               |  | Study Start Date:                 | 13-Sep-88           |
|               |  | ACUTE/ACUTE INTRAVENOUS           |                     |
| Animal:       | 88F00293   | Sex:                              | Male                |
| Day of death: | 4  | Status:                           | Interim sacrifice 1 |
| Tissue        | Finding, severity  | << Gross Observations >>          |                     |
| WHOLE BODY    | NO GROSS LESIONS   | Gross Free-Text Comments          |                     |
| Tissue        | Necropsy memos   | << Necropsy Memos >>              |                     |
|               | No necropsy memos recorded on animal   |                                   |                     |
| Tissue        | Histopathologic diagnoses / special histological comments  | << Pathology Observations >>      |                     |
| SPLEEN        | HEMATOPLEISIS, Mild, Diffuse.  |                                   |                     |
| LIVER         | HEPATITIS, LYMPHOGRANULOMATOUS, PORTAL TRACKS, Moderate, Diffuse.  |                                   |                     |
| KIDNEY        | NEPHRITIS, SUBACUTE, INTERSTITIUM, Slight, Focal.<br>INFLAMMATION, SUBACUTE, PERIPELVIC FAT, Slight, Multifocal. |                                   |                     |
| BRAIN         | LEPTOMENINGITIS, NONSUPPURATIVE, Slight, Multifocal.   |                                   |                     |

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

PRINTED: 19-Apr-89  
 Page: 16

## ACUTE/ACUTE INTRAVENOUS

Study Start Date: 13-Sep-88

Group: 2

Dose:

20.00

ML/KG/day

3.88

kms)

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## Appendix I (cont.): PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

|                                      |   |                          |                                  |
|--------------------------------------|---|--------------------------|----------------------------------|
| Animal: 88F00289                     | Sex: Male   | Group: 2                 | Dose level: 20.00 ML/KG/day      |
| Day of death: 15                     | Status: Final sacrifice                                   |                          | Terminal body weight (kms): 3.29 |
| Tissue                               | Finding, severity   | << Gross Observations >> | Gross Free-Text Comments         |
| WHOLE BODY                           | NO GROSS LESIONS  | << Necropsy Memos >>     |                                  |
| Tissue                               | Necropsy memos  |                          |                                  |
| No necropsy memos recorded on animal |   |                          |                                  |
| Tissue                               | << Pathology Observations >>                              |                          |                                  |
| LUNGS                                | Histopathologic diagnoses / Special histological comments |                          |                                  |
|                                      | PNEUMONIA, PYGRANULOMATOUS, INTERSTITIUM, Mild, Focal.    |                          |                                  |

## Appendix I (cont.): PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

| Animal:       | 88F00290 | Sex:              | Male                     | Group: | 2 | Dose Level:                 | 20.00 ML/KG/day |
|---------------|----------|-------------------|--------------------------|--------|---|-----------------------------|-----------------|
| Day of death: | 15       | Status:           | Final sacrifice          |        |   | Terminal body weight (kgs): | 2.99            |
| Tissue        |          | Finding, severity | << Gross Observations >> |        |   | Gross Free-Text Comments    |                 |
| WHOLE BODY    |          | NO GROSS LESIONS  |                          |        |   |                             |                 |

Tissue Necropsy memos

No necropsy memos recorded on animal

| Tissue | << Pathologic diagnoses / Special histological comments >>         |
|--------|--|
| LIVER  | HEPATITIS, LYMPHOGRANULOMATOUS, PORTAL TRACKS, Slight, Multifocal. |

## Appendix I (cont.): PATHOLOGY REPORT

LETERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

|                                      |  | Individual Animal Data Dump Table |                 | PRINTED: 19-Apr-89               |
|--------------------------------------|--|-----------------------------------|-----------------|----------------------------------|
|                                      |  | Study Number: 880002              |                 | Page: 19                         |
|                                      |  | Study Start Date: 13-Sep-88       |                 | ACUTE/ACUTE INTRAVENOUS          |
| Animal:                              | 88F00279   | Sex:                              | Male            | Group: 2                         |
| Day of death:                        | 15   | Status:                           | Final sacrifice | Dose Level: 20.00 ML/KG/day      |
| Tissue                               | Finding, severity  | << Gross Observations >>          |                 | Terminal body weight (kms): 3.19 |
| WHOLE BODY                           | NO GROSS LESIONS   |                                   |                 | Gross Free-Text Comments         |
| Tissue                               | Necropsy memos   | << Necropsy Memos >>              |                 |                                  |
| No necropsy memos recorded on animal |  |                                   |                 |                                  |
| Tissue                               | Histopathologic diagnoses / special histological comments      | << Pathology Observations >>      |                 |                                  |
| LIVER                                | HEPATITIS, LYMPHOGANULOMATOUS, PORTAL TRACKS, Mild, Diffuse.   |                                   |                 |                                  |
| KIDNEY                               | NEPHRITIS, CHRONIC, INTERSTITIUM, Slight, Focal.               |                                   |                 |                                  |
| LUNGS                                | PNEUMONIA, PYOGRANULOMATOUS, INTERSTITIUM, Slight, Multifocal. |                                   |                 |                                  |
| BRAIN                                | LEPTOMENINGITIS, NONSUPPURATIVE, Mild, Diffuse.                |                                   |                 |                                  |



## Appendix I (cont.): PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

|                                      |  | Individual Animal Data Dump Table |                         | PRINTED: 19-Apr-89          | Page: 21        |
|--------------------------------------|--|-----------------------------------|-------------------------|-----------------------------|-----------------|
|                                      |  | Study Start Date: 13-Sep-88       | ACUTE/ACUTE INTRAVENOUS |                             |                 |
| Animal:                              | 88F00273   | Sex: Male                         | Group: 3                | Dose level:                 | 20.00 ML/KG/day |
| Day of death:                        | 4  | Status: Interim sacrifice 1       |                         | Terminal body weight (kms): | 3.05            |
| Tissue                               | Finding, severity  | << Gross Observations >>          |                         | Gross Free-Text Comments    |                 |
| WHOLE BODY                           | NO GROSS LESIONS   |                                   |                         |                             |                 |
| Tissue                               | Necropsy memos   | << Necropsy Memos >>              |                         |                             |                 |
| No necropsy memos recorded on animal |  |                                   |                         |                             |                 |
| Tissue                               | Histopathologic diagnoses / Special histological comments  | << Pathology Observations >>      |                         |                             |                 |
| LIVER                                | MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Slight, Diffuse.   |                                   |                         |                             |                 |
| LUNGS                                | PNEUMONIA, PYGRAMULOMATOUS, INTERSTITIUM, Slight, Multifocal.<br>INTRA-ALVEOLAR MACROPHAGES, Mild, Multifocal. |                                   |                         |                             |                 |

## Appendix I (cont.): PATHOLOGY REPORT

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 RABBIT/NEW ZEALAND WHITE

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 Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

|               |          |             |                     |
|---------------|----------|-------------|---------------------|
| Animal:       | 88F00294 | Sex:        | Male                |
| Day of death: | 4        | Status:     | Interim sacrifice 1 |
|               |          | Group:      | 3                   |
|               |          | Dose level: | 20.00 ML/KG/day     |

|            |                   |                          |
|------------|-------------------|--------------------------|
| Tissue     | Finding, severity | << Gross Observations >> |
| WHOLE BODY | NO GROSS LESIONS  | Gross Free-Text Comments |

|                                      |                |                      |
|--------------------------------------|----------------|----------------------|
| Tissue                               | Necropsy memos | << Necropsy Memos >> |
| No necropsy memos recorded on animal |                |                      |

|        |   |                              |
|--------|---|------------------------------|
| Tissue | Histopathologic diagnoses / Special histological comments | << Pathology Observations >> |
| SPLEEN | HEMATOPOIESIS, Slight, Diffuse.                           |                              |

|       |   |
|-------|---|
| LIVER | HEPATITIS, LYMPHOMAULOMATOUS, PORTAL TRACKS, Slight, Diffuse.<br>MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Moderate, Diffuse. |
| HEART | MYOCARDITIS, SUBACUTE, INTERSTITIUM, Slight, Multifocal.  |

## Appendix I (cont.): PATHOLOGY REPORT

## LETTERMAN ARMY INSTITUTE OF RESEARCH

DIV OF RES SUPP, PATH SERV GP  
PRESIDIO OF SAN FRANCISCO, CA 94129  
RABBIT/NEW ZEALAND WHITE

## Individual Animal Data Dump Table

Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

| Animal:  | Sex: | Day of death: | Status:             | Finding, severity        | No gross lesions | Tissue | Necropsy memos       | Tissue | Necropsy memos                       | Tissue | Histopathologic diagnoses / Special histological comments   |
|----------|------|---------------|---------------------|--------------------------|------------------|--------|----------------------|--------|--------------------------------------|--------|---|
| 88F00265 | Male | 4             | Interim sacrifice 1 | << Gross Observations >> | NO GROSS LESIONS |        | << Necropsy Memos >> |        | No necropsy memos recorded on animal |        | << Pathology Observations >>                                |
|          |      |               |                     | Gross Free-Text Comments |                  |        |                      |        |                                      |        | HEMATOPOIESIS, Slight, Diffuse.                             |
|          |      |               |                     |                          |                  |        |                      |        |                                      |        | INTRA-ALVEOLAR ERYTHROCYTES, Slight, Diffuse.               |
|          |      |               |                     |                          |                  |        |                      |        |                                      |        | PNEUMONIA, PYGRANULOMATOUS, INTERSTITIUM, Mild, Multifocal. |
|          |      |               |                     |                          |                  |        |                      |        |                                      |        | LUNGS   |
|          |      |               |                     |                          |                  |        |                      |        |                                      |        |   |

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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Individual Animal Data Dump Table  
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|               |   | ACUTE/ACUTE INTRAVENOUS     |                          |
|---------------|---|-----------------------------|--------------------------|
|               |   | Study Start Date: 13-Sep-88 |                          |
| Animal:       | 88F00266  | Sex: Male                   | Group: 3                 |
| Day of death: | 4   | Status: Interim sacrifice   | 1                        |
|               |   | Dose level:                 | 20.00 ML/KG/day          |
|               |   | Terminal body weight (kms): | 3.68                     |
| Tissue        | Finding, severity   | << Gross Observations >>    |                          |
| WHOLE BODY    | NO GROSS LESIONS  |                             | Gross Free-Text Comments |
| Tissue        | Necropsy memos  | << Necropsy Memos >>        |                          |
|               | No necropsy memos recorded on animal  |                             |                          |
| Tissue        | << Pathology Observations >>  |                             |                          |
| LIVER         | Histopathologic diagnoses / Special histological comments   |                             |                          |
| LUNGS         | MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Mild, Diffuse.<br>INTRA-ALVEOLAR MACROPHAGES, Mild, Multifocal. |                             |                          |

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

|   |                             |                          |                                  |
|---|-----------------------------|--------------------------|----------------------------------|
| Animal: 88F00267  | Sex: Male                   | Group: 3                 | Dose Level: 20.00 ML/KG/day      |
| Day of death: 4   | Status: Interim sacrifice 1 |                          | Terminal body weight (kms): 3.53 |
| Tissue  | Finding, severity           | << Gross Observations >> | Gross Free-Text Comments         |
| WHOLE BODY  | NO GROSS LESIONS            |                          |                                  |
| Tissue  | Necropsy memos              | << Necropsy Memos >>     |                                  |
| WHOLE BODY  | NO ANIMAL TAG               |                          |                                  |
| << Pathology Observations >><br>Histopathologic diagnoses / special histological comments<br>HEPATITIS, LYMPHOGRANULOMATOUS, PORTAL TRACKS, Slight, Multifocal.<br>INTRA-ALVEOLAR ERYTHROCYTES, Slight, Multifocal. |                             |                          |                                  |

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
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 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 880002

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## ACUTE/ACUTE INTRAVENOUS

|               | Animal:  | Sex: | Male      | Status:      | Final sacrifice | Group: | 3 | Dose level:                 | 20.00 MU/KG/day |
|---------------|--|------|-----------|--------------|-----------------|--------|---|-----------------------------|-----------------|
| Day of death: | 15   |      |           |              |                 |        |   | Terminal body weight (kms): | 3.45            |
| Tissue        | Finding, severity  | <<   | Gross     | Observations | >>              |        |   | Gross Free-Text Comments    |                 |
| WHOLE BODY    | NO GROSS LESIONS   |      |           |              |                 |        |   |                             |                 |
| Tissue        | Necropsy memos   | <<   | Necropsy  | Memos        | >>              |        |   |                             |                 |
|               | No necropsy memos recorded on animal                               |      |           |              |                 |        |   |                             |                 |
| Tissue        | Histopathologic diagnoses / Special histological comments          | <<   | Pathology | Observations | >>              |        |   |                             |                 |
| LIVER         | MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, slight, Diffuse. |      |           |              |                 |        |   |                             |                 |
| LUNGS         | INTRALVEOLAR ERYTHROCYTES, Mild, Multifocal.                       |      |           |              |                 |        |   |                             |                 |

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

|  |   |  |                                  |
|--|---|--|----------------------------------|
| Animal: 88F00259   | Sex: Male   | Group: 3   | Dose level: 20.00 ML/KG/day      |
| Day of death: 15   | Status: Final sacrifice                                   |  | Terminal body weight (kms): 3.23 |
| DISSEMINATED FOCI, Mild  |   |  |                                  |
| Tissue   | Finding, severity   | << Gross Observations >>                                   | Gross Free-Text Comments         |
| LIVER  |   | MULTIPLE <1MM WHT. FOCI AT HILUS OF RT.& ACC. LIVER LOBES. |                                  |
| Tissue   | Necropsy memos  | << Necropsy Memos >>                                       |                                  |
| No necropsy memos recorded on animal                             |   |  |                                  |
| Tissue   | << Pathology Observations >>                              |  |                                  |
| SPLEEN   | Histopathologic diagnoses / special histological comments |  |                                  |
| LIVER  | Required protocol tissue is missing.                      |  |                                  |
| MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Mild, Diffuse. |   |  |                                  |

## Appendix I (cont.): PATHOLOGY REPORT

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Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

## ACUTE/ACUTE INTRAVENOUS

|                  |                         |                          |                                  |
|------------------|-------------------------|--------------------------|----------------------------------|
| Animal: 88F00292 | Sex: Male               | Group: 3                 | Dose level: 20.00 ML/KG/day      |
| Day of death: 15 | Status: Final sacrifice |                          | Terminal body weight (kms): 3.47 |
|                  |                         |                          |                                  |
| Tissue           | Finding, severity       | << Gross Observations >> | Gross Free-Text Comments         |
| WHOLE BODY       | NO GROSS LESIONS        |                          |                                  |
|                  |                         |                          |                                  |

Tissue

Necropsy memos

<< Necropsy Memos >>

No necropsy memos recorded on animal

Tissue Histopathologic diagnoses / Special histological comments

LUNGS

HYPERPLASIA, BRONCHIAL-ASSOCIATED LYMPHOID TISSUE, Slight, Multifocal.

HEART

MYOCARDITIS, SUBACUTE, INTERSTITIUM, slight, Multifocal.

## Appendix I (cont.): PATHOLOGY REPORT

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Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

Animal: 88F00286 Sex: Male Status: Final sacrifice

Day of death: 15 Group: 3 Dose Level: 20.00 ML/KG/day

Day of death: 15 Terminal body weight (kms): 3.33

Tissue Finding, severity << Gross Observations >>  
 WHOLE BODY NO GROSS LESIONS

Tissue Necropsy memos << Necropsy Memos >>

No necropsy memos recorded on animal

Tissue Histopathologic diagnoses / Special histological comments << Pathology Observations >>

SPLEEN Required protocol tissue is missing.

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Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

Animal: 88F00276      Sex: Male      Group: 3      Dose level: 20.00 ML/KG/day  
 Day of death: 15      Status: Final sacrifice      Terminal body weight (kms): 3.45

Tissue      Finding, severity      << Gross Observations >>  
 WHOLE BODY      NO GROSS LESIONS      Gross Free-Text Comments

Tissue      Necropsy memos      << Necropsy Memos >>  
 No necropsy memos recorded on animal

Tissue      Histopathologic diagnoses / Special histological comments  
 SPLEEN      HEMATOPOIESIS, Mild, Diffuse.

LIVER      MULTIVISCULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Slight, Diffuse.

HEART      MYOCARDITIS, SUBACUTE, INTERSTITIUM, Slight, Multifocal.

## Appendix I (cont.) : PATHOLOGY REPORT

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Individual Animal Data Dump Table  
 Study Number: 88002  
 Study Start Date: 13-Sep-88

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ACUTE/ACUTE INTRAVENOUS

Animal: 88F00261      Sex: Male      Status: Interim sacrifice 1  
 Day of death: 4      Group: 4  
 Dose level: 20.00 ML/KG/day

Finding, severity      << Gross Observations >>  
 Tissue      WHOLE BODY      NO GROSS LESIONS  
 Gross Free Text Comments

Tissue      Necropsy memos  
 Tissue      Necropsy memos  
 No necropsy memos recorded on animal

<< Pathological observations >>  
 Tissue      Histopathologic diagnoses / Special histological comments

LIVER      HEPATITIS, LYMPHOGANULOMATOUS, PORTAL TRACKS, Mild, Multifocal.  
 KIDNEY      NEPHRITIS, SUBACUTE, INTERSTITIUM, Mild, Multifocal.

LUNGS      INTRA-ALVEOLAR MACROPHAGES, Mild, Multifocal.  
 HYPERPLASIA, BRONCHIAL-ASSOCIATED LYMPHOID TISSUE, Slight, Multifocal.

BRAIN      ENCEPHALITIS, LYMPHOGANULOMATOUS, Mild, Multifocal.

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|               |                   | ACUTE/ACUTE INTRAVENOUS     |                          |
|---------------|-------------------|-----------------------------|--------------------------|
|               |                   | Study Start Date: 13-Sep-88 |                          |
| Animal:       | 88F00296          | Sex:                        | Male                     |
| Day of death: | 4                 | Status:                     | Interim sacrifice 1      |
|               |                   | Group:                      | 4                        |
|               |                   | Dose level:                 | 20.00 ML/KG/day          |
|               |                   | Terminal body weight (kms): | 3.69                     |
| Tissue        | Finding, severity | << Gross Observations >>    | Gross Free-Text Comments |
| WHOLE BODY    | NO GROSS LESIONS  |                             |                          |

|        |                                      | << Necropsy Memos >> |  |
|--------|--------------------------------------|----------------------|--|
|        |                                      | << Necropsy Memos >> |  |
| Tissue | No necropsy memos recorded on animal |                      |  |

|       |   | << Pathology Observations >>                              |  |
|-------|---|---|--|
|       |   | Histopathologic diagnoses / Special histological comments |  |
| LUNGS | PNEUMONIA, PYGRANULOMATOUS, INTERSTITIUM, Slight, Multifocal. |   |  |

## Appendix I (cont.): PATHOLOGY REPORT

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Individual Animal Data Dump Table

Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

Animal: 88F00277 Sex: Male Group: 4 Dose level: 20.00 ML/KG/day

Day of death: 4 Status: Interim sacrifice 1 Terminal body weight (kms): 3.48

Finding, severity << Gross Observations >>

Tissue WHOLE BODY NO GROSS LESIONS Gross Free-Text Comments

Tissue Necropsy Memos << Necropsy Memos >>

No necropsy memos recorded on animal

Tissue Histopathologic diagnoses / Special histological comments << Pathology Observations >>

LIVER HEPATITIS, LYMPHOGRANULOMATOUS, PORTAL TRACKS, Slight, Multifocal.

KIDNEY VACUOLIZATION, TUBULAR EPITHELIUM, Slight, Focal.

LUNGS HYPERPLASIA, BRONCHIAL-ASSOCIATED LYMPHOID TISSUE, Slight, Focal.

BRAIN LEPTOMENINGITIS, NONSUPPURATIVE, Slight, Focal.

## Appendix I (cont.): PATHOLOGY REPORT

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 Individual Animal Data Dump Table  
 Study Number: 88002  
 Study Start Date: 13-Sep-88      ACUTE/ACUTE INTRAVENOUS

|                  |                             |                          |                             |                 |
|------------------|-----------------------------|--------------------------|-----------------------------|-----------------|
| Animal: 88F00287 | Sex: Male                   | Group: 4                 | Dose level:                 | 20.00 ML/KG/day |
| Day of death: 4  | Status: Interim sacrifice 1 |                          | Terminal body weight (kms): | 3.19            |
| Tissue           | Finding, severity           | << Gross Observations >> | Gross Free-Text Comments    |                 |
| WHOLE BODY       | NO GROSS LESIONS            |                          |                             |                 |

|                                      |                |                      |
|--------------------------------------|----------------|----------------------|
| Tissue                               | Necropsy Memos | << Necropsy Memos >> |
| No necropsy memos recorded on animal |                |                      |

|        |   |
|--------|---|
| Tissue | << Pathologic observations / Special histological comments            |
| LIVER  | MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Slight, Multifocal. |
| KIDNEY | VACUOLIZATION, TUBULAR EPITHELIUM, Mild, Multifocal.                  |
| HEART  | MYOCARDITIS, SUBACUTE, INTERSTITIUM, Slight, Focal.                   |

## Appendix I (cont.): PATHOLOGY REPORT

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Individual Animal Data Dump Table  
 Study Number: 88002

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ACUTE/ACUTE INTRAVENOUS

|               |                                      | Study Start Date: 13-Sep-88   |   |                                  |
|---------------|--------------------------------------|---|---|----------------------------------|
| Animal:       | 88F00281                             | Sex: Male   | Group: 4  | Dose level: 20.00 ML/KG/day      |
| Day of death: | 4                                    | Status: Interim sacrifice 1   |   | Terminal body weight (kms): 3.53 |
| Tissue        | Finding, severity                    | << Gross Observations >>  | Gross Free-Text Comments                                  |                                  |
| WHOLE BODY    | NO GROSS LESIONS                     |   |   |                                  |
| Tissue        | Necropsy memos                       | << Necropsy Memos >>  |   |                                  |
|               | No necropsy memos recorded on animal |   |   |                                  |
| Tissue        |                                      | << Pathology Observations >>  | Histopathologic diagnoses / Special histological comments |                                  |
| LIVER         |                                      | MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Mild, Diffuse.  |   |                                  |
| LUNGS         |                                      | INTRA-ALVEOLAR ERYTHROCYTES, Slight, Multifocal.<br>PNEUMONIA, PYGRANULOMATOUS, INTERSTITIUM, Mild, Multifocal.<br>INTRA-ALVEOLAR MACROPHAGES, Mild, Multifocal.<br>INTRA-ALVEOLAR PROTEIN (EDEMA), ACUTE, Slight, Focal. |   |                                  |
| HEART         |                                      | HEMORRHAGE, ACUTE, EPICARDIUM, Mild, Focal.   |   |                                  |

## Appendix I (cont.) : PATHOLOGY REPORT

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Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

## ACUTE/ACUTE INTRAVENOUS

Animal: 88F00302      Sex: Male      Status: Final sacrifice

Group: 4      Dose Level: 20.00 ML/KG/day

Day of death: 15      Terminal body weight (kms): 3.27

Tissue      Finding, severity      << Gross Observations >>

Gross Free-Text Comments

WHOLE BODY      NO GROSS LESIONS

Tissue      Necropsy memos      << Necropsy Memos >>

No necropsy memos recorded on animal

Tissue      << Pathology Observations >>

Histopathologic diagnoses / Special histological comments

LUNGS      PNEUMONIA, PYOGRAMULMATOUS, INTERSTITIUM, Slight, Multifocal.

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## Individual Animal Data Dump Table

Study Number: 880002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

Animal: 88F00283      Sex: Male      Status: Final sacrifice  
 Day of death: 15      Group: 4      Dose level: 20.00 ML/KG/day

Finding, severity      << Gross Observations >>  
 Tissue      WHOLE BODY      NO GROSS LESIONS      Gross Free-Text Comments

Tissue      Necropsy memos      << Necropsy Memos >>

No necropsy memos recorded on animal  
 Tissue      Histopathologic diagnoses / Special histological comments  
 LIVER      MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Slight, Multifocal.

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Animal: 88F00284      Sex: Male  
 Day of death: 15      Status: Final sacrifice

Tissue      Finding, severity      << Gross Observations >>  
 WHOLE BODY      NO GROSS LESIONS      Gross Free-Text Comments

Tissue      Necropsy memos      << Necropsy Memos >>

No necropsy memos recorded on animal

Tissue      Histopathologic diagnoses / Special histological comments  
 LIVER      HEPATITIS, LYMPHOGANULOMATOUS, PORTAL TRACKS, Slight, Multifocal.  
              MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Mild, Diffuse.

KIDNEY      NEPHRITIS, SUBACUTE, INTERSTITIUM, Mild, Multifocal.

LUNGS      PNEUMONIA, PYOGANULOMATOUS, INTERSTITIUM, Mild, Multifocal.

BRAIN      LEPTOMENINGITIS, NONSUPPURATIVE, Mild, Multifocal.

<< Pathology Observations >>

Individual Animal Data Dump Table  
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ACUTE/ACUTE INTRAVENOUS

Study Start Date: 13-Sep-88

Group: 4

Dose level:

20.00 ML/KG/day

Terminal body weight (kms):

3.12

## Appendix I (cont.): PATHOLOGY REPORT

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|                                      |  |                          |                         |
|--------------------------------------|--|--------------------------|-------------------------|
| Animal: 88F00268                     | Sex: Male  | Group: 4                 | PRINTED: 19-Apr-89      |
| Day of death: 15                     | Status: Final sacrifice  |                          | Page: 39                |
| Tissue                               | Finding, severity  | << Gross Observations >> | ACUTE/ACUTE INTRAVENOUS |
| WHOLE BODY                           | NO GROSS LESIONS   | Gross Free Text Comments |                         |
| Tissue                               | Necropsy memos   | << Necropsy Memos >>     |                         |
| No necropsy memos recorded on animal |  |                          |                         |
| Tissue                               | << Pathologic diagnoses / Special histological comments >>         |                          |                         |
| LIVER                                | HEPATITIS, LYMPHOGANULOMATOUS, PARTIAL TRACKS, Slight, Multifocal. |                          |                         |
| LUNGS                                | PNEUMONIA, PYOGRANULOMATOUS, INTERSTITIUM, Slight, Multifocal.     |                          |                         |

## Appendix I (cont.): PATHOLOGY REPORT

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Individual Animal Data Dump Table  
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ACUTE/ACUTE INTRAVENOUS

Study Start Date: 13-Sep-88

Group: 4

Dose level:

20.00

ML/KG/day

3.48

Animal: 88F00269

Day of death: 15

Sex: Male

Status: Final sacrifice

Tissue

Finding, severity

<< Gross Observations >>

Gross Free-Text Comments

Tissue

Necropsy memos

<< Necropsy Memos >>

No necropsy memos recorded on animal

Tissue

Histopathologic diagnoses / special histological comments

LIVER

MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Mild, Diffuse.

LUNGS

INTRA-ALVEOLAR ERYTHROCYTES, Mild, Diffuse.

<< Pathology Observations >>

## Appendix I (cont.): PATHOLOGY REPORT

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|--|---|--|----------------------------------|--------------------------------|--|--|
|  |   | Study Start Date: 13-Sep-88                              |                                  | ACUTE/ACUTE INTRAVENOUS        |  |  |
| Animal: 88F00315   | Sex: Female   | Group: 1   | Dose level: 20.00 ML/KG/day      |                                |  |  |
| Day of death: 1  | Status: FOUND DEAD  |  | Terminal body weight (kgs): 3.88 |                                |  |  |
| Tissue   | Finding, severity   | << Gross observations >>                                 | Gross Free-Text Comments         |                                |  |  |
| LIVER  | CONGESTED, Moderate   |  | ACUTE, DIFFUSE                   |                                |  |  |
| LUNGS  | HEMORRHAGE(S), Moderate<br>CONGESTION, Moderate   |  | PETECHIAE<br>DIFFUSE             |                                |  |  |
| PERITONEAL CAV.  | FRANK BLOOD PRESENT, Mild<br>HEMORRHAGE, Moderate   |  | CLOT<br>RETROPERITONEAL          |                                |  |  |
| EYES & OPTIC N.  | EXOPHTHALMUS, Moderate  |  | CORNEA CLEAR                     |                                |  |  |
| SKIN   | HEMORRHAGE, SUBCUTANEOUS, Moderate  |  | THORAX                           |                                |  |  |
| Tissue   | Necropsy memos  | << Necropsy Memos >>                                     |                                  |                                |  |  |
| No necropsy memos recorded on animal   |   |  |                                  |                                |  |  |
| Tissue   | << Pathology Observations >>  |  |                                  |                                |  |  |
| SPLEEN   | HISTOPATHOLOGIC DIAGNOSES / Special histological comments   |  |                                  |                                |  |  |
| LIVER  | HEMATOPOESIS, Slight, Diffuse.  |  |                                  |                                |  |  |
| LUNGS  | MULTIVESICULAR (GLYCOGEN) CHANGE, HEPATOCELLULAR, Slight, Diffuse.<br>INTRA-ALVEOLAR ERYTHROCYTES, Mild, Diffuse. |  |                                  |                                |  |  |

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RABBIT/NEW ZEALAND WHITE

Animal: 88F00339      Sex: Female

Day of death: 1      Status: FOUND DEAD

Tissue      Finding, severity

NOSE/TURBINATES      BLOOD WITHIN NARES, Moderate

EYES & OPTIC N.

EXOPHTHALMUS, Moderate

PERITONEAL CAV.

FRANK BLOOD PRESENT, Mild

LUNGS      HEMORRHAGE(S), Moderate

CONGESTION, Moderate

LIVER      CONGESTED, Moderate

TRACHEA      FLUID FILLED LUMEN, Moderate

Tissue      Necropsy memos

No necropsy memos recorded on animal

Tissue      No necropsy memos

<< Pathology observations >>

Histopathologic diagnoses / Special histological comments

SPLEEN      HEMATOPOIESIS, Mild, Multifocal.

LUNGS      INTRA-ALVEOLAR ERYTHROCYTES, Slight, Diffuse.

Individual Animal Data Dump Table  
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ACUTE/ACUTE INTRAVENOUS

Study Start Date: 13-Sep-88

Group: 1      Dose level: 20.00 ML/KG/day

Terminal body weight (kms): 4.21

<< Gross Observations >>  
 Gross Free-Text Comments

CORNEA CLEAR

CLOT

PETECHIAE

ACUTE

ACUTE

FOAM

<< Necropsy Memos >>

<< Pathology Observations >>  
 Histopathologic diagnoses / Special histological comments

## Appendix I (cont.): PATHOLOGY REPORT

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Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

Animal: 88F00345

Day of death: 4

Sex: Female

Status: Interim sacrifice 2

Group: 1

Dose Level: 20.00 ML/KG/day

Terminal body weight (kms): 4.42

Finding, severity

<< Gross Observations >>

Gross Free-Text Comments

NO GROSS LESIONS

<< Necropsy Memos >>

Necropsy memos

No necropsy memos recorded on animal

<< Pathology Observations >>

Histopathologic diagnoses / Special histological comments

SPLEEN HEMOSIDEROSIS, Mild, Multifocal.

## Appendix I (cont.) : PATHOLOGY REPORT

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 RABBIT/NEW ZEALAND WHITE

Animal: 88F00348      Sex: Female      Status: Interim sacrifice 2

Day of death: 4

Finding, severity

WHOLE BODY

NO GROSS LESIONS

Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

Group: 1      Dose Level: 20.00 ML/KG/day

3.64

<< Gross Observations >>

Gross Free-Text Comments

<< Necropsy Memos >>

No necropsy memos recorded on animal

Tissue      << Pathology Observations >>  
 Histopathologic diagnoses / Special histological comments

LIVER      HEPATITIS, LYMPHOGRANULOMATOUS, PORTAL TRACKS, Slight, Multifocal.

## Appendix I (cont.) : PATHOLOGY REPORT

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## Individual Animal Data Dump Table

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Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

Dose Level: 20.00 ML/KG/day

Dose (kms): 4.19

Group: 1

Terminal body weight (kms):

Sex: Female

Status: FOUND DEAD

Day of death: 1

Finding, severity

&lt;&lt; Gross Observations &gt;&gt;

Comments

CORNEA CLEAR

FOAM

EXOPHTHALMUS, Moderate

Fluid filled lumen, Moderate

CONGESTION, Marked

EDEMATOUS, Moderate

CONGESTED, Marked

HEMORRHAGE, SUBCUTANEOUS, Moderate

ECCHYMOSIS

FOAM

ACUTE

## Tissue

&lt;&lt; Necropsy memos &gt;&gt;

No necropsy memos recorded on animal

## Tissue

&lt;&lt; Pathologic diagnoses / Special histological comments &gt;&gt;

LUNGS CONGESTION, ACUTE, VASCULATURE, Mild, Diffuse.

BRAIN LEPTOMENINGITIS, NONSUPPURATIVE, Mild, Multifocal.

## Appendix I (cont.) : PATHOLOGY REPORT

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Individual Animal Data Dump Table  
 Study Number: 88002

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Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

Animal: 88F00310 Sex: Female Status: Interim sacrifice 2

Day of death: 4 Group: 1 Dose level: 20.00 ML/KG/day

Terminal body weight (kms): 3.74

Tissue Finding, severity << Gross Observations >>  
 NO GROSS LESIONS

Gross Free-Text Comments

Tissue Necropsy memos << Necropsy Memos >>

No necropsy memos recorded on animal

Tissue << Pathology Observations >>  
 SPLEEN Histopathologic diagnoses / Special histological comments

HENOSIDEROSIS, Slight, Diffuse.

Appendix I (cont.): PATHOLOGY REPORT

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Individual Animal Data Dump Table  
Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

|                                      |   |                                  |                             |
|--------------------------------------|---|----------------------------------|-----------------------------|
| Animal: 88r00331                     | Sex: Female   | Group: 1                         | Dose level: 20.00 ML/KG/day |
| Day of death: 15                     | Status: Final sacrifice                                   | Terminal body weight (kms): 4.03 |                             |
| Finding, severity                    |   | << Gross Observations >>         |                             |
| Tissue                               |   | Gross Free-Text Comments         |                             |
| WHOLE BODY                           | NO GROSS LESIONS  |                                  |                             |
| Tissue                               | Necropsy memos  | << Necropsy Memos >>             |                             |
| No necropsy memos recorded on animal |   |                                  |                             |
| Tissue                               | Histopathologic diagnoses / Special histological comments | << Pathology Observations >>     |                             |
| SPLEEN                               | LYMPHOID HYPERPLASIA, Moderate.                           |                                  |                             |



## Appendix I (cont.) : PATHOLOGY REPORT

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## Individual Animal Data Dump Table

Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

Animal: 88F00341

Sex: Female

Status: Final sacrifice

Day of death: 15

Group: 1

Terminal body weight (kms):

Dose level: 20.00 ML/KG/day

3.88

&lt;&lt; Gross Observations &gt;&gt;

Gross Free Text Comments

Finding, severity

&lt;&lt; Necropsy Memos &gt;&gt;

No gross lesions

&lt;&lt; Necropsy Memos &gt;&gt;

Necropsy memos

No necropsy memos recorded on animal

&lt;&lt; Pathologic Observations &gt;&gt;

Histopathologic diagnoses / Special histological comments

Tissue

HEMOSIDEROSIS, slight, diffuse.

SPLEEN

HEPATITIS, LYMPHOGRANULOMATOUS, PORTAL TRACKS, Mild, diffuse.

LIVER

INTRA-ALVEOLAR MACROPHAGES, Slight, Diffuse.

LUNGS

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

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|               |  | Study Start Date: 13-Sep-88 |                 | ACUTE/ACUTE INTRAVENOUS     |                 |
|---------------|--|-----------------------------|-----------------|-----------------------------|-----------------|
|               |  | Group:                      | 1               | Dose level:                 | 20.00 ML/KG/day |
| Animal:       | 88F00305   | Sex:                        | Female          | Terminal body weight (kms): | 4.08            |
| Day of death: | 15   | Status:                     | Final sacrifice | Gross Observations >>       |                 |
| Tissue        | Finding severity   | << Gross Observations >>    |                 | Gross Free-Text Comments    |                 |
| WHOLE BODY    | NO GROSS LESIONS   |                             |                 |                             |                 |
| Tissue        | Necropsy memos   | << Necropsy Memos >>        |                 |                             |                 |
|               | No necropsy memos recorded on animal                                 |                             |                 |                             |                 |
| Tissue        | << Pathology Observations >>   |                             |                 |                             |                 |
| SPLEEN        | Histopathologic diagnoses / Special histological comments            |                             |                 |                             |                 |
| LIVER         | HEMOSIDEROSIS, Mild, Multifocal.                                     |                             |                 |                             |                 |
| KIDNEY        | VACUOLIZATION, TUBULAR EPITHELIUM, Slight, Multifocal.               |                             |                 |                             |                 |
| LUNGS         | INTRA-AUVEOLAR MACROPHAGES, Slight, Diffuse.                         |                             |                 |                             |                 |
|               | HYPERPLASIA, BRONCHIAL-ASSOCIATED LYMPHOID TISSUE, Mild, Multifocal. |                             |                 |                             |                 |
| BRAIN         | LEPTOMENINGITIS, NONSUPPURATIVE, Mild, Multifocal.                   |                             |                 |                             |                 |
|               | ENCEPHALITIS, LYMPHOGANULOMATOUS, Moderate, Multifocal.              |                             |                 |                             |                 |

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/INTRAVENOUS

Animal: 88F00313 Sex: Female Status: Interim sacrifice 2

Dose level:

20.00 ML/KG/day

Group: 2 Terminal body weight (kms):

3.88

Tissue Finding, severity << Gross Observations >>  
 WHOLE BODY NO GROSS LESIONS

Gross Free-Text Comments

Tissue Necropsy memos << Necropsy Memos >>

No necropsy memos recorded on animal

Tissue << Pathology Observations >>

Histopathologic diagnoses / Special histological comments

KIDNEY

VACUOLIZATION, TUBULAR EPITHELIUM, Mild, Multifocal.

LUNGS

INTRA-ALVEOLAR MACROPHAGES, Mild, Multifocal.

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 880002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

Animal: 88F00308

Sex: Female

Status: Interim sacrifice 2

Group: 2

Dose level:

20.00

ML/KG/day

Day of death: 4

Finding, severity

Terminal body weight (kms):

3.75

Tissue WHOLE BODY

No GROSS LESIONS

Gross Observations >>

Gross Free Text Comments

Tissue No necropsy memos recorded on animal

<< Necropsy Memos >>

Tissue No necropsy memos recorded on animal

<< Pathology Observations >>

Tissue Histopathologic diagnoses / Special histological comments

LIVER HEPATITIS, LYMPHOGRANULOMATOUS, PORTAL TRACKS, Mild, Diffuse.

MULTIVESICULAR GLYCOGEN CHANGE, HEPATOCELLULAR, Slight, Diffuse.

KIDNEY VACUOLIZATION, TUBULAR EPITHELIUM, Slight, Focal.

LUNGS INTRA-ALVEOLAR ERYTHROCYTES, Slight, Diffuse.



## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

Animal: 88F00337      Sex: Female      Group: 2      Dose level: 20.00 ML/KG/day  
 Day of death: 4      Status: Interim sacrifice 2      Terminal body weight (kms): 3.66

Finding, severity      << Gross Observations >>  
 Tissue      WHOLE BODY      NO GROSS LESIONS  
 NO necropsy memos      << Necropsy Memos >>

No necropsy memos recorded on animal

Tissue      << Pathology Observations >>  
 SPLEEN      Histopathologic diagnoses / Special histological comments  
 HEMOSIDEROSIS, Slight, Diffuse.

KIDNEY

VACUOLIZATION, TUBULAR EPITHELIUM, Mild, Multifocal.

LUNGS

PNEUMONIA, PYOGANULOMATOUS, INTERSTITIUM, Slight, Multifocal.

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

Animal: 88F00349      Sex: Female      Status: Interim sacrifice 2

Day of death: 4

Group: 2

Dose level:

20.00 ML/KG/day

Terminal body weight (kms):

3.96

Finding, severity  
 WHOLE BODY  
 NO GROSS LESIONS

<< Gross Observations >>  
 Gross Free-Text Comments

Tissue  
 No necropsy memos recorded on animal

<< Necropsy Memos >>

Tissue  
 SPLEEN

<< Pathologic Observations >>

Histopathologic diagnoses / Special histological comments

HEMOSEDEROSIS, Slight, Diffuse.  
 HEMATOPOIESIS, Mild, Diffuse.

LUNGS  
 INTRA-ALVEOLAR MACROPHAGES, Slight, Multifocal.

<< Pathology Annex (cont.)

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

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|                                      |                   | ACUTE / ACUTE INTRAVENOUS   |   |
|--------------------------------------|-------------------|-----------------------------|---|
| Animal:                              | 88-00334          | Sex:                        | Female                                      |
| Day of death:                        | 15                | Status:                     | Final sacrifice                             |
| Tissue                               | Finding, severity | << Gross Observations >>    | Terminal body weight (kms): 20.00 ML/KG/day |
| WHOLE BODY                           | NO GROSS LESIONS  | >> Gross Free-Text Comments |   |
| Tissue                               | Necropsy Memos    | << Necropsy Memos >>        |   |
| No necropsy memos recorded on animal |                   |                             |   |

<< Pathology Observations >>  
 Histopathologic diagnoses / Special histological comments  
 LYMPHOID HYPERPLASIA, Moderate.

NEPHRITIS, SUBACUTE, INTERSTITIUM, Mild, Multifocal.

MYOCARDITIS, SUBACUTE, INTERSTITIUM, Slight, Focal.

LEPTOMENINGITIS, NONSUPPURATIVE, Mild, Diffuse.  
 ENCEPHALITIS, LYMPHOGANULOMATOUS, Moderate, Multifocal.

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERTMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
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ACUTE/ACUTE INTRAVENOUS

Study Start Date: 13-Sep-88

Dose level:

20.00 ML/KG/day

Group: 2

Terminal body weight (kms):

3.82

Sex: Female

Status: Final sacrifice

Finding, severity

<< Gross Observations >>

Gross Free-Text Comments

Day of death: 15

No gross lesions

Whole Body

Tissue

Necropsy memos

No necropsy memos recorded on animal

Tissue

No necropsy memos

## Appendix I (cont.) : PATHOLOGY REPORT

| LETTERMAN ARMY INSTITUTE OF RESEARCH<br>DIV OF RES SUPP, PATH SERV GP<br>PRESIDIO OF SAN FRANCISCO, CA 94129 |   | Individual Animal Data Dump Table |                                  | PRINTED: 19-Apr-89      | Page: 58 |
|--|---|-----------------------------------|----------------------------------|-------------------------|----------|
| RABBIT/NEW ZEALAND WHITE   |   | Study Start Date: 13-Sep-88       |                                  | ACUTE/ACUTE INTRAVENOUS |          |
| Animal: 88F00353   | Sex: Female   | Group: 2                          | Dose Level: 20.00 ML/KG/day      |                         |          |
| Day of death: 15   | Status: Final sacrifice   |                                   | Terminal body weight (kms): 4.21 |                         |          |
| Tissue   | Finding, severity   | << Gross Observations >>          |                                  |                         |          |
| WHOLE BODY   | NO GROSS LESIONS  | Gross Free-Text Comments          |                                  |                         |          |
| Tissue   | Necropsy Memos  | << Necropsy Memos >>              |                                  |                         |          |
| .....  | .....   | .....                             |                                  |                         |          |
| No necropsy  | Memos recorded on animal  |                                   |                                  |                         |          |
| Tissue   | Histopathologic diagnoses / Special histological comments   | << Pathology Observations >>      |                                  |                         |          |
| LIVER  | HEPATITIS, LYMPHOGRANULOMATOUS, PORTAL TRACKS, Slight, Multifocal.  |                                   |                                  |                         |          |
| KIDNEY   | NEPHRITIS, CHRONIC, INTERSTITIUM, Moderate, Focal.  |                                   |                                  |                         |          |
| BRAIN  | LEPTOMENINGITIS, NONSUPPURATIVE, SLIGHT, Multifocal.<br>ENCEPHALITIS, LYMPHOGRANULOMATOUS, Moderate, Focal. |                                   |                                  |                         |          |

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

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Study Start Date: 13-Sep-88  
 ACUTE/ACUTE INTRAVENOUS  
 Animal: 88F00333 Sex: Female Group: 2 Dose level: 20.00 ML/KG/day  
 Day of death: 15 Status: Final sacrifice Terminal body weight (kms): 4.34

Finding, severity << Gross Observations >>  
 Tissue WHOLE BODY NO GROSS LESIONS

<< Necropsy Memos >>

Tissue Necropsy memos  
 No necropsy memos recorded on animal

<< Pathological Observations >>  
 Tissue Histopathologic diagnoses / Special histological comments

LIVER HEPATITIS, LYMPHOGRANULOMATOUS, PORTAL TRACKS, Mild, Multifocal.

KIDNEY NEPHRITIS, SUBACUTE, INTERSTITIUM, Mild, Multifocal,  
 VACUOLIZATION, TUBULAR EPITHELIUM, Mild, Multifocal.

LUNGS INTRA-ALVEOLAR ERYTHROCYTES, Mild, Multifocal.

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

Animal: 88F00318      Sex: Female      Status: Final sacrifice

Day of death: 15      Group: 2      Study Start Date: 13-Sep-88      ACUTE/ACUTE INTRAVENOUS

Finding, severity      << Gross      Observations      Dose level: 20.00 ML/KG/day

Tissue      WHOLE BODY      NO GROSS LESIONS      Terminal body weight (kms): 3.94

Tissue      Necropsy memos      << Necropsy      Hemos >>

No necropsy memos recorded on animal

Tissue      LUNGS      Histopathologic diagnoses / Special histological comments      << Pathology observations >>

PNEUMONIA, PYOGANULOMATOUS, INTERSTITIUM, Mild, Focal.  
 INTRA-ALVEOLAR MACROPHAGES, Slight, Multifocal.

## Appendix I (cont.): PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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PRESIDIO OF SAN FRANCISCO, CA 94129

RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table

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ACUTE/ACUTE INTRAVENOUS

Animal: 88F00311      Sex: Female      Status: Interim sacrifice 2

Day of death: 4      Status: Interim sacrifice 2

Group: 3

Dose level:

20.00 ML/KG/day

Terminal body weight (kms):

3.4~

Tissue      Finding, severity      << Gross Observations >>

WHOLE BODY      NO GROSS LESIONS      << Necropsy Memos >>

Necropsy memos

No necropsy memos recorded on animal

Tissue      << Pathological Observations >>

Histopathologic diagnoses / Special histological comments

SPLEEN      HEMOSIDEROSIS, Mild, Multifocal.

LUNGS      INTRA-ALVEOLAR ERYTHROCYTES, Slight, Multifocal.

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GF  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

Animal: 88F00314      Sex: Female  
 Day of death: 4      Status: Interim sacrifice 2

Group: 3      Dose level: 20.00 ML/KG/day  
 Terminal body weight (kms): 3.84

Finding, severity  
 WHOLE BODY      NO GROSS LESIONS

<< Gross Observations >>  
 Gross Free-Text Comments

Tissue      Necropsy memos  
 No necropsy memos recorded on animal

<< Pathology Observations >>  
 Histopathologic diagnoses / Special histological comments

Tissue      HEMATOPOIESIS, Slight, Diffuse.

SPLEEN      HEPATITIS, LYMPHOGRANULOMATOUS, PORTAL TRACKS, Slight, Multifocal.

LIVER      NEPHRITIS, SUBACUTE, INTERSTITIUM, Mild, Multifocal.

KIDNEY      VACUOLIZATION, TUBULAR EPITHELIUM, Mild, Multifocal.

LUNGS      INTRA-ALVEOLAR ERYTHROCYTES, Mild, Multifocal.

PNEUMONIA, PYOGRANULOMATOUS, INTERSTITIUM, Slight, Multifocal.

HEART      MYOCARDITIS, SUBACUTE, INTERSTITIUM, Slight, Focal.

BRAIN      LEPTOMENINGITIS, NONSUPPURATIVE, Mild, Multifocal.

## Appendix I (cont.): PATHOLOGY REPORT

LETERMAN ARMY INSTITUTE OF RESEARCH  
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 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

## Individual Animal Data Dump Table

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## ACUTE/ACUTE INTRAVENOUS

| Animal:           | Sex:  | Status:                      | Group: | Dose level:     |
|-------------------|---|------------------------------|--------|-----------------|
| 88F00338          | Female  | Interim sacrifice 2          | 3      | 20.00 ML/KG/day |
| Day of death:     |   |                              |        |                 |
| Finding, severity | << Gross Observations >>                                  |                              |        |                 |
| Tissue            |   | Gross Free-Text Comments     |        |                 |
| WHOLE BODY        | NO GROSS LESIONS  |                              |        |                 |
| Tissue            | Necropsy memos  | << Necropsy Memos >>         |        |                 |
|                   | No necropsy memos recorded on animal                      |                              |        |                 |
| Tissue            | Histopathologic diagnoses / special histological comments | << Pathology Observations >> |        |                 |
| SPLEEN            | LYMPHOID HYPERPLASIA, Mild.                               |                              |        |                 |

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
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 RABBIT/NEW ZEALAND WHITE

| Individual Animal Data Dump Table |   | PRINTED: 19-Apr-89   |                          |
|-----------------------------------|---|----------------------|--------------------------|
|                                   |   | Page: 64             |                          |
| Study Start Date: 13-Sep-88       |   |                      |                          |
| ACUTE/ACUTE INTRAVENOUS           |   |                      |                          |
| Animal: 88F00344                  | Sex: Female   | Group: 3             | Dose (level:             |
| Day of death: 4                   | Status: Interim sacrifice 2                               |                      | 20.00 ML/KG/day          |
|                                   |   |                      | 3.98                     |
| Finding, severity                 | << Gross Observations >>                                  |                      |                          |
| WHOLE BODY                        | NO GROSS LESIONS  |                      | Gross Free-Text Comments |
| Tissue                            | Necropsy memos  | << Necropsy Memos >> |                          |
|                                   | No necropsy memos recorded on animal                      |                      |                          |
| Tissue                            | << Pathologic Observations >>                             |                      |                          |
| SPLEEN                            | Histopathologic diagnoses / Special histological comments |                      |                          |
| LUNGS                             | HEMATOPOESIS, Slight, Diffuse.                            |                      |                          |
|                                   | INTRA-ALVEOLAR ERYTHROCYTES, slight, Diffuse.             |                      |                          |



## Appendix I (cont.) : PATHOLOGY REPORT

LEITERMAN ARMY INSTITUTE OF RESEARCH  
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 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
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ACUTE/ACUTE INTRAVENOUS  
 Study Start Date: 13-Sep-88

Animal: 88F00319      Sex: Female

Status: Final sacrifice

Day of death: 15      Group: 3

Dose level: 20.00 ML/KG/day

Finding, severity

<< Gross Observations >>

Tissue

Gross Free-Text Comments

WHOLE BODY

NO GROSS LESIONS

<< Necropsy Memos >>

Tissue

Necropsy memos

No necropsy memos recorded on animal

<< Pathology Observations >>

Tissue

Histopathologic diagnoses / Special histological comments

SPLEEN

HEMATOPOIESIS, Mild, Multifocal.

HEART

HYOCARDITIS, SUBACUTE, INTERSTITIUM, Slight, Multifocal.

## Appendix I (cont.): PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

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Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

|                   |                                      |   |                             |
|-------------------|--------------------------------------|---|-----------------------------|
| Animal: 88F00304  | Sex: Female                          | Group: 3  | Dose Level:                 |
| Date of death: 15 | Status: Final sacrifice              |   | Terminal body weight (kms): |
|                   |                                      | << Gross Observations >>                                    | 20.00 ML/KG/day             |
|                   |                                      | Gross Free-Text Comments                                    | 3.68                        |
| Tissue            | Finding, severity                    |   |                             |
| WHOLE BODY        | NO GROSS LESIONS                     | << Necropsy Memos >>  |                             |
| Tissue            | Necropsy memos                       |   |                             |
|                   | No necropsy memos recorded on animal |   |                             |
| Tissue            |                                      | << Pathology Observations >>                                |                             |
|                   |                                      | Histopathologic diagnoses / Special histological comments   |                             |
| KIDNEY            |                                      | NEPHRITIS, CHRONIC, INTERSTITIUM, Mild, Multifocal.         |                             |
|                   |                                      | NEPHRITIS, SUBACUTE, INTERSTITIUM, Moderate, Multifocal.    |                             |
| LUNGS             |                                      | PNEUMONIA, PYGRANULOMATOUS, INTERSTITIUM, Mild, Multifocal. |                             |
| HEART             |                                      | MYOCARDITIS, SUBACUTE, INTERSTITIUM, slight, Multifocal.    |                             |
| BRAIN             |                                      | LEPTOMENINGITIS, NONSUPPURATIVE, Moderate, Multifocal.      |                             |
|                   |                                      | ENCEPHALITIS, LYMPHOGRANULOMATOUS, Mild, Focal.             |                             |

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

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## ACUTE/ACUTE INTRAVENOUS

Study Start Date: 13-Sep-88

.....

Animal: 8800326      Sex: Female

Status: Final sacrifice

Group: 3

.....

Day of death: 15      Dose level: 20.00 ML/KG/day

.....

Finding, severity      << Gross Observations >>

.....

Tissue      Gross Free-Text Comments

.....

WHOLE BODY      NO GROSS LESIONS

.....

Tissue      Necropsy Memos

.....

No necropsy memos recorded on animal

.....

Tissue      << Pathology Observations >>

.....

Histopathologic diagnoses / Special histological comments

.....

SPLEEN      HEMOSIDEROSIS, Mild, Multifocal.

.....

LIVER

HEPATITIS, LYMPHOGRANULOMATOUS, PORTAL TRACKS, Slight, Multifocal.

## Appendix I (cont.): PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

Animal: 88F00312

Day of death: 15      Sex: Female      Status: Final sacrifice

Group: 3

Dose level: 20.00 ML/KG/day

Finding, severity

<< G r o s s      O b s e r v a t i o n s >>

Gross Free-Text Comments

WHOLE BODY

NO GROSS LESIONS

<< N e c r o p s y      M e m o s >>

Necropsy memos

No necropsy memos recorded on animal

Tissue

<< P a t h o l o g y      O b s e r v a t i o n s >>

Histopathologic diagnoses / Special histological comments

LIVER

HEPATITIS, LYMPHOGANULOMATOUS, PORTAL TRACKS, Slight, Multifocal.

LUNGS

PNEUMONIA, PYOGRANULOMATOUS, INTERSTITIUM, Mild, Multifocal.

## Appendix I (cont.): PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

ACUTE/ACUTE INTRAVENOUS

Animal: 88F00321 Sex: Female

Status: Final sacrifice

Group: 3

Dose Level:

20.00 ML/KG/day

Terminal body weight (kms):

4.07

Tissue Finding severity

<< Gross Observations >>

Gross Free-Text Comments

Tissue WHOLE BODY NO GROSS LESIONS

<< Necropsy Memos >>

Tissue Necropsy memos

No necropsy memos recorded on animal

Tissue << Pathology Observations >>

Histopathologic diagnoses / Special histological comments

All protocol required tissues normal.

## Appendix I (cont.): PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
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|               |  |                              | Study Start Date: 13-Sep-88 | ACUTE/ACUTE INTRAVENOUS                     |
|---------------|--|------------------------------|-----------------------------|---|
| Animal:       | 88F00323   | Sex:                         | Female                      | Group: 4                                    |
| Day of death: | 4  | Status:                      | Interim sacrifice 2         | Terminal body weight (kms): 20.00 ML/KG/day |
| Tissue        | Finding, severity  | << Gross Observations >>     |                             | Dose level: 4.34                            |
| WHOLE BODY    | NO GROSS LESIONS   |                              |                             | Gross Free-Text Comments                    |
| Tissue        | Necropsy memos   | << Necropsy Memos >>         |                             |   |
|               | No necropsy memos recorded on animal   |                              |                             |   |
| Tissue        | Histopathologic diagnoses / Special histological comments  | << Pathology Observations >> |                             |   |
| LIVER         | HEPATITIS, LYMPHOGANULOMATOUS, PORTAL TRACKS, Mild, Diffuse.   |                              |                             |   |
| KIDNEY        | NEPHRITIS, SUBACUTE, INTERSTITIUM, Slight, Multifocal.   |                              |                             |   |
| LUNGS         | PNEUMONIA, PYOGANULOMATOUS, INTERSTITIUM, Mild, Multifocal.  |                              |                             |   |
| BRAIN         | LEPTOMENINGITIS, NONSUPPURATIVE, Mild, Diffuse.<br>ENCEPHALITIS, LYMPHOGANULOMATOUS, Slight, Multifocal. |                              |                             |   |

## APPENDIX I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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PRESIDIO OF SAN FRANCISCO, CA 94129  
RABBIT/NEW ZEALAND WHITE

**Individual Animal Data Dump Table**  
**Study Number: 88002**

**RABBIT/NEW ZEALAND WHITE**  
**Animal:** 88F00336      **Sex:** Female  
**Day of death:** 4      **Status:** Interim sacrifice 2  
**Tissue**      **Finding, severity**      **<< Gross Observations >>**  
**WHOLE BODY**      NO GROSS LESIONS      Gross Free-Text Comments

**Study Start Date:** 13-Sep-88      **ACUTE/ACUTE INTRAVENOUS**

|                             |      |             |                 |
|-----------------------------|------|-------------|-----------------|
| Group:                      | 4    | Dose Level: | 20.00 ML/KG/day |
| Terminal body weight (kms): | 4.38 |             |                 |

**Tissue**                  << Pathology Observations >>  
Histopathologic diagnoses / Special histological comments  
All protocol required tissues normal.

All protocol required tissues normal.

## Appendix I (cont.): PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
 PRESIDIO OF SAN FRANCISCO, CA 94129  
 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13 Sep 88

ACUTE/ACUTE INTRAVENOUS

Animal: 88F00330 Sex: Female

Status: Interim sacrifice 2

Day of death: 4 Group: 4

Day of birth: .....

Finding, severity << Gross Observations >>

Tissue: WHOLE BODY NO GROSS LESIONS

Tissue: Necropsy memos << Necropsy Memos >>

No necropsy memos recorded on animal

Tissue: Histopathologic diagnoses / Special histological comments << Pathology Observations >>

SPLEEN

HEMOSIDEROSIS, Mild, Diffuse.

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## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 880002

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 Page: 74

## ACUTE/ACUTE INTRAVENOUS

Study Start Date: 13-Sep-88

Group: 4 Dose Level: 20.00 ML/KG/day

Terminal body weight (kms): 3.89

<< Gross Observations >>

Gross Free-Text Comments

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Pathology Annex (cont.)



## Appendix : (cont.) : PATHOLOGY REPORT

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 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 880002

|                                      |          | ACUTE/ACUTE INTRAVENOUS  |          |                                  |
|--------------------------------------|----------|--|----------|----------------------------------|
|                                      |          | Study Start Date: 13-Sep-88                                      | Group: 4 | Dose Level: 20.00 ML/KG/day      |
|                                      |          |  |          | Terminal body weight (kms): 4.50 |
| Animal:                              | 88F00346 | Sex: Female  |          |                                  |
| Day of death:                        | 15       | Status: Final sacrifice  |          |                                  |
| Tissue                               |          | << Gross observations >>   |          |                                  |
| WHOLE BODY                           |          | Gross Free-Text Comments   |          |                                  |
| NO GROSS LESIONS                     |          |  |          |                                  |
| Tissue                               |          | << Necropsy Memos >>   |          |                                  |
|                                      |          | Necropsy memos   |          |                                  |
| No necropsy memos recorded on animal |          |  |          |                                  |
| Tissue                               |          | << Pathology Observations >>                                     |          |                                  |
|                                      |          | Histopathologic diagnoses / Special histological comments        |          |                                  |
| SPLEEN                               |          | HEMOSIDEROSIS, Slight, Multifocal.                               |          |                                  |
| LIVER                                |          | HEPATITIS, LYMPHOGRANULOMATOUS, PORTAL TRACKS, Mild, Multifocal. |          |                                  |
| LUNGS                                |          | INTRA-ALVEOLAR MACROPHAGES, Slight, Multifocal.                  |          |                                  |
| HEART                                |          | MYOCARDITIS, SUBACUTE, INTERSTITIUM, Slight, Multifocal.         |          |                                  |
| BRAIN                                |          | LEPTOMENINGITIS, NONSUPPURATIVE, Moderate, Multifocal.           |          |                                  |

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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RABBIT/NEW ZEALAND WHITE

| Individual Animal Data Dump Table |   | PRINTED: 19-Apr-89           |                                  |
|-----------------------------------|---|------------------------------|----------------------------------|
| Study Number: 88002               |   | Page: 77                     |                                  |
|                                   |   | Study Start Date: 13-Sep-88  |                                  |
|                                   |   | ACUTE/ACUTE INTRAVENOUS      |                                  |
| Animal: 88F00351                  | Sex: Female   | Group: 4                     | Dose (level: 20.00 ML/KG/day)    |
| Day of death: 15                  | Status: Final sacrifice                                   |                              | Terminal body weight (kms): 4.01 |
| Tissue                            | Finding, severity   | << Gross Observations >>     |                                  |
| WHOLE BODY                        | NO GROSS LESIONS  |                              | Gross Free Text Comments         |
| Tissue                            | Necropsy memos  | << Necropsy Memos >>         |                                  |
|                                   | No necropsy memos recorded on animal                      |                              |                                  |
| Tissue                            | Histopathologic diagnoses / special histological comments | << Pathology Observations >> |                                  |
| SPLEEN                            | HEMATOPESIS, Mild, Multifocal.                            |                              |                                  |

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

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## ACUTE/ACUTE INTRAVENOUS

Study Start Date: 13-Sep-88

| Animal:       | Sex:   | Final sacrifice         | Group: | Dose level:                      |
|---------------|--------|-------------------------|--------|----------------------------------|
| 88F00325      | Female |                         | 4      | 20.00 ML/KG/day                  |
| Day of death: | 15     | Status: Final sacrifice |        | Terminal body weight (kms): 4.09 |

| Tissue     | Finding, severity | << Gross Observations >> |
|------------|-------------------|--------------------------|
| WHOLE BODY | NO GROSS LESIONS  | Gross Free-Text Comments |

| Tissue            | Necropsy memos     | << Necropsy Memos >> |
|-------------------|--------------------|----------------------|
| No necropsy memos | recorded on animal |                      |

| Tissue | Mistopathologic diagnoses / Special histological comments     | << Pathology Observations >> |
|--------|---|------------------------------|
| LUNGS  | PNEUMONIA, PYOGANULOMATOUS, INTERSTITIUM, Slight, Multifocal. |                              |
| HEART  | MYOCARDITIS, SUBACUTE, INTERSTITIUM, Slight, Focal.           |                              |

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
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 RABBIT/NEW ZEALAND WHITE

|                                   |   |                             |
|-----------------------------------|---|-----------------------------|
| Individual Animal Data Dump Table |   | PRINTED: 19-Apr-89          |
|                                   |   | Page: 79                    |
| Study Start Date: 13-Sep-88       |   | ACUTE/ACUTE INTRAVENOUS     |
| Animal: 88F00307                  | Sex: Female   | Group: 4                    |
| Day of death: 15                  | Status: Final sacrifice   | Dose level:                 |
|                                   |   | 20.00 ML/KG/day             |
| Tissue                            | Finding, severity   | Terminal body weight (kms): |
|                                   | << Gross observations >>  | 4.00                        |
| WHOLE BODY                        | NO GROSS LESIONS  | Gross Free-Text Comments    |
| Tissue                            | Necropsy memos  | << Necropsy Hematos >>      |
|                                   | No necropsy memos recorded on animal                            |                             |
| Tissue                            | << Pathology Observations >>                                    |                             |
| LIVER                             | Histopathologic diagnoses / Special histological comments       |                             |
| LIVER                             | HEPATITIS, LYMPHOGRANULOMATOUS, PORTAL TRACKS, Slight, Diffuse. |                             |

## Appendix I (cont.) : PATHOLOGY REPORT

LETTERMAN ARMY INSTITUTE OF RESEARCH  
 DIV OF RES SUPP, PATH SERV GP  
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 RABBIT/NEW ZEALAND WHITE

Individual Animal Data Dump Table  
 Study Number: 88002

Study Start Date: 13-Sep-88

Animal: 88F00340      Sex: Female      Status: Final sacrifice  
 Day of death: 15      Group: 4      Dose Level: 20.00 ML/KG/day

Tissue      Finding, severity      << Gross Observations >>

WHOLE BODY      NO GROSS LESIONS      Gross Free-Text Comments

Tissue      Necropsy memos      << Necropsy Memos >>

No necropsy memos recorded on animal

Tissue      << Pathological Observations >>  
 Histopathologic diagnoses / Special histological comments

LIVER

HEPATITIS, LYMPHORANULOMATOUS, PORTAL TRACKS, Slight, Multifocal.

LUNGS

PNEUMONIA, PYORANULOMATOUS, INTERSTITIUM, Slight, Focal.

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