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PHASE 2  
TOXICOLOGICAL STUDY NO. 75-51-0743-88(2)  
TRICHLOROMELAMINE  
14-DAY RANGE FINDING AND 90-DAY  
SUBCHRONIC STUDIES IN RATS  
3 AUGUST 1988 - 17 JANUARY 1989

93-00257

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| 19. ABSTRACT (Continue on reverse if necessary and identify by block number)<br>The subchronic study examined the toxicity of the food service disinfectant trichloromelamine (TCM) in rats following oral administration for 90 days. Associated with the administration of TCM in rats were lesions in the stomach and trachea, while also causing engorgement of the small blood vessels of the adrenals, brain, kidneys, liver, lung and pituitary. The no observed adverse effect level in the 90-day study was 30 mg/kg/day. Trichloromelamine should be considered moderately toxic when ingested acutely, and continuous ingestion could cause serious health effects. |       |                                                   |                                                                                   |                                                   |                                 |
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DEPARTMENT OF THE ARMY  
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY  
ABERDEEN PROVING GROUND, MARYLAND 21010-5422



EXECUTIVE SUMMARY  
PHASE 2  
TOXICOLOGICAL STUDY NO. 75-51-0743-88(2)  
TRICHLOROMELAMINE  
14-DAY RANGE FINDING AND 90-DAY  
SUBCHRONIC STUDIES IN RATS  
3 AUGUST 1988 - 17 JANUARY 1989

1. PURPOSE. Information provided by this study will be used to establish safety criteria for human exposure. A preliminary 14-day range finding study was conducted to determine the effects of oral administration of TCM to establish reasonable dosage levels for the 90-day study. The subchronic study examined the toxicity of the food service disinfectant trichloromelamine (TCM) in rats following oral administration for 90 days.

2. CONCLUSIONS. Associated with the subchronic oral administration of TCM in rats were lesions in the stomach and trachea while also causing engorgement of the small blood vessels of the adrenals, brain, kidneys, liver, lung and pituitary, as well as pulmonary edema. The no observed adverse effect level for the oral administration of TCM to rats was 30 mg/kg/day in the 90-day study. Trichloromelamine should be considered moderately toxic when ingested acutely, and continuous ingestion could cause serious health effects.

3. RECOMMENDATIONS. Proceed with the use of TCM as a food service disinfectant. Use of TCM as directed will limit overexposure and resulting health effects.

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3 AUGUST 1988 - 17 JANUARY 1989

1. REFERENCES. See Appendix A.

2. AUTHORITY.

a. Letter, HSCL-P, 26 August 1987, subject: Toxicity Clearance for Trichloromelamine, Active Ingredient in Disinfectant, Food Service (MIL-D-11309).

b. Letter, United States Environmental Protection Agency (EPA), 4 Mar 1987, subject: Data Call-In Notice for Subchronic Toxicological Data for Antimicrobial Pesticide Active Ingredients.

3. PURPOSE.

a. A preliminary 14-day range finding study was conducted to determine the effects of oral administration of trichloromelamine (TCM) over a 14-day period. Results of this study were used to establish appropriate dosage levels for the subsequent 90-day study.

b. To determine the toxicity of the food service disinfectant TCM in rats following oral administration for 90 days. Information provided from this study will be used to establish safety criteria for human exposure.

4. BACKGROUND.

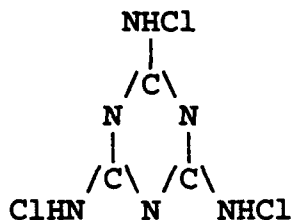
a. The U.S. Army Environmental Hygiene Agency (USAEHA) was initially tasked to evaluate the acute toxicities of TCM in July 1976, USAEHA Study Nos. 75-51-0124-76 and 75-51-0195-84 (reference 1). Mutagenicity, aquatic lethality studies, dominant lethal, and Shimkin Mouse assays were completed between 1984 and 1987 under USAEHA contract Study Nos. 75-51-0195-87 and 75-51-0668-86 (references 2-6).

b. In 1987, the U.S. Environmental Protection Agency (EPA) issued a Data Call-In Notice for subchronic toxicity data on all antimicrobial pesticide active ingredients. A search of available literature revealed a lack of subchronic animal toxicity data for TCM. This 90-day study was initiated to

further assess the subchronic toxicity of TCM, and to support required testing set forth by the EPA to maintain the Army's registration of TCM as a food service disinfectant.

## 5. MATERIALS AND METHODS.

a. Test Substance. The test material, trichloromelamine (CAS Registry Number 7673-09-8), technical grade, lot number 2342, was procured from Dorex Inc., 121 Ontario St., Frankfort, IL 60423. Trichloromelamine is a fine, white to light tan powder with a solubility in water of 0.34 grams/liter at 25 °C. The molecular formula is C<sub>3</sub>-H<sub>3</sub>-Cl<sub>3</sub>-N<sub>6</sub>, with a molecular weight of 229.47, and a chemical structure as follows:



Trichloromelamine is an oxidizing compound that reacts with reducing agents or organic compounds. Mixtures of TCM with rodent chow will produce a reaction that binds all free chlorine. Analysis of feed by free chlorine determination (Standard Methods 408A - Appendix B) to ascertain TCM concentrations in the feed was therefore not possible. Gavage was chosen as the method of compound administration to enable dosages to be verified by analytical means. Due to the low solubility of TCM in water, suspensions of the compound in water were used to achieve necessary concentrations, while keeping dosing volumes within guidelines.

b. Animals. Young, adult Sprague-Dawley male and female rats used in the studies were supplied by Charles River Laboratories Incorporated, Wilmington, Massachusetts. Female rats were both nulliparous and nonpregnant. Animals were toe clipped for identification purposes.

c. Diet. Certified Rodent Ration, manufactured by Zeigler Brothers, Inc., Gardners, Pennsylvania (Appendix C), was given ad libitum throughout the studies. Water was also continuously available to all rats throughout the study.

d. Environment. Temperature and relative humidity in the housing area were maintained at  $72 \pm 6$  °F, and 40 to 70 percent, respectively, with 12 hours of lighting each day.

e. Housing. Rats were housed individually in hanging stainless-steel cages measuring 40 cm high X 60 cm wide X 60 cm deep, equipped with bottled water and wire-lab block feeder.

f. 14-Day Study.

(1) A 14-day range finding study was conducted in male and female rats in accordance with the Toxicology Division standing operating procedure (SOP) for 14- and 90-Day Feeding Studies (reference 7).

(2) Forty-eight male and forty-eight female Sprague Dawley, Caesarean-derived, Barrier Restrained rats 6 to 8 weeks old were purchased from Charles River Laboratories of Wilmington, Massachusetts. Following a 1-week acclimation period, animals were randomly distributed into eight dosage groups of six rats, each sex. Daily dosage levels were set at 0, 25, 50, 100, 200, 400, 800, and 1,600 mg/kg/day. Animals were dosed by gavage on a 7 day per week basis, with a staggered start between males and females to accommodate terminal necropsies.

(3) A fresh 100 mg/ml working suspension of TCM in distilled water was made daily. The suspension was randomly sampled and independently verified for content by free chlorine analysis. Daily doses were calculated automatically by computer and reflected updated body weight values as they occurred.

(4) Body weights and food consumption were measured and recorded on days 0, 1, 3, 7, and 14. Animals were observed daily for toxic signs. Water consumption was not monitored during this study.

(5) Prior to necropsy on the final day of test, blood samples were collected by intracardiac puncture from all study rats. Clinical chemistry and hematology values were determined from all valid samples. The Table lists the clinical tests performed on the blood samples taken.

(6) Following the 14-day study period, surviving rats were sacrificed by decapitation and necropsied. The brain, liver, kidneys, spleen, and testes/ovaries were removed and weighed. These weights were used for calculations of organ-to-brain and organ-to-body weight ratios. Vital organs were saved for possible histological examination.

TABLE. CLINICAL TESTS

| Clinical Chemistry                        | Hematology         |
|-------------------------------------------|--------------------|
| Alkaline phosphatase                      | Hemoglobin         |
| Glutamate oxalacetate transaminase (SGOT) | Hematocrit         |
| Glutamate pyruvate transaminase (SGPT)    | Erythrocyte count  |
| Glutamyltranspeptidase (GGTP)             | Leukocyte count    |
| Glucose                                   | Differential count |
| Calcium                                   | Platelet count     |
| Total bilirubin                           |                    |
| Blood urea nitrogen (BUN)                 |                    |
| Total protein                             |                    |

g. 90-Day Study.

(1) A 90-day gavage study was conducted in rats in accordance with the Toxicology Division SOP for 14- and 90-day studies (reference 7).

(2) Rats were acclimated for a 1-week period, then randomly distributed into five groups of ten of each sex. Dose levels were set at 0, 30, 150, and 300 mg/kg/day, based on clinical chemistry effects seen in the range finding study. A vehicle control was also included in the study to determine the toxic effects, if any, of the addition of a surfactant.

(3) A fresh working suspension of 75 mg/mL TCM in distilled water was again made daily. Random samples were analyzed to verify the TCM concentrations of the working suspension. To keep the TCM suspended in the distilled water solution, constant stirring was required during compound administration. Due to foaming of the TCM during this procedure (observed during the 14-day study), a surfactant was added to diminish the effect. Triton X-100 (Octyl phenoxy polyethoxyethanol), distributed by Sigma Chemical Company, St. Louis, Missouri, was added to the working solution at a concentration of .08 percent. The vehicle control group received distilled water with a Triton X-100 concentration mimicking the TCM suspension.

(4) Animals were dosed every day for the 90-day duration, with a staggered start between sexes. Rats in the control and vehicle control group were given volumes based on the



300 mg/kg dosage level. Body weights were recorded for all rats once per week. Dosage volumes were recalculated automatically by the laboratory software when body weights were updated.

(5) Food and water were available ad libitum throughout the study. Food consumption was monitored on a Monday, Wednesday, and Friday basis during the study. Water consumption was not observed. Observations of toxic signs were made and recorded daily.

(6) Animals not surviving to term or determined to be moribund, were subjected to full necropsies at the time of death, unless autolysis had occurred. On the final day of testing, prior to necropsy, animals were bled by intracardiac puncture for clinical chemistry and hematology determinations.

(7) Rats surviving the 90-day duration were sacrificed by decapitation for necropsy. Following examination of external surfaces and internal cavities, major organs were removed, trimmed, and weighed for organ-to-body and organ-to-brain weight ratio calculations. Other organs and tissues collected and processed for microscopic examination (reference 8) included all gross lesions, brain, eye, pituitary, salivary gland, heart, thyroid, parathyroid, lungs, lymph node, trachea, esophagus, stomach, small and large intestines, adrenals, pancreas, liver, kidneys, urinary bladder, testes, prostate, ovaries, corpus and cervix uteri, skeletal muscle, and sections of sternbrae, vertebrae, and tibia-femoral joint with marrow.

## 6. RESULTS.

### a. 14-Day Study.

(1) Verification of the TCM working solution by standard methods (Appendix B) showed the suspension to contain an average of 96.5 percent of the predicted concentration.

(2) Deaths occurred in 11 of 12 high dosage (1,600 mg/kg) male and female rats by day 3 of the study. The remaining female rat in this dosage group survived to term, becoming lethargic and emaciated. Two male rats from the 800 mg/kg group died after dosing on day 2, while a female rat of that same group died following dosing on day 9. Deaths in the 400 mg/kg dosage group occurred on day 9 and 10 for one male and one female rat, respectively (Appendix D). All other rats survived the 14-day dosing regimen with varying degrees of toxic signs, i.e., ruffled pelt, lethargy, diarrhea, emaciation, and labored breathing.

(3) Analysis of variance using Duncan's procedure showed female rats in the highest dosage group had lowered food consumption by day 1 of the study, and again on days 3-7, when compared to the control group. Male rats in the high dosage group exhibited lowered food consumption by day 1 with associated deaths of all by day 3. Male rats in the 800 mg/kg group also showed reduced consumption on day 1 but returned to normal consumption by day 3 and for the remainder of the study (Appendix E).

(4) Weight loss occurred in the two highest dosage groups (800 and 1,600 mg/kg) in both female and male rats by day 1 of the 14-day study (Appendix F). All remaining female rats in these groups recovered to normal consumption by day 3, but again experienced significant weight loss between days 3 to 7. The 800 mg/kg dosage group of male rats continued with weight loss through day 3 but reverted to normal gains for the remainder of the study. TCM did not significantly effect weight gains of the 25-400 mg/kg TCM groups.

(5) Significant decreases in clinical chemistry values were seen in both sexes of rats at 14 days when compared to their respective control groups. Compound related changes occurred in total bilirubin, total protein and BUN values beginning in the 100 mg/kg dose and continuing through the 1,600 mg/kg dosage group in female rats. Males showed decreases in SGOT levels in the 200-1,600 mg/kg doses, decreases in BUN values in the 50-1,600 mg/kg levels, decreases in total protein values in the 100-1,600 mg/kg dosages, and increases in blood glucose levels in the 200-1,600 mg/kg dose groups (Appendix G).

(6) No significant changes were seen in hematological parameters of TCM rats after 14 days, when compared to control group rats (Appendix H).

(7) Gross necropsy of both sexes of rats revealed lung changes consisting of mottled, raised areas associated with the physical oral administration of the compound and control. The frequency of these changes was common to all groups and no dose response relationship associated with compound administration could be established. Foaming of dosing solutions due to continuous stirring seemed to be contributing to some lung congestion and lung changes.

(8) Organs taken at necropsy showed no significant differences in weight when TCM groups were compared with control organ weights (Appendix I). An analysis of organ-to-body weight ratios and organ-to-brain weight ratios also revealed no significant difference between controls and TCM groups.

b. 90-Day Study.

(1) Analysis of random samples taken from the TCM working suspension during the study yielded an average recovery of 101 percent of the expected concentration.

(2) No significant effects were observed in the surfactant (Triton-X 100) control group, indicating its addition to the TCM solutions had no bearing on the outcome of the study.

(3) Weekly food consumption figures for the 90-day study are displayed in Appendix J. Female rats in the high dosage group showed significantly lower food consumption (when compared to that of the control group) during the eighth week, but returned to normal the following week. No significant depression in food consumption was seen with male rats.

(4) Appendix K shows graphic representations of weight gains (loses) for both male and female rats. Significant weight loses were experienced during weeks 7 and 11 in female and male rats respectively. Both sexes returned to nonsignificant weight gains (loses) for the remainder of the study.

(5) Blood taken prior to necropsy at 90 days revealed only minor significant changes in clinical chemistry values (Appendix L). Female rats in the 150 and 300 mg/kg dosage groups showed a decrease in calcium content, while male rats had decreased total protein values in the high-dose group and elevated sugar levels in the 150 mg/kg group. No trends could be established related to compound administration.

(6) Examination of 90-day hematology values showed a significant decrease in the number of red blood cells in the 300 mg/kg male rats (Appendix M). No other significance was noted and again changes could not be directly related to TCM administration.

(7) Appendix N lists 90-day organ weights, organ-to-body weight ratios, and organ-to-brain weight ratios. Liver weights of female rats in the 300 mg/kg dosage group showed a significant increase when taken as a percentage of their body weight.

(8) Gross necropsies of animals in the 300 mg/kg and 150 mg/kg dosage groups, dying during the study, showed hemorrhagic erosion of the stomach mucosa as well as stomach and intestinal distention. Lungs from these rats exhibited varying degrees of congestion with white spotting. Rats surviving to term necropsy showed similar incidental signs across all groups with no dose response patterns being established.

(9) The majority of nonsurviving rats were found to have congestion of multiple organs (adrenal glands, brain, kidneys, liver, lung and pituitary) following histopathologic evaluation. This condition consisted of engorgement of the small blood vessels with blood. One male and female rat from the high dosage group had suppurative tracheitis which consisted of neutrophilic infiltration in the wall of the trachea, with accumulation of inflammatory cells and debris in the trachea lumen. This unusual lesion was considered to be associated with compound administration, despite the overall low incidence rate.

(10) Histopathologic examination of tissues and organs taken at necropsy revealed a low incidence of lesions in the nonglandular region of the stomach of male and female rats from the 300 mg/kg group (reference 9). Similar hyperplasia was noted in one male rat from the 150 mg/kg group. Chronic inflammation of the stomach consisted of a mixed inflammatory cell infiltration and a variable degree of inflammatory edema. Hyperplasia of the nonglandular epithelium consisted of thickening and irregularity of epithelial lining. These lesions were graded as mild or moderate and were considered to be associated with compound administration.

## 7. DISCUSSION.

a. Necropsies of high dosage (300 mg/kg/day or greater) rats dying during the conduct of the 14- and 90-day studies showed deaths were associated with the physical aspects of oral administration of TCM. Irritation and erosion of the mucosal linings of the stomach and intestine as well as multiple organ congestion were common to animals not surviving to term. Surviving high dosage animals generally suffered from labored breathing, lethargy and diarrhea with resulting weight loss.

b. Histopathological examination of tissues and organs from the 90-day study also showed chronic inflammation of the stomach with edema and thickening of the epithelial lining. These mild to moderate lesions were seen in one 150 mg/kg/day rat and several at the 300 mg/kg/day level. One male and female rat from

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the 300 mg/kg/day dosage group had suppurative tracheitis which was considered associated with compound administration, despite the overall low incidence.

c. Short term exposure to TCM caused significant blood chemistry changes seen in the 100-200 mg/kg/day TCM range, after 14 days. Surviving rats recovering from the initial insult and blood taken after the 90-day study showed little effect relating to chemistry values. Blood taken at 90-days from the 300 mg/kg/day male rats had a significant decrease in red blood cells, while hemoglobin and hematocrits for the same animals appear to be near significance when compared to other groups. This anemia is possibly linked to subchronic TCM exposure, although no clear dose response was established as conformation.

8. CONCLUSIONS. The conclusions from the 90-day study follow:

a. The no observed adverse effect level for oral administration of TCM to rats was 30 mg/kg/day.

b. The effect level for oral TCM administration to rats was 150 mg/kg/day, where moderate lesions were seen in the non-glandular epithelial lining of the stomach.

c. The subchronic oral administration of TCM in rats was associated with lesions in the stomach and trachea, while causing engorgement of the small blood vessels of the adrenal glands, brain, kidneys, liver, lung and pituitary as well as pulmonary edema. Red blood cell anemia was observed in high dosage male rats, which may have been associated with TCM exposure.

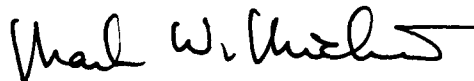
d. Trichloromelamine should be considered moderately toxic when ingested acutely, and continuous ingestion could cause serious health effects.

9. RECOMMENDATIONS.

a. Proceed with the use of TCM as a food service disinfectant. Use of TCM as directed will limit overexposure and resulting health effects.

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b. Continue with recommended animal testing required to  
support the Army's registration for TCM usage with the EPA.



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RICHARD A. ANGERHOFER  
Biologist  
Toxicology Division

APPROVED:



MAURICE H. WEEKS  
Chief, Toxicology Division

## APPENDIX A

### REFERENCES

1. Technical Report, Study No. 75-51-0195-84, this Agency, subject: Preliminary Assessment of the Relative Toxicity of Candidate Disinfectant, Food Service (Chlorine-Iodine Type), NSN 6840-00-810-6396 and Trichloromelamine.
2. Technical Report, Study No. 75-51-0195-87, Hazelton Laboratories America, Inc., January 1987, subject: Mutagenicity of Trichloromelamine in a Mouse Lymphoma Mutation Assay.
3. Technical Report, Study No. 75-51-0668-86, Hazelton Laboratories America, Inc., December 1986, subject: Clastogenic Evaluation of Trichloromelamine in a In Vitro Cytogenic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells.
4. Technical Report, Study No. 75-51-0195-87, Hazelton Laboratories America, Inc., January 1987, subject: Evaluation of Trichloromelamine in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay.
5. Technical Report, Study No. 75-51-0668-87, Hazelton Laboratories America Inc., January 1987, subject: Mutagenicity Evaluation of Trichloromelamine, Lot #1933, Dorex, Inc., in the Ames Salmonella/Microsome Reverse Mutation Assay.
6. Technical Reports, Study Nos. 34811, 34812, 34813, Analytical Biochemistry Laboratories, August 1986, Acute Toxicity of Trichloromelamine to Bluegill Sunfish, Rainbow Trout, and Daphnia magna.
7. Standing Operating Procedure No. 63, USAEHA, Toxicology Division, December 1987, 14-Day Range Finding and 90-Day Feeding Study in Rats.
8. Standing Operating Procedure, Pathology Laboratory, Pathology and Animal Care Branch, Toxicology Division, Room 3201, Building E-2100.
9. Termination Pathology Report, Trichloromelamine: 90-Day Feeding Study in Rats, Study #40-0743-88, George A. Parker, D.V.M., Ltd, 27 July 1989.

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## APPENDIX B

### VERIFICATION OF TCM BY STANDARD METHODS



## 408 A. Iodometric Method I

## 1. General Discussion

*a. Principle:* Chlorine will liberate free iodine from potassium iodide (KI) solutions at pH 8 or less. The liberated iodine is titrated with a standard solution of sodium thiosulfate ( $\text{Na}_2\text{S}_2\text{O}_3$ ) with starch as the indicator. Titrate at pH 3 to 4 because the reaction is not stoichiometric at neutral pH due to partial oxidation of thiosulfate to sulfate.

*b. Interference:* Oxidized forms of manganese and other oxidizing agents interfere. Reducing agents such as organic sulfides also interfere. Although the neutral titration minimizes the interfering effect of ferric and nitrite ions, the acid titration is preferred because some forms of combined chlorine do not react at pH 7. Use only acetic acid for the acid titration; sulfuric acid ( $\text{H}_2\text{SO}_4$ ) will increase interferences; *never use hydrochloric acid (HCl)*. See Section 408.1 for discussion of other interferences.

*c. Minimum detectable concentration:* The minimum detectable concentration approximates  $40 \mu\text{g Cl as Cl}_2/\text{L}$  if  $0.01N \text{ Na}_2\text{S}_2\text{O}_3$  is used with a 1000-mL sample. Concentrations below  $1 \text{ mg/L}$  cannot be determined accurately by the starch-iodide end point used in this method. Lower concentrations can be measured with the amperometric end point in Methods B and C.

## 2. Reagents

*a. Acetic acid, conc (glacial).*

*b. Potassium iodide, KI, crystals.*

*c. Standard sodium thiosulfate, 0.1N:* Dissolve 25 g  $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$  in 1 L freshly boiled distilled water and standardize against potassium bi-iodate or potassium dichromate after at least 2 weeks storage.

This initial storage is necessary to allow oxidation of any bisulfite ion present. Use boiled distilled water and add a few milliliters chloroform ( $\text{CHCl}_3$ ) to minimize bacterial decomposition.

Standardize  $0.1N \text{ Na}_2\text{S}_2\text{O}_3$  by one of the following:

1) Iodate method—Dissolve 3.249 g anhydrous potassium bi-iodate,  $\text{KH}(\text{IO}_3)_2$ , primary standard quality, or 3.567 g  $\text{KIO}_3$ , dried at  $103 \pm 2^\circ\text{C}$  for 1 h, in distilled water and dilute to 1000 mL to yield a  $0.1000N$  solution. Store in a glass-stoppered bottle.

To 80 mL distilled water, add, with constant stirring, 1 mL conc  $\text{H}_2\text{SO}_4$ , 10.00 mL  $0.1000N \text{ KH}(\text{IO}_3)_2$ , and 1 g KI. Titrate immediately with  $0.1N \text{ Na}_2\text{S}_2\text{O}_3$  titrant until the yellow color of the liberated iodine almost is discharged. Add 1 mL starch indicator solution and continue titrating until the blue color disappears.

2) Dichromate method—Dissolve 4.904 g anhydrous potassium dichromate,  $\text{K}_2\text{Cr}_2\text{O}_7$ , of primary standard quality, in distilled water and dilute to 1000 mL to yield a  $0.1000N$  solution. Store in a glass-stoppered bottle.

Proceed as in the iodate method, with the following exceptions: Substitute 10.00 mL  $0.1000N \text{ K}_2\text{Cr}_2\text{O}_7$  for iodate and let reaction mixture stand 6 min in the dark before titrating with  $0.1N \text{ Na}_2\text{S}_2\text{O}_3$  titrant.

$$\text{Normality } \text{Na}_2\text{S}_2\text{O}_3 = \frac{1}{\text{mL } \text{Na}_2\text{S}_2\text{O}_3 \text{ consumed}}$$

*d. Standard sodium thiosulfate titrant, 0.01N or 0.025N:* Improve the stability of  $0.01N$  or  $0.025N \text{ Na}_2\text{S}_2\text{O}_3$  by diluting an aged  $0.1N$  solution, made as directed above, with freshly boiled distilled water. Add 4

g sodium borate and 10 mg mercuric iodide/L solution. For accurate work, standardize this solution daily in accordance with the directions given above, using 0.01*N* or 0.025*N* iodate or  $K_2Cr_2O_7$ . Use sufficient volumes of these standard solutions so that their final dilution is not greater than 1 + 4. To speed up operations where many samples must be titrated use an automatic buret of a type in which rubber does not come in contact with the solution. Standard titrants, 0.0100*N* and 0.0250*N*, are equivalent, respectively, to 354.5  $\mu$ g and 886.3  $\mu$ g Cl as  $Cl_2$ /1.00 mL.

e. *Starch indicator solution*: To 5 g starch (potato, arrowroot, or soluble), add a little cold water and grind in a mortar to a thin paste. Pour into 1 L of boiling distilled water, stir, and let settle overnight. Use clear supernate. Preserve with 1.25 g salicylic acid, 4 g zinc chloride, or a combination of 4 g sodium propionate and 2 g sodium azide/L starch solution. Some commercial starch substitutes are satisfactory.

f. *Standard iodine, 0.1*N**: See 408B.3g.

g. *Dilute standard iodine, 0.0282*N**: See 408B.3h.

### 3. Procedure

a. *Volume of sample*: Select a sample volume that will require no more than 20 mL 0.01*N*  $Na_2S_2O_3$ , and no less than 0.2 mL for the starch-iodide end point. For a chlorine range of 1 to 10 mg/L, use a 500-mL sample; above 10 mg/L, use proportionately less sample. Use smaller samples and volumes of titrant with the amperometric end point.

b. *Preparation for titration*: Place 5 mL acetic acid, or enough to reduce the pH to between 3.0 and 4.0, in a flask or white porcelain casserole. Add about 1 g KI estimated on a spatula. Pour sample in and mix with a stirring rod.

c. *Titration*: Titrate away from direct sunlight. Add 0.025*N* or 0.01*N*  $Na_2S_2O_3$  from a buret until the yellow color of the

liberated iodine almost is discharged. Add 1 mL starch solution and titrate until blue color is discharged.

If the titration is made with 0.025*N*  $Na_2S_2O_3$ , instead of 0.01*N*, then, with a 1-L sample, 1 drop is equivalent to about 50  $\mu$ g/L. It is not possible to discern the end point with greater accuracy.

d. *Blank titration*: Correct result of sample titration by determining blank contributed by oxidizing or reducing reagent impurities. The blank also compensates for the concentration of iodine bound to starch at the end point.

Take a volume of distilled water corresponding to the sample used for titration in ¶s 3a-c, add 5 mL acetic acid, 1 g KI, and 1 mL starch solution. Perform blank titration as in 1) or 2) below, whichever applies.

1) If a blue color develops, titrate with 0.01*N* or 0.025*N*  $Na_2S_2O_3$ , to disappearance of blue color and record result.

2) If no blue color occurs, titrate with 0.0282*N* iodine solution until a blue color appears. Back-titrate with 0.01*N* or 0.025*N*  $Na_2S_2O_3$ , and record the difference.

Before calculating the chlorine concentration, subtract the blank titration of ¶ 1) from the sample titration; or, if necessary, add the net equivalent value of the blank titration of ¶ 2).

### 4. Calculation

For standardizing chlorine solution for temporary standards:

$$\text{mg Cl as } Cl_2/\text{mL} = \frac{(A \pm B) \times N \times 35.45}{\text{mL sample}}$$

For determining total available residual chlorine in a water sample:

$$\text{mg Cl as } Cl_2/L = \frac{(A \pm B) \times N \times 35.450}{\text{mL sample}}$$

where:

$A$  = mL titration for sample,

$B$  = mL titration for blank (positive or negative), and

$N$  = normality of  $Na_2S_2O_3$ .

### 5. Precision and Accuracy

References 1 and 2 give the results of nine methods used to analyze synthetic

water samples without interferences; variations of five of the methods appear in this edition. More current data are not now available.

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APPENDIX C  
CERTIFIED RODENT RATION

**35-553**  
**CERTIFIED RODENT RATION**  
**(ABERDEEN - 07)**

**NET WT. 22.7 Kg (50 Lbs.)**

**GUARANTEED ANALYSIS**

|                     |            |
|---------------------|------------|
| Crude Protein ..... | Min. 20.0% |
| Crude Fat .....     | Min. 4.5%  |
| Crude Fiber .....   | Max. 5.0%  |
| Ash .....           | Max. 7.0%  |

**MANUFACTURED BY:**  
**ZEIGLER BROS., INC.**  
P.O. Box 95  
Gardners, PA. 17324

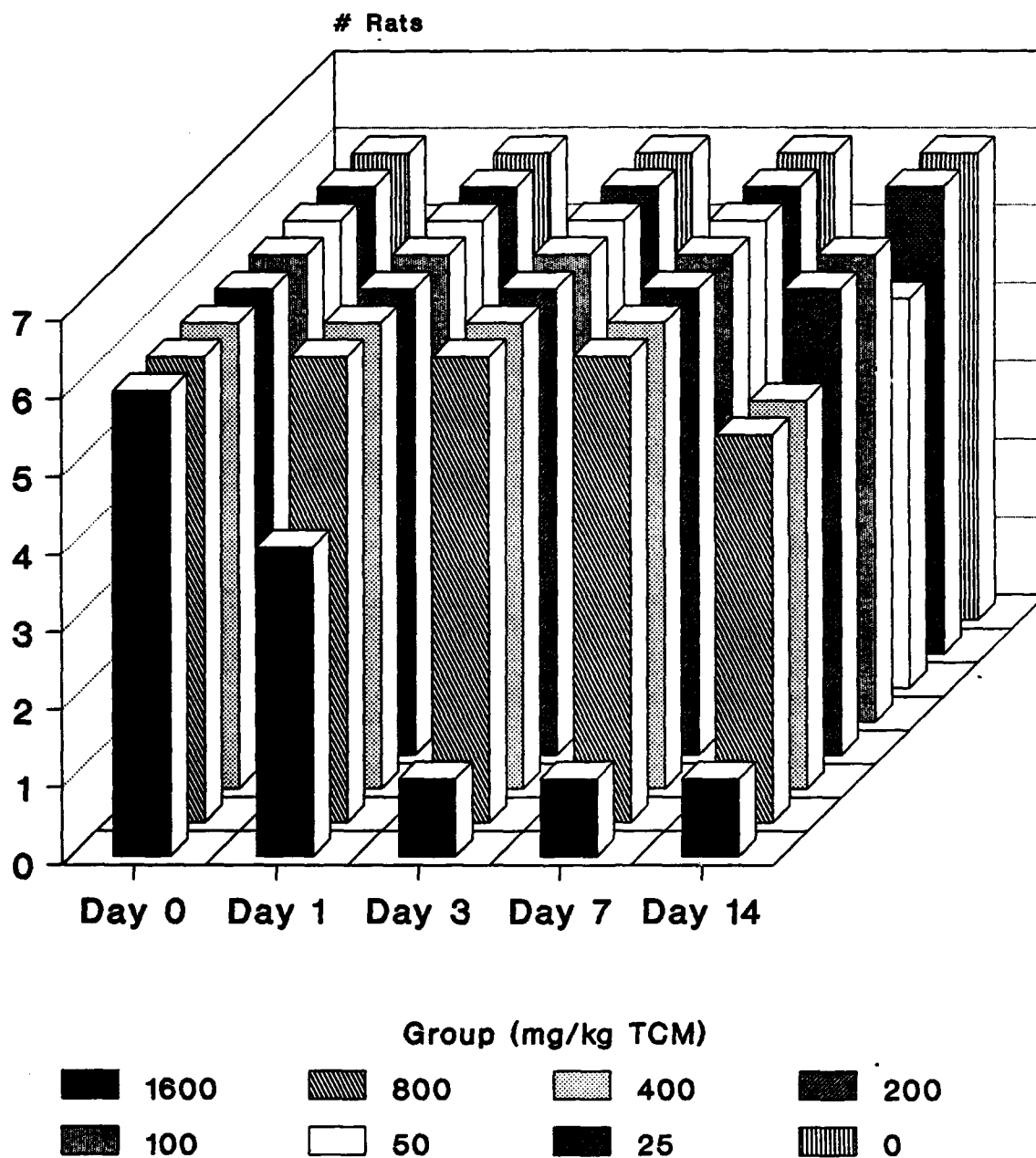
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#### APPENDIX D

#### 14-DAY SURVIVABILITY OF MALE AND FEMALE RATS

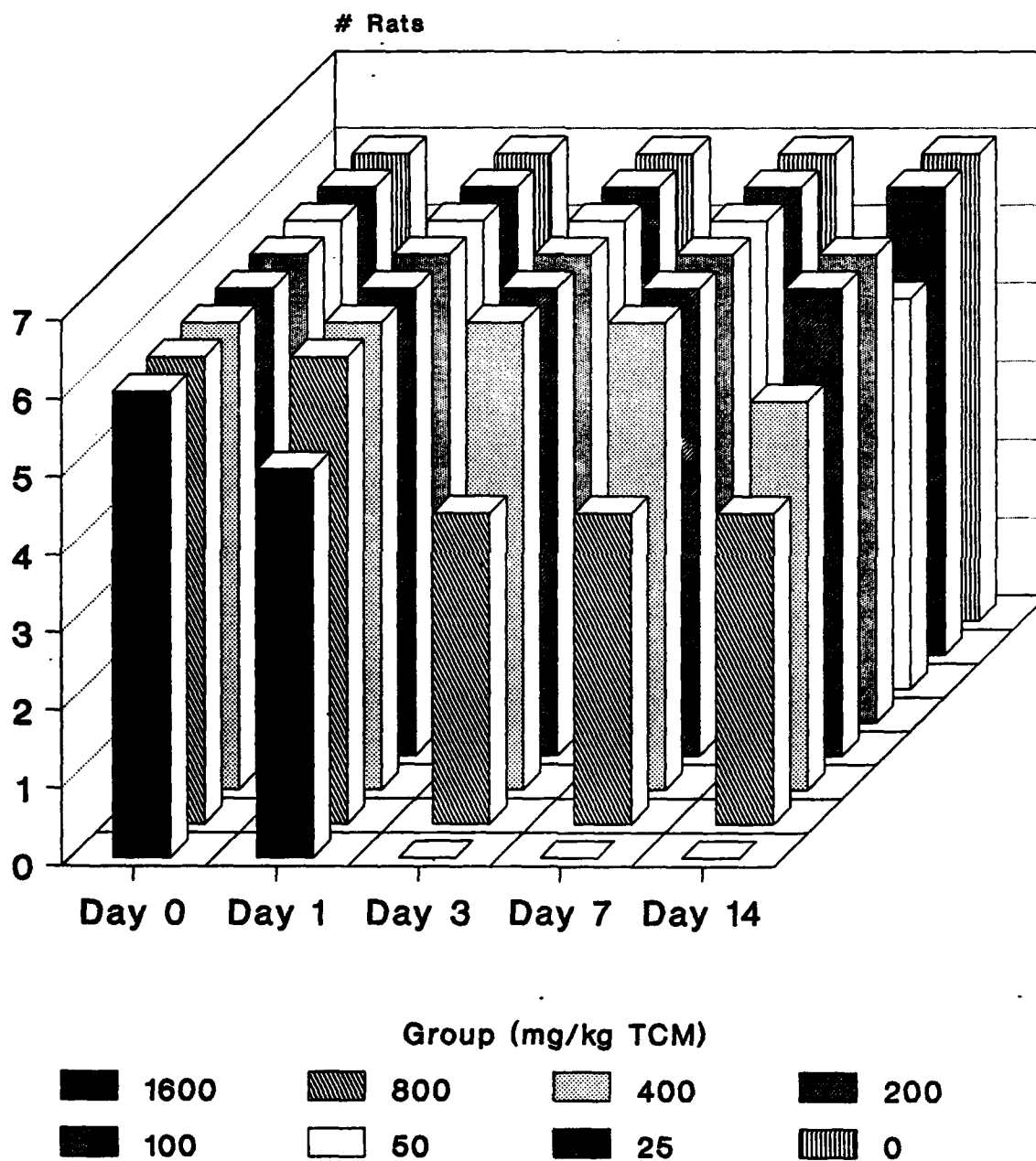
# 14-DAY TCM STUDY #75-51-0743-88

## SURVIVABILITY - FEMALE RATS



# 14-DAY TCM STUDY #75-51-0743-88

## SURVIVABILITY - MALE RATS





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#### APPENDIX E

#### 14-DAY FOOD CONSUMPTION OF MALE AND FEMALE RATS

14-DAY TCM STUDY NO. 75-51-0743-88(2)  
SUMMARY OF FOOD CONSUMPTION (GRAMS)  
FEMALE RATS

| Period   | Group | 1<br>Control | 2<br>25mg/kg | 3<br>50mg/kg | 4<br>100mg/kg | 5<br>200mg/kg | 6<br>400mg/kg | 7<br>800mg/kg | 8<br>1600mg/kg |
|----------|-------|--------------|--------------|--------------|---------------|---------------|---------------|---------------|----------------|
| Day 0-1  | MEAN  | 20.8         | 20.3         | 21.2         | 21.2          | 19.5          | 20.3          | 13.8          | 6.8*           |
|          | S.D.  | 1.6          | 3.0          | 2.1          | 3.3           | 3.0           | 3.7           | 5.5           | 3.1            |
|          | N     | 6            | 6            | 6            | 6             | 6             | 6             | 6             | 4              |
| Day 1-3  | MEAN  | 43.2         | 41.2         | 44.5         | 40.2          | 35.8          | 40.3          | 35.0          | 30.0           |
|          | S.D.  | 4.0          | 3.6          | 3.9          | 3.5           | 13.0          | 7.1           | 12.6          | -              |
|          | N     | 6            | 6            | 6            | 6             | 6             | 6             | 6             | 1              |
| Day 3-7  | MEAN  | 85.7         | 80.7         | 87.5         | 79.5          | 82.8          | 73.7          | 64.8          | 46.0*          |
|          | S.D.  | 10.0         | 11.0         | 8.7          | 4.1           | 6.6           | 14.7          | 14.5          | -              |
|          | N     | 6            | 6            | 6            | 6             | 6             | 6             | 6             | 1              |
| Day 7-14 | MEAN  | 151.5        | 142.3        | 149.0        | 140.2         | 150.8         | 132.0         | 133.3         | 140.0          |
|          | S.D.  | 13.1         | 17.5         | 27.3         | 9.5           | 9.8           | 23.2          | 18.7          | -              |
|          | N     | 6            | 6            | 5            | 6             | 6             | 5             | 5             | 1              |

\* Indicates significance at the 0.05 level.

14-DAY TCM STUDY NO. 75-51-0743-88 (2)  
SUMMARY OF FOOD CONSUMPTION (GRAMS)  
MALE RATS

| Period   | Group | 1<br>Control | 2<br>25mg/kg | 3<br>50mg/kg | 4<br>100mg/kg | 5<br>200mg/kg | 6<br>400mg/kg | 7<br>800mg/kg | 8<br>1600mg/kg |
|----------|-------|--------------|--------------|--------------|---------------|---------------|---------------|---------------|----------------|
| Day 0-1  | MEAN  | 28.7         | 27.2         | 28.5         | 28.5          | 26.0          | 27.7          | 14.8*         | 6.2*           |
|          | S.D.  | 2.0          | 5.9          | 3.6          | 3.1           | 5.1           | 2.7           | 11.3          | 6.5            |
|          | N     | 6            | 6            | 6            | 6             | 6             | 6             | 6             | 5              |
| Day 1-3  | MEAN  | 54.5         | 41.0         | 53.8         | 54.0          | 64.3          | 49.0          | 28.0          | -              |
|          | S.D.  | 5.3          | 22.1         | 5.3          | 3.5           | 12.5          | 18.9          | 14.9          | -              |
|          | N     | 6            | 6            | 6            | 6             | 6             | 6             | 4             | 0              |
| Day 3-7  | MEAN  | 113.7        | 103.7        | 111.2        | 115.3         | 101.2         | 114.0         | 103.0         | -              |
|          | S.D.  | 9.6          | 22.0         | 5.3          | 7.4           | 17.6          | 14.6          | 4.7           | -              |
|          | N     | 6            | 6            | 6            | 6             | 6             | 6             | 6             | 0              |
| Day 7-14 | MEAN  | 207.5        | 210.8        | 196.2        | 210.3         | 193.3         | 209.6         | 178.3         | -              |
|          | S.D.  | 27.8         | 15.9         | 17.5         | 18.6          | 22.7          | 42.5          | 19.9          | -              |
|          | N     | 6            | 6            | 6            | 6             | 6             | 5             | 4             | 0              |

\* Indicates significance at the 0.05 level.

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APPENDIX F

14-DAY WEIGHT GAINS/LOSS OF  
MALE AND FEMALE RATS

14-DAY TCM STUDY NO. 75-51-0743-88 (2)  
SUMMARY OF WEIGHT GAINS (GRAMS)  
FEMALE RATS

| Period     | Group | 1<br>Control | 2<br>25mg/kg | 3<br>50mg/kg | 4<br>100mg/kg | 5<br>200mg/kg | 6<br>400mg/kg | 7<br>800mg/kg | 8<br>1600mg/kg |
|------------|-------|--------------|--------------|--------------|---------------|---------------|---------------|---------------|----------------|
| Days 0-1   | MEAN  | 5.3          | 4.0          | 5.0          | 4.5           | 2.2           | 2.5           | -1.8*         | -11.5*         |
|            | S.D.  | 1.4          | 2.4          | 3.5          | 2.8           | 4.7           | 5.0           | 5.5           | 6.95           |
|            | N     | 6            | 6            | 6            | 6             | 6             | 6             | 6             | 4              |
| Day 1-3    | MEAN  | 6.8          | 5.7          | 6.3          | 7.2           | 2.7           | 4.7           | 6.2           | 6.0            |
|            | S.D.  | 4.6          | 1.8          | 3.6          | 2.0           | 8.7           | 6.9           | 6.2           | 0.0            |
|            | N     | 6            | 6            | 6            | 6             | 6             | 6             | 6             | 1              |
| Day 3-7    | MEAN  | 11.7         | 10.2         | 13.2         | 10.0          | 11.8          | 0.5           | -5.3*         | -20.0*         |
|            | S.D.  | 4.2          | 3.1          | 2.5          | 3.6           | 4.1           | 16.3          | 17.8          | 0.0            |
|            | N     | 6            | 6            | 6            | 6             | 6             | 6             | 6             | 1              |
| Day 7-14   | MEAN  | 23.5         | 21.0         | 25.4         | 19.2          | 29.2          | 23.0          | 24.2          | 44.0           |
|            | S.D.  | 6.6          | 3.3          | 7.1          | 5.5           | 4.7           | 9.8           | 22.3          | 0.0            |
|            | N     | 6            | 6            | 5            | 6             | 6             | 5             | 5             | 1              |
| Total Gain | MEAN  | 47.3         | 40.8         | 59.4         | 40.8          | 45.8          | 28.8          | 23.2*         | 24.0           |
|            | S.D.  | 6.3          | 7.4          | 10.5         | 6.1           | 12.6          | 13.1          | 21.1          | 0.0            |
|            | N     | 6            | 6            | 5            | 6             | 6             | 5             | 5             | 1              |

\* Indicates significance at the 0.05 level.

14-DAY TCM STUDY NO. 75-51-0743-88 (2)  
SUMMARY OF WEIGHT GAINS (GRAMS)  
MALE RATS

| Period     | Group | 1<br>Control | 2<br>25mg/kg | 3<br>50mg/kg | 4<br>100mg/kg | 5<br>200mg/kg | 6<br>400mg/kg | 7<br>800mg/kg | 8<br>1600mg/kg |
|------------|-------|--------------|--------------|--------------|---------------|---------------|---------------|---------------|----------------|
| Day 0-1    | MEAN  | 9.3          | 3.2          | 8.5          | 7.2           | 6.8           | 6.0           | -7.3*         | -16.2*         |
|            | S.D.  | 2.1          | 10.4         | 2.8          | 2.2           | 3.6           | 1.7           | 14.0          | 11.3           |
|            | N     | 6            | 6            | 6            | 6             | 6             | 6             | 6             | 5              |
| Day 1-3    | MEAN  | 11.7         | 1.3          | 12.0         | 14.5          | 6.5           | 7.3           | -8.0*         | -              |
|            | S.D.  | 3.6          | 21.0         | 2.9          | 1.4           | 14.3          | 18.4          | 15.8          | -              |
|            | N     | 6            | 6            | 6            | 6             | 6             | 6             | 4             | 0              |
| Day 3-7    | MEAN  | 33.5         | 34.3         | 30.0         | 30.5          | 26.3          | 33.5          | 28.8          | -              |
|            | S.D.  | 5.1          | 6.1          | 2.5          | 3.9           | 11.5          | 6.9           | 9.3           | -              |
|            | N     | 6            | 6            | 6            | 6             | 6             | 6             | 4             | 0              |
| Day 7-14   | MEAN  | 50.5         | 55.0         | 44.7         | 52.7          | 51.5          | 51.6          | 42.3          | -              |
|            | S.D.  | 10.1         | 9.2          | 13.0         | 4.6           | 6.8           | 11.4          | 13.5          | -              |
|            | N     | 6            | 6            | 6            | 6             | 6             | 5             | 4             | 0              |
| Total Gain | MEAN  | 105.0        | 93.8         | 95.2         | 104.8         | 91.2          | 98.2          | 67.5          | -              |
|            | S.D.  | 17.3         | 22.9         | 13.2         | 9.1           | 18.8          | 33.4          | 27.2          | -              |
|            | N     | 6            | 6            | 6            | 6             | 6             | 5             | 4             | 0              |

\* Indicates significance at the 0.05 level.

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APPENDIX G

14-DAY CLINICAL CHEMISTRY  
SUMMARY OF MALE AND FEMALE RATS

14-DAY TCM STUDY NO. 75-51-0743-88 (2)  
CLINICAL CHEMISTRY SUMMARY  
FEMALE RATS

| Test                | Group | 1<br>Control | 2<br>25mg/kg | 3<br>50mg/kg | 4<br>100mg/kg | 5<br>200mg/kg | 6<br>400mg/kg | 7<br>800mg/kg | 8<br>1600mg/kg |
|---------------------|-------|--------------|--------------|--------------|---------------|---------------|---------------|---------------|----------------|
| ALK. PHOS.<br>IU/L  | MEAN  | 330.6        | 463.2        | 336.5        | 396.7         | 420.7         | 262.5         | 265.8         | 205.0          |
|                     | S.D.  | 226.3        | 100.8        | 84.7         | 172.1         | 131.3         | 51.4          | 40.9          | -              |
|                     | N     | 6            | 6            | 6            | 4             | 5             | 5             | 3             | 1              |
| SGOT<br>IU/L        | MEAN  | 117.2        | 103.1        | 86.7         | 88.5          | 78.8          | 70.4          | 63.7          | 132.3          |
|                     | S.D.  | 37.2         | 10.4         | 15.4         | 6.5           | 55.7          | 10.3          | 9.4           | -              |
|                     | N     | 6            | 6            | 6            | 4             | 5             | 5             | 3             | 1              |
| SGPT<br>IU/L        | MEAN  | 34.8         | 37.1         | 38.6         | 38.9          | 36.4          | 35.1          | 38.3          | 41.5           |
|                     | S.D.  | 7.7          | 3.1          | 7.8          | 10.4          | 3.3           | 4.9           | 11.8          | -              |
|                     | N     | 6            | 6            | 6            | 4             | 5             | 5             | 3             | 1              |
| GLUCOSE<br>IU/L     | MEAN  | 144.2        | 152.6        | 140.5        | 135.9         | 147.7         | 152.0         | 148.7         | 181.4          |
|                     | S.D.  | 23.6         | 25.2         | 19.6         | 11.1          | 9.3           | 7.0           | 8.4           | -              |
|                     | N     | 6            | 6            | 6            | 4             | 5             | 5             | 3             | 1              |
| TOT. BILI.<br>MG/DL | MEAN  | 0.6          | 0.5          | 0.5          | 0.5*          | 0.4*          | 0.3*          | 0.4*          | 0.3*           |
|                     | S.D.  | 0.1          | 0.1          | 0.1          | 0.1           | 0.1           | 0.1           | 0.1           | -              |
|                     | N     | 6            | 6            | 6            | 4             | 5             | 5             | 3             | 1              |
| BUN<br>MG/DL        | MEAN  | 25.8         | 25.5         | 26.9         | 24.1*         | 21.2*         | 18.3*         | 17.7*         | 17.6           |
|                     | S.D.  | 1.6          | 1.2          | 4.4          | 3.0           | 2.4           | 3.0           | 4.9           | -              |
|                     | N     | 6            | 6            | 6            | 4             | 5             | 5             | 3             | 1              |
| TOT. PROT.<br>G/DL  | MEAN  | 7.2          | 7.3          | 7.2          | 7.3*          | 7.1*          | 6.3*          | 6.0           | 6.0            |
|                     | S.D.  | 0.5          | 0.5          | 0.4          | 0.8           | 0.6           | 0.2           | 0.3           | -              |
|                     | N     | 6            | 6            | 6            | 4             | 5             | 5             | 3             | 1              |
| CALCIUM<br>MG/DL    | MEAN  | 9.0          | 10.6         | 10.4         | 10.2          | 10.5          | 10.7          | 10.5          | 12.5           |
|                     | S.D.  | 4.0          | 0.7          | 0.7          | 0.4           | 0.4           | 0.5           | 0.5           | -              |
|                     | N     | 6            | 6            | 6            | 4             | 5             | 5             | 3             | 1              |

\* Indicates significance at the 0.05 level.

ALK. PHOS. - Alkaline Phosphatase  
SGOT - Serum Glutamic Oxaloacetic Transaminase  
SGPT - Serum Glutamic Pyruvic Transaminase  
TOT. BILI. - Total Bilirubin  
BUN - Blood Urea Nitrogen  
TOT. PROT. - Total Protein



14-DAY TCM STUDY NO. 75-51-0743-88 (2)  
CLINICAL CHEMISTRY SUMMARY  
MALE RATS

| Test                | Group | 1<br>Control | 2<br>25mg/kg | 3<br>50mg/kg | 4<br>100mg/kg | 5<br>200mg/kg | 6<br>400mg/kg | 7<br>800mg/kg | 8<br>1600mg/kg |
|---------------------|-------|--------------|--------------|--------------|---------------|---------------|---------------|---------------|----------------|
| ALK. PHOS.<br>IU/L  | MEAN  | 619.3        | 590.4        | 639.2        | 647.6         | 557.6         | 417.1         | 481.6         | -              |
|                     | S.D.  | 204.4        | 194.6        | 224.2        | 142.6         | 144.7         | 147.6         | 203.6         | -              |
|                     | N     | 6            | 6            | 6            | 6             | 6             | 5             | 4             | -              |
| SGOT<br>IU/L        | MEAN  | 121.0        | 118.2        | 113.1        | 117.5         | 85.5*         | 85.5*         | 75.4*         | -              |
|                     | S.D.  | 23.2         | 11.9         | 13.2         | 16.4          | 8.2           | 20.8          | 7.9           | -              |
|                     | N     | 6            | 6            | 6            | 6             | 6             | 5             | 4             | -              |
| SGPT<br>IU/L        | MEAN  | 46.7         | 42.9         | 43.9         | 46.2          | 40.0          | 38.3          | 39.2          | -              |
|                     | S.D.  | 12.7         | 5.0          | 2.8          | 5.4           | 5.0           | 11.9          | 7.6           | -              |
|                     | N     | 6            | 6            | 6            | 6             | 6             | 5             | 4             | -              |
| GLUCOSE<br>IU/L     | MEAN  | 119.8        | 135.0        | 129.7        | 126.4         | 158.5*        | 151.1*        | 171.9*        | -              |
|                     | S.D.  | 9.5          | 47.3         | 13.2         | 7.6           | 25.8          | 4.2           | 7.9           | -              |
|                     | N     | 6            | 6            | 6            | 6             | 6             | 5             | 4             | -              |
| TOT. BILI.<br>MG/DL | MEAN  | 0.5          | 0.4          | 0.4          | 0.5           | 0.4           | 0.4           | 0.4           | -              |
|                     | S.D.  | 0.1          | 0.1          | 0.1          | 0.1           | 0.1           | 0.1           | 0.1           | -              |
|                     | N     | 6            | 6            | 6            | 6             | 6             | 5             | 4             | -              |
| BUN<br>MG/DL        | MEAN  | 25.9         | 23.4         | 22.6*        | 22.2*         | 16.3*         | 17.6*         | 16.6*         | -              |
|                     | S.D.  | 1.7          | 3.4          | 1.1          | 2.0           | 2.6           | 2.1           | 3.0           | -              |
|                     | N     | 6            | 6            | 6            | 6             | 6             | 5             | 4             | -              |
| TOT. PROT.<br>G/DL  | MEAN  | 7.3          | 6.8          | 6.7          | 6.8*          | 6.4*          | 6.1*          | 6.2*          | -              |
|                     | S.D.  | 0.6          | 0.4          | 0.3          | 0.6           | 0.2           | 0.4           | 0.2           | -              |
|                     | N     | 6            | 6            | 6            | 6             | 6             | 5             | 4             | -              |
| CALCIUM<br>MG/DL    | MEAN  | 10.4         | 10.6         | 10.4         | 10.4          | 10.6          | 10.3          | 10.5          | -              |
|                     | S.D.  | 0.5          | 1.0          | 0.6          | 0.6           | 0.8           | 0.4           | 0.4           | -              |
|                     | N     | 6            | 6            | 6            | 6             | 6             | 5             | 4             | -              |

\* Indicates significance at the 0.05 level.

ALK. PHOS. - Alkaline Phosphatase  
SGOT - Serum Glutamic Oxaloacetic Transaminase  
SGPT - Serum Glutamic Pyruvic Transaminase  
TOT. BILI. - Total Bilirubin  
BUN - Blood Urea Nitrogen  
TOT. PROT. - Total Protein

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#### APPENDIX H

#### 14-DAY HEMATOLOGY VALUES OF MALE AND FEMALE RATS

## 14-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - HEMOGLOBIN (g/dl)

H-2

| Source         | Sum of Squares | Deg. of Freedom | Mean Square | F Ratio |
|----------------|----------------|-----------------|-------------|---------|
| Between Groups | 2.03           | 7               | 0.29        | 0.38    |
| Within Groups  | 22.32          | 29              | 0.77        |         |
| Totals         | 24.35          | 36              |             |         |

|                                    |      |
|------------------------------------|------|
| F-table Lookup (num. 7, denom. 29) | 2.35 |
| F RATIO .05 -                      | 3.33 |
| F RATIO .01 -                      |      |

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

# ANALYSIS OF VARIANCE

14-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - HEMOGLOBIN (g/dl)

| ANIMAL # | GROUPS    |         |         |          |          |          |          |           |     |      | GRAND TOTALS | SUM OF SQUARES |       |       |       |       |       |      |      |        |         |
|----------|-----------|---------|---------|----------|----------|----------|----------|-----------|-----|------|--------------|----------------|-------|-------|-------|-------|-------|------|------|--------|---------|
|          | *DATA     |         |         |          |          |          |          |           |     |      |              |                |       |       |       |       |       |      |      |        |         |
|          | * 1       | * 2     | * 3     | * 4      | * 5      | * 6      | * 7      | * 8       | * 9 | * 10 |              |                |       |       |       |       |       |      |      |        |         |
|          | * control | 25mg/kg | 50mg/kg | 100mg/kg | 200mg/kg | 400mg/kg | 800mg/kg | 1600mg/kg |     |      |              |                |       |       |       |       |       |      |      |        |         |
| 823      | 811       | 812     | 816     | 813      | 815      | 827      |          |           |     |      |              | 1466.75        |       |       |       |       |       |      |      |        |         |
| 826      | 822       | 831     | 841     | 834      | 825      | 835      |          |           |     |      |              | 1338.61        |       |       |       |       |       |      |      |        |         |
| 829      | 824       | 836     | 842     | 837      | 844      | 851      |          |           |     |      |              | 1450.95        |       |       |       |       |       |      |      |        |         |
| 838      | 845       | 839     | 850     | 846      | 853      | 858      |          |           |     |      |              | 1554.83        |       |       |       |       |       |      |      |        |         |
| 848      | 854       | 843     | 852     | 849      | 857      |          |          |           |     |      |              | 1374.43        |       |       |       |       |       |      |      |        |         |
| 863      | 817       | 862     | 855     | 861      |          |          |          |           |     |      |              | 1285.80        |       |       |       |       |       |      |      |        |         |
| -----    |           |         |         |          |          |          |          |           |     |      |              |                |       |       |       |       |       |      |      |        |         |
| Totals   |           |         |         |          |          |          |          |           |     |      | 88.40        | 88.10          | 88.80 | 89.10 | 89.20 | 74.70 | 56.00 | 0.00 | 0.00 | 574.30 | 8471.37 |

NS - INSUFFICIENT SAMPLE

## ANALYSIS OF VARIANCE TABLE

| Source         | Sum of Squares | Deg. of Freedom | Mean Square | F Ratio |
|----------------|----------------|-----------------|-------------|---------|
| Between Groups | 2.59           | 6               | 0.43        | 1.17    |
| Within Groups  | 11.84          | 32              | 0.37        |         |
| Totals         | 14.43          | 38              |             |         |

F-table Lookup (num. 6, denom. 32)  
F RATIO .05 = 2.40  
F RATIO .01 = 3.42

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

## ANALYSIS OF VARIANCE

14-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - HEMATOCRIT (%)

| ANIMAL #    | GROUPS |     |     |     |     |     |     |   |   |    | *DATA*                   | GROUPS  |         |         |          |          |          |          |           |      |       | GRAND TOTALS | SUM OF SQUARES |
|-------------|--------|-----|-----|-----|-----|-----|-----|---|---|----|--------------------------|---------|---------|---------|----------|----------|----------|----------|-----------|------|-------|--------------|----------------|
|             | 1      | 2   | 3   | 4   | 5   | 6   | 7   | 8 | 9 | 10 |                          | control | 25mg/kg | 50mg/kg | 100mg/kg | 200mg/kg | 400mg/kg | 800mg/kg | 1600mg/kg |      |       |              |                |
| 771         | 759    | 767 | 764 | 760 | 781 | 761 | 793 |   |   |    | *                        | 40.5    | 35.2    | 42.6    | 40.2     | 40.6     | 39.2     | 47.0     | 36.6      |      |       | 13115.05     |                |
| 779         | 763    | 778 | 766 | 769 | 782 | 770 |     |   |   |    | *                        | 41.0    | 38.1    | 38.6    | 38.5     | 40.8     | 41.0     | 37.7     |           |      |       | 10871.75     |                |
| 787         | 791    | 783 | 768 | 784 | 794 | 773 |     |   |   |    | *                        | 41.6    | 40.5    | 40.5    | 41.9     | 38.5     | 40.3     | 39.1     |           |      |       | 11401.82     |                |
| 790         | 795    | 786 | 774 | 789 | 797 | 775 |     |   |   |    | *                        | 41.1    | 43.7    | 37.3    | NS       | 39.5     | 38.3     | 40.6     |           |      |       | 9665.69      |                |
| 796         | 798    | 799 | 780 | 792 | 801 | 788 |     |   |   |    | *                        | 39.2    | 41.3    | 41.5    | 38.2     | NS       | 41.3     | 37.6     |           |      |       | 9543.27      |                |
| 802         | 803    | 806 | 809 | 808 |     |     |     |   |   |    | *                        | NS      | 37.8    | 41.6    | NS       | 42.4     |          |          |           |      |       | 4957.16      |                |
| Totals      |        |     |     |     |     |     |     |   |   |    | 203.40                   | 237.60  | 242.10  | 158.80  | 201.80   | 200.10   | 202.00   | 36.60    | 0.00      | 0.00 | 0.00  | 1482.40      | 59554.74       |
| Observation |        |     |     |     |     |     |     |   |   |    | 5.00                     | 6.00    | 6.00    | 4.00    | 5.00     | 5.00     | 5.00     | 1.00     | 1.00      | 1.00 | 37.00 |              |                |
| Mean        |        |     |     |     |     |     |     |   |   |    | 40.68                    | 39.60   | 40.35   | 39.70   | 40.36    | 40.02    | 40.40    | 36.60    | 0.00      | 0.00 | 0.00  | 40.06        |                |
| Std Dev     |        |     |     |     |     |     |     |   |   |    | 0.82                     | 2.50    | 1.84    | 1.48    | 1.31     | 1.12     | 3.48     | 0.00     | ERR       | ERR  | ERR   |              |                |
|             |        |     |     |     |     |     |     |   |   |    | NS = INSUFFICIENT SAMPLE |         |         |         |          |          |          |          |           |      |       |              |                |
| # of Group  |        |     |     |     |     |     |     |   |   |    | 8                        |         |         |         |          |          |          |          |           |      |       |              |                |

### ANALYSIS OF VARIANCE TABLE

| Source         | Sum of Squares | Deg. of Freedom | Mean Square | F Ratio |
|----------------|----------------|-----------------|-------------|---------|
| Between Groups | 17.22          | 7               | 2.46        | 0.49    |
| Within Groups  | 145.36         | 29              | 5.01        |         |
| Totals         | 162.58         | 36              |             |         |

|                                    |      |
|------------------------------------|------|
| F-table Lookup (num. 7, denom. 29) | 2.35 |
| F RATIO .05 =                      | 3.33 |
| F RATIO .01 =                      |      |

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

## 14-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - HEMATOCRIT (%)

| ANIMAL #    | GROUPS |     |     |     |     |     |   |   |    |    | *DATA*  | GROUPS                   |         |          |          |          |          |           |      |          |         | GRAND TOTALS | SUM OF SQUARES |
|-------------|--------|-----|-----|-----|-----|-----|---|---|----|----|---------|--------------------------|---------|----------|----------|----------|----------|-----------|------|----------|---------|--------------|----------------|
|             | 1      | 2   | 3   | 4   | 5   | 6   | 7 | 8 | 9  | 10 |         | 1                        | 2       | 3        | 4        | 5        | 6        | 7         | 8    | 9        | 10      |              |                |
| 1           | 2      | 3   | 4   | 5   | 6   | 7   | 8 | 9 | 10 | *  | control | 25mg/kg                  | 50mg/kg | 100mg/kg | 200mg/kg | 400mg/kg | 800mg/kg | 1600mg/kg |      |          |         |              |                |
| 823         | 811    | 812 | 816 | 813 | 815 | 827 |   |   |    | *  | 42.0    | 40.3                     | 41.8    | 40.2     | 40.5     | 39.1     | 39.9     |           |      | 11512.44 |         |              |                |
| 826         | 822    | 831 | 841 | 834 | 825 | 835 |   |   |    | *  | 42.5    | 44.1                     | 42.9    | 42.3     | 40.8     | NS       | 36.3     |           |      | 10363.09 |         |              |                |
| 829         | 824    | 836 | 842 | 837 | 844 | 851 |   |   |    | *  | 41.8    | 39.6                     | 38.7    | 41.9     | 40.8     | 42.5     | 35.0     |           |      | 11264.59 |         |              |                |
| 838         | 845    | 839 | 850 | 846 | 853 | 858 |   |   |    | *  | 39.6    | 41.2                     | 39.4    | 41.6     | 43.2     | 40.3     | 40.5     |           |      | 11679.10 |         |              |                |
| 848         | 854    | 843 | 852 | 849 | 857 |     |   |   |    | *  | 40.0    | 43.9                     | 42.8    | 38.1     | 41.2     | 42.1     | 41.2     |           |      | 10280.51 |         |              |                |
| 863         | 817    | 862 | 855 | 861 |     |     |   |   |    | *  | 39.0    | 40.5                     | 39.1    | 39.4     | 38.6     | 40.3     |          |           |      | 9356.47  |         |              |                |
| Totals      |        |     |     |     |     |     |   |   |    |    | 244.90  | 249.60                   | 244.70  | 243.50   | 245.10   | 204.30   | 151.70   | 0.00      | 0.00 | 0.00     | 1583.80 | 64456.20     |                |
| Observation |        |     |     |     |     |     |   |   |    |    | 6.00    | 6.00                     | 6.00    | 6.00     | 6.00     | 5.00     | 4.00     | 1.00      | 1.00 | 1.00     | 39.00   |              |                |
| Mean        |        |     |     |     |     |     |   |   |    |    | 40.82   | 41.60                    | 40.78   | 40.58    | 40.85    | 40.86    | 37.93    | 0.00      | 0.00 | 0.00     | 40.61   |              |                |
| Std Dev     |        |     |     |     |     |     |   |   |    |    | 1.33    | 1.76                     | 1.76    | 1.50     | 1.34     | 1.26     | 2.33     | ERR       | ERR  | ERR      | ERR     |              |                |
| # of Group  |        |     |     |     |     |     |   |   |    |    | 7       | NS - INSUFFICIENT SAMPLE |         |          |          |          |          |           |      |          |         |              |                |

## ANALYSIS OF VARIANCE TABLE

|                   | Sum of<br>Source Squares | Deg. of<br>Freedom | Mean<br>Square | F Ratio |
|-------------------|--------------------------|--------------------|----------------|---------|
| Between<br>Groups | 35.82                    | 6                  | 5.97           | 1.88    |
| Within<br>Groups  | 101.86                   | 32                 | 3.18           |         |
| Totals            | 137.68                   | 38                 |                |         |

F-table Lookup (num. 6, denom. 32)  
F RATIO .05 = 2.40  
F RATIO .01 = 3.42

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
; AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

# ANALYSIS OF VARIANCE

14-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - RED BLOOD CELLS (10E+6/ $\mu$ L)

| ANIMAL #                                                                | GROUPS |     |     |     |     |     |     |   |    |  | GRAND TOTALS | SUM OF SQUARES |
|-------------------------------------------------------------------------|--------|-----|-----|-----|-----|-----|-----|---|----|--|--------------|----------------|
|                                                                         | *DATA  |     |     |     |     |     |     |   |    |  |              |                |
|                                                                         |        |     |     |     |     |     |     |   |    |  |              |                |
| 1                                                                       | 2      | 3   | 4   | 5   | 6   | 7   | 8   | 9 | 10 |  |              |                |
| * control 25mg/kg 50mg/kg 100mg/kg 200mg/kg 400mg/kg 800mg/kg 1600mg/kg |        |     |     |     |     |     |     |   |    |  |              |                |
| 771                                                                     | 759    | 767 | 764 | 760 | 781 | 761 | 793 |   |    |  |              |                |
|                                                                         |        |     |     |     |     |     |     |   |    |  |              |                |
| 779                                                                     | 763    | 778 | 766 | 769 | 782 | 770 |     |   |    |  |              |                |
| 787                                                                     | 791    | 783 | 768 | 784 | 794 | 773 |     |   |    |  |              |                |
| 790                                                                     | 795    | 786 | 774 | 789 | 797 | 775 |     |   |    |  |              |                |
| 796                                                                     | 798    | 799 | 780 | 792 | 801 | 788 |     |   |    |  |              |                |
| 802                                                                     | 803    | 806 | 809 | 808 |     |     |     |   |    |  |              |                |
| -----                                                                   |        |     |     |     |     |     |     |   |    |  |              |                |
| Totals                                                                  |        |     |     |     |     |     |     |   |    |  |              |                |
|                                                                         |        |     |     |     |     |     |     |   |    |  |              |                |
| Observation                                                             |        |     |     |     |     |     |     |   |    |  |              |                |
|                                                                         |        |     |     |     |     |     |     |   |    |  |              |                |
| Mean                                                                    |        |     |     |     |     |     |     |   |    |  |              |                |
|                                                                         |        |     |     |     |     |     |     |   |    |  |              |                |
| Std Dev                                                                 |        |     |     |     |     |     |     |   |    |  |              |                |
|                                                                         |        |     |     |     |     |     |     |   |    |  |              |                |
| NS - INSUFFICIENT SAMPLE                                                |        |     |     |     |     |     |     |   |    |  |              |                |

## ANALYSIS OF VARIANCE TABLE

| Source         | Sum of Squares | Deg. of Freedom | Mean Square | F Ratio |
|----------------|----------------|-----------------|-------------|---------|
| Between Groups | 1.09           | 7               | 0.16        | 1.12    |
| Within Groups  | 4.01           | 29              | 0.14        |         |
| Totals         | 5.09           | 36              |             |         |

F-table Lookup (num. 7, denom. 29)  
F RATIO .05 = 2.35  
F RATIO .01 = 3.33

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

# ANALYSIS OF VARIANCE

14-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - RED BLOOD CELLS (10E+6/ $\mu$ L)

| ANIMAL #    | GROUPS |     |     |     |     |     |   |   |   |    | *DATA | GROUPS                   |         |         |          |          |          |          |           |      |        | GRAND TOTALS | SUM OF SQUARES |  |
|-------------|--------|-----|-----|-----|-----|-----|---|---|---|----|-------|--------------------------|---------|---------|----------|----------|----------|----------|-----------|------|--------|--------------|----------------|--|
|             | 1      | 2   | 3   | 4   | 5   | 6   | 7 | 8 | 9 | 10 | *     | 1                        | 2       | 3       | 4        | 5        | 6        | 7        | 8         | 9    | 10     |              |                |  |
|             |        |     |     |     |     |     |   |   |   |    | *     | * control                | 25mg/kg | 50mg/kg | 100mg/kg | 200mg/kg | 400mg/kg | 800mg/kg | 1600mg/kg |      |        |              |                |  |
| 823         | 811    | 812 | 816 | 813 | 815 | 827 |   |   |   |    | *     | 6.78                     | 6.30    | 6.63    | 6.55     | 6.21     | 6.33     | 6.63     |           |      | 295.11 |              |                |  |
| 826         | 822    | 831 | 841 | 834 | 825 | 835 |   |   |   |    | *     | 6.75                     | 6.96    | 6.95    | 6.61     | 6.64     | NS       | 5.96     |           |      | 265.61 |              |                |  |
| 829         | 824    | 836 | 842 | 837 | 844 | 851 |   |   |   |    | *     | 6.61                     | 6.41    | 6.21    | 6.49     | 6.56     | 6.45     | 5.61     |           |      | 281.57 |              |                |  |
| 838         | 845    | 839 | 850 | 846 | 853 | 858 |   |   |   |    | *     | 6.59                     | 6.57    | 6.43    | 6.62     | 6.94     | 6.27     | 6.29     |           |      | 298.80 |              |                |  |
| 848         | 854    | 843 | 852 | 849 | 857 |     |   |   |   |    | *     | 6.27                     | 6.82    | 7.00    | 5.94     | 6.81     | 6.66     |          |           |      | 260.84 |              |                |  |
| 863         | 817    | 862 | 855 | 861 |     |     |   |   |   |    | *     | 6.14                     | 6.33    | 6.37    | 6.47     | 6.10     | 6.27     |          |           |      | 236.73 |              |                |  |
| Totals      |        |     |     |     |     |     |   |   |   |    | 39.14 | 39.39                    | 39.59   | 38.68   | 39.26    | 31.98    | 24.49    | 0.00     | 0.00      | 0.00 | 0.00   | 252.53       | 1638.66        |  |
| Observation |        |     |     |     |     |     |   |   |   |    | 6.00  | 6.00                     | 6.00    | 6.00    | 6.00     | 5.00     | 4.00     | 1.00     | 1.00      | 1.00 | 1.00   | 39.00        |                |  |
| Mean        |        |     |     |     |     |     |   |   |   |    | 6.52  | 6.57                     | 6.60    | 6.45    | 6.54     | 6.40     | 6.12     | 0.00     | 0.00      | 0.00 | 0.00   | 6.48         |                |  |
| Std Dev     |        |     |     |     |     |     |   |   |   |    | 0.24  | 0.25                     | 0.29    | 0.23    | 0.30     | 0.15     | 0.38     | ERR      | ERR       | ERR  | ERR    |              |                |  |
| # of Group  |        |     |     |     |     |     |   |   |   |    | 7     | NS - INSUFFICIENT SAMPLE |         |         |          |          |          |          |           |      |        |              |                |  |

## ANALYSIS OF VARIANCE TABLE

| Source         | Sum of  |                 | Mean   |         | F Ratio |  |
|----------------|---------|-----------------|--------|---------|---------|--|
|                | Squares | Deg. of Freedom | Square | F Ratio |         |  |
| Between Groups | 0.71    | 6               | 0.12   | 1.37    |         |  |
| Within Groups  | 2.78    | 32              | 0.09   |         |         |  |
| Totals         | 3.50    | 38              |        |         |         |  |

F-table Lookup (num. 6, denom. 32)  
F RATIO .05 = 2.40  
F RATIO .01 = 3.42

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.



# ANALYSIS OF VARIANCE

14-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - MEAN CELL VOLUME (CL)

| ANIMAL #    | GROUPS    |         |         |          |          |          |          |           |   |    | GRAND TOTALS | SUM OF SQUARES |                          |        |        |        |        |       |       |       |         |           |       |
|-------------|-----------|---------|---------|----------|----------|----------|----------|-----------|---|----|--------------|----------------|--------------------------|--------|--------|--------|--------|-------|-------|-------|---------|-----------|-------|
|             | *DATA     |         |         |          |          |          |          |           |   |    |              |                |                          |        |        |        |        |       |       |       |         |           |       |
|             | 1         | 2       | 3       | 4        | 5        | 6        | 7        | 8         | 9 | 10 |              |                |                          |        |        |        |        |       |       |       |         |           |       |
|             | * control | 25mg/kg | 50mg/kg | 100mg/kg | 200mg/kg | 400mg/kg | 800mg/kg | 1600mg/kg |   |    |              |                |                          |        |        |        |        |       |       |       |         |           |       |
| 771         | 759       | 767     | 764     | 760      | 781      | 761      | 793      |           |   |    |              | 29657.00       |                          |        |        |        |        |       |       |       |         |           |       |
| 779         | 763       | 778     | 766     | 769      | 782      | 770      |          |           |   |    |              | 25327.00       |                          |        |        |        |        |       |       |       |         |           |       |
| 787         | 791       | 783     | 768     | 784      | 794      | 773      |          |           |   |    |              | 25688.00       |                          |        |        |        |        |       |       |       |         |           |       |
| 790         | 795       | 786     | 774     | 789      | 797      | 775      |          |           |   |    |              | 21848.00       |                          |        |        |        |        |       |       |       |         |           |       |
| 796         | 798       | 799     | 780     | 792      | 801      | 788      |          |           |   |    |              | 18494.00       |                          |        |        |        |        |       |       |       |         |           |       |
| 802         | 803       | 806     | 809     | 808      |          |          |          |           |   |    |              | 10933.00       |                          |        |        |        |        |       |       |       |         |           |       |
| -----       |           |         |         |          |          |          |          |           |   |    |              |                |                          |        |        |        |        |       |       |       |         |           |       |
| Totals      |           |         |         |          |          |          |          |           |   |    | 301.00       | 362.00         | 367.00                   | 240.00 | 301.00 | 307.00 | 240.00 | 61.00 | 0.00  | 0.00  | 2179.00 | 131947.00 |       |
| Observation |           |         |         |          |          |          |          |           |   |    |              |                | 5.00                     | 6.00   | 6.00   | 4.00   | 5.00   | 5.00  | 4.00  | 1.00  | 1.00    | 1.00      | 36.00 |
| Mean        |           |         |         |          |          |          |          |           |   |    |              |                | 60.20                    | 60.33  | 61.17  | 60.00  | 60.20  | 61.40 | 60.00 | 61.00 | 0.00    | 0.00      | 60.53 |
| Std Dev     |           |         |         |          |          |          |          |           |   |    |              |                | 0.75                     | 1.70   | 1.34   | 0.71   | 0.75   | 1.20  | 1.00  | 0.00  | ERR     | ERR       |       |
|             |           |         |         |          |          |          |          |           |   |    |              |                | MS = INSUFFICIENT SAMPLE |        |        |        |        |       |       |       |         |           |       |
| # of Group  |           |         |         |          |          |          |          |           |   |    |              |                | 8                        |        |        |        |        |       |       |       |         |           |       |

## ANALYSIS OF VARIANCE TABLE

| Source         | Sum of Squares | Deg. of Freedom | Mean Square | F Ratio |
|----------------|----------------|-----------------|-------------|---------|
| Between Groups | 10.01          | 7               | 1.43        | 0.85    |
| Within Groups  | 46.97          | 28              | 1.68        |         |
| Totals         | 56.97          | 35              |             |         |

F-table Lookup (num. 7, denom. 28)  
F RATIO .05 = 2.35  
F RATIO .01 = 3.33

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

# ANALYSIS OF VARIANCE

14-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - MEAN CELL VOLUME (FL)

| ANIMAL #    | GROUPS   |         |         |          |          |          |          |           |      |      | GRAND TOTALS | SUM OF SQUARES    |
|-------------|----------|---------|---------|----------|----------|----------|----------|-----------|------|------|--------------|-------------------|
|             | *DATA*   | 1       | 2       | 3        | 4        | 5        | 6        | 7         | 8    | 9    |              |                   |
| 1           | *control | 25mg/kg | 50mg/kg | 100mg/kg | 200mg/kg | 400mg/kg | 800mg/kg | 1600mg/kg |      |      |              |                   |
| 2           | *        | 61      | 63      | 62       | 61       | 65       | 61       | 60        |      |      |              |                   |
| 3           | *        | 62      | 63      | 61       | 63       | 61       | NS       | 60        |      |      |              |                   |
| 4           | *        | 63      | 61      | 62       | 64       | 61       | 65       | 62        |      |      |              |                   |
| 5           | *        | 59      | 62      | 61       | 62       | 62       | 64       | 64        |      |      |              |                   |
| 6           | *        | 63      | 63      | 60       | 64       | 60       | 63       |           |      |      |              |                   |
| 7           | *        | 63      | 63      | 61       | 60       | 63       | 64       |           |      |      |              |                   |
| Totals      |          | 371.00  | 375.00  | 367.00   | 374.00   | 372.00   | 317.00   | 246.00    | 0.00 | 0.00 | 0.00         | 2422.00 150498.00 |
| Observation |          | 6.00    | 6.00    | 6.00     | 6.00     | 6.00     | 5.00     | 4.00      | 1.00 | 1.00 | 1.00         | 39.00             |
| Mean        |          | 61.83   | 62.50   | 61.17    | 62.33    | 62.00    | 63.40    | 61.50     | 0.00 | 0.00 | 0.00         | 62.10             |
| Std Dev     |          | 1.46    | 0.76    | 0.69     | 1.49     | 1.63     | 1.36     | 1.66      | ERR  | ERR  | ERR          | ERR               |
| # of Group  |          | 7       |         |          |          |          |          |           |      |      |              |                   |

NS = INSUFFICIENT SAMPLE

## ANALYSIS OF VARIANCE TABLE

| Source         | Sum of Squares | Deg. of Freedom | Mean Square | F Ratio |
|----------------|----------------|-----------------|-------------|---------|
| Between Groups | 16.89          | 6               | 2.81        | 1.31    |
| Within Groups  | 68.70          | 32              | 2.15        |         |
| Totals         | 85.59          | 38              |             |         |

F-table Lookup (num. 6, denom. 32)  
F RATIO .05 = 2.40  
F RATIO .01 = 3.42

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

# ANALYSIS OF VARIANCE

14-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - WHITE BLOOD CELLS (10E+3/ $\mu$ L)

| ANIMAL #    | GROUPS |     |     |     |     |     |     |   |   |    | *DATA*    | GROUPS  |                          |          |          |          |          |           |       |      |      | GRAND TOTALS | SUM OF SQUARES |
|-------------|--------|-----|-----|-----|-----|-----|-----|---|---|----|-----------|---------|--------------------------|----------|----------|----------|----------|-----------|-------|------|------|--------------|----------------|
|             | 1      | 2   | 3   | 4   | 5   | 6   | 7   | 8 | 9 | 10 | * control | 25mg/kg | 50mg/kg                  | 100mg/kg | 200mg/kg | 400mg/kg | 800mg/kg | 1600mg/kg | 8     | 9    | 10   |              |                |
| 771         | 759    | 767 | 764 | 760 | 781 | 761 | 793 |   |   |    | *         | 7.1     | 8.0                      | 11.0     | 16.3     | 13.4     | 15.6     | 7.0       | 11.1  |      |      | 1096.23      |                |
| 779         | 763    | 778 | 766 | 769 | 782 | 770 |     |   |   |    | *         | 3.6     | 7.5                      | 11.5     | 11.7     | 5.4      | 7.2      | 5.6       |       |      |      | 450.71       |                |
| 787         | 791    | 783 | 768 | 784 | 794 | 773 |     |   |   |    | *         | 9.6     | 7.3                      | 7.5      | 8.0      | 6.8      | 11.8     | 9.4       |       |      |      | 539.54       |                |
| 790         | 795    | 786 | 774 | 789 | 797 | 775 |     |   |   |    | *         | 7.4     | 8.2                      | 6.0      | NS       | 10.6     | 11.3     | 11.6      |       |      |      | 532.61       |                |
| 796         | 798    | 799 | 780 | 792 | 801 | 788 |     |   |   |    | *         | 5.6     | 16.4                     | 6.2      | 9.8      | NS       | 11.1     | 7.3       |       |      |      | 611.30       |                |
| 802         | 803    | 806 | 809 | 808 |     |     |     |   |   |    | *         | NS      | 8.7                      | 10.9     | NS       | 14.5     |          |           |       |      |      | 404.75       |                |
| Totals      |        |     |     |     |     |     |     |   |   |    |           | 33.30   | 56.10                    | 53.10    | 45.80    | 50.70    | 57.00    | 40.90     | 11.10 | 0.00 | 0.00 | 348.00       | 3635.14        |
| Observation |        |     |     |     |     |     |     |   |   |    |           | 5.00    | 6.00                     | 6.00     | 4.00     | 5.00     | 5.00     | 5.00      | 1.00  | 1.00 | 1.00 | 37.00        |                |
| Mean        |        |     |     |     |     |     |     |   |   |    |           | 6.66    | 9.35                     | 8.85     | 11.45    | 10.14    | 11.40    | 8.18      | 11.10 | 0.00 | 0.00 | 9.41         |                |
| Std Dev     |        |     |     |     |     |     |     |   |   |    |           | 1.99    | 3.19                     | 2.34     | 3.09     | 3.56     | 2.67     | 2.10      | 0.00  | ERR  | ERR  |              |                |
| # of Group  |        |     |     |     |     |     |     |   |   |    |           | 8       | NS - INSUFFICIENT SAMPLE |          |          |          |          |           |       |      |      |              |                |

## ANALYSIS OF VARIANCE TABLE

| Source         | Sum of Squares | Deg. of Freedom | Mean Square | F Ratio |
|----------------|----------------|-----------------|-------------|---------|
| Between Groups | 89.25          | 7               | 12.75       | 1.36    |
| Within Groups  | 272.81         | 29              | 9.41        |         |
| Totals         | 362.06         | 36              |             |         |

F-table Lookup (num. 7, denom. 29)  
F RATIO .05 = 2.35  
F RATIO .01 = 3.33

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

# ANALYSIS OF VARIANCE

14-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - WHITE BLOOD CELLS (10E+3/ $\mu$ L)

| ANIMAL #    | GROUPS |     |     |     |     |     |   |   |   |    | *DATA | GROUPS    |                          |         |          |          |          |          |           |      |         | GRAND TOTALS | SUM OF SQUARES |
|-------------|--------|-----|-----|-----|-----|-----|---|---|---|----|-------|-----------|--------------------------|---------|----------|----------|----------|----------|-----------|------|---------|--------------|----------------|
|             | 1      | 2   | 3   | 4   | 5   | 6   | 7 | 8 | 9 | 10 | *     | 1         | 2                        | 3       | 4        | 5        | 6        | 7        | 8         | 9    | 10      |              |                |
|             |        |     |     |     |     |     |   |   |   |    | *     | * control | 25mg/kg                  | 50mg/kg | 100mg/kg | 200mg/kg | 400mg/kg | 800mg/kg | 1600mg/kg |      |         |              |                |
| 823         | 811    | 812 | 816 | 813 | 815 | 827 |   |   |   |    | *     | 12.1      | 6.4                      | 12.7    | 23.0     | 12.6     | 15.2     | 17.8     |           |      | 1584.30 |              |                |
| 826         | 822    | 831 | 841 | 834 | 825 | 835 |   |   |   |    | *     | 11.1      | 13.3                     | 13.6    | 15.1     | 8.3      | NS       | 9.2      |           |      | 366.60  |              |                |
| 829         | 824    | 836 | 842 | 837 | 844 | 851 |   |   |   |    | *     | 6.8       | 13.1                     | 14.7    | 16.9     | 18.5     | 15.6     | 19.2     |           |      | 1673.80 |              |                |
| 838         | 845    | 839 | 850 | 846 | 853 | 858 |   |   |   |    | *     | 6.2       | 14.9                     | 11.9    | 13.1     | 10.9     | 13.8     | 16.7     |           |      | 1161.81 |              |                |
| 848         | 854    | 843 | 852 | 849 | 857 |     |   |   |   |    | *     | 15.3      | 6.4                      | 11.0    | 18.1     | 14.7     | 13.9     |          |           |      | 1132.96 |              |                |
| 863         | 817    | 862 | 855 | 861 |     |     |   |   |   |    | *     | 20.6      | 10.4                     | 15.3    | 10.7     | 14.8     | 12.2     |          |           |      | 1248.98 |              |                |
| Totals      |        |     |     |     |     |     |   |   |   |    |       | 72.10     | 64.50                    | 79.20   | 96.90    | 79.80    | 70.70    | 62.90    | 0.00      | 0.00 | 0.00    | 526.10       | 7668.45        |
| Observation |        |     |     |     |     |     |   |   |   |    |       | 6.00      | 6.00                     | 6.00    | 6.00     | 6.00     | 5.00     | 4.00     | 1.00      | 1.00 | 1.00    | 39.00        |                |
| Mean        |        |     |     |     |     |     |   |   |   |    |       | 12.02     | 10.75                    | 13.20   | 16.15    | 13.30    | 14.14    | 15.73    | 0.00      | 0.00 | 0.00    | 13.49        |                |
| Std Dev     |        |     |     |     |     |     |   |   |   |    |       | 4.94      | 3.35                     | 1.51    | 3.90     | 3.23     | 1.20     | 3.87     | ERR       | ERR  | ERR     |              |                |
| # of Group  |        |     |     |     |     |     |   |   |   |    |       | 7         | NS - INSUFFICIENT SAMPLE |         |          |          |          |          |           |      |         |              |                |

## ANALYSIS OF VARIANCE TABLE

| Source         | Sum of Squares | Deg. of Freedom | Mean Square | F Ratio |
|----------------|----------------|-----------------|-------------|---------|
| Between Groups | 123.34         | 6               | 20.56       | 1.47    |
| Within Groups  | 448.16         | 32              | 14.00       |         |
| Totals         | 571.50         | 38              |             |         |

F-table Lookup (num. 6, denom. 32)  
F RATIO .05 = 2.40  
F RATIO .01 = 3.42

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

Phase 2, Toxicological Study No. 75-51-0743-88(2), 3 Aug 88 -  
17 Jan 89

APPENDIX I

14-DAY SUMMARY OF ORGAN WEIGHTS

14-DAY TCM STUDY #75-51-0743-88(2)  
SUMMARY OF ORGAN WEIGHTS (GRAMS)  
MALE RATS

| ORGAN       | GROUP      | 1<br>Control | 2<br>25mg/kg | 3<br>50mg/kg | 4<br>100mg/kg | 5<br>200mg/kg | 6<br>400mg/kg | 7<br>800mg/kg | 8<br>1600mg/kg |
|-------------|------------|--------------|--------------|--------------|---------------|---------------|---------------|---------------|----------------|
| Body Weight | MEAN       | 302          | 293          | 295          | 305           | 285           | 303           | 262           | ---            |
|             | S.D.       | 25.0         | 28.2         | 16.9         | 18.3          | 30.8          | 38.6          | 17.3          | ---            |
|             | N          | 6            | 6            | 6            | 6             | 6             | 5             | 4             | ---            |
| Brain       | MEAN       | 1.90         | 1.86         | 1.84         | 1.86          | 1.78          | 1.81          | 1.76          | ---            |
|             | S.D.       | 0.067        | 0.118        | 0.063        | 0.129         | 0.027         | 0.062         | 0.057         | ---            |
|             | % BODY WT  | 0.631        | 0.639        | 0.624        | 0.610         | 0.632         | 0.605         | 0.677         | ---            |
|             | S.D.       | 0.053        | 0.047        | 0.034        | 0.050         | 0.065         | 0.073         | 0.061         | ---            |
|             | N          | 6            | 6            | 6            | 6             | 6             | 5             | 4             | ---            |
| Adrenals    | MEAN       | 0.067        | 0.065        | 0.060        | 0.063         | 0.059         | 0.061         | 0.060         | ---            |
|             | S.D.       | 0.011        | 0.007        | 0.002        | 0.006         | 0.009         | 0.008         | 0.010         | ---            |
|             | % BODY WT  | 0.022        | 0.022        | 0.020        | 0.021         | 0.021         | 0.020         | 0.023         | ---            |
|             | S.D.       | 0.002        | 0.002        | 0.001        | 0.003         | 0.002         | 0.002         | 0.005         | ---            |
|             | % BRAIN WT | 3.52         | 3.50         | 3.26         | 3.40          | 3.29          | 3.36          | 3.38          | ---            |
|             | S.D.       | 0.5          | 0.3          | 0.2          | 0.4           | 0.5           | 0.4           | 0.5           | ---            |
|             | N          | 6            | 6            | 6            | 6             | 6             | 5             | 4             | ---            |
| Kidneys     | MEAN       | 2.69         | 2.74         | 2.53         | 2.59          | 2.43          | 2.65          | 2.42          | ---            |
|             | S.D.       | 0.277        | 0.221        | 0.295        | 0.167         | 0.184         | 0.253         | 0.278         | ---            |
|             | % BODY WT  | 0.891        | 0.940        | 0.856        | 0.850         | 0.856         | 0.879         | 0.925         | ---            |
|             | S.D.       | 0.057        | 0.067        | 0.063        | 0.018         | 0.063         | 0.067         | 0.090         | ---            |
|             | % BRAIN WT | 141.94       | 147.28       | 137.51       | 139.90        | 136.17        | 146.21        | 137.24        | ---            |
|             | S.D.       | 13.7         | 6.5          | 12.9         | 10.3          | 10.7          | 14.9          | 16.1          | ---            |
|             | N          | 6            | 6            | 6            | 6             | 6             | 5             | 4             | ---            |
| Testes      | MEAN       | 2.79         | 2.99         | 2.85         | 2.78          | 2.77          | 2.70          | 2.39          | ---            |
|             | S.D.       | 0.212        | 0.284        | 0.113        | 0.317         | 0.196         | 0.173         | 0.490         | ---            |
|             | % BODY WT  | 0.926        | 1.025        | 0.969        | 0.914         | 0.981         | 0.899         | 0.925         | ---            |
|             | S.D.       | 0.068        | 0.093        | 0.065        | 0.105         | 0.122         | 0.098         | 0.232         | ---            |
|             | % BRAIN WT | 147.31       | 160.43       | 155.32       | 150.17        | 155.31        | 148.89        | 135.20        | ---            |
|             | S.D.       | 13.3         | 9.6          | 6.9          | 16.1          | 11.4          | 11.4          | 23.4          | ---            |
|             | N          | 6            | 6            | 6            | 6             | 6             | 5             | 4             | ---            |
| Liver       | MEAN       | 15.64        | 14.52        | 14.19        | 14.99         | 12.98         | 14.80         | 13.24         | ---            |
|             | S.D.       | 2.823        | 1.636        | 1.509        | 2.324         | 1.653         | 3.414         | 1.716         | ---            |
|             | % BODY WT  | 5.142        | 4.957        | 4.799        | 4.915         | 4.546         | 4.829         | 5.049         | ---            |
|             | S.D.       | 0.560        | 0.232        | 0.295        | 0.682         | 0.169         | 0.592         | 0.355         | ---            |
|             | % BRAIN WT | 822.82       | 779.08       | 772.59       | 813.82        | 727.14        | 814.61        | 753.15        | ---            |
|             | S.D.       | 139.3        | 69.1         | 86.5         | 161.5         | 89.7          | 179.3         | 114.4         | ---            |
|             | N          | 6            | 6            | 6            | 6             | 6             | 5             | 4             | ---            |

\* Indicates significance at the 0.05 level.

14-DAY TCM STUDY #75-51-0743-88(2)  
SUMMARY OF ORGAN WEIGHTS (GRAMS)  
FEMALE RATS

| ORGAN          | GROUP      | 1<br>Control | 2<br>25mg/kg | 3<br>50mg/kg | 4<br>100mg/kg | 5<br>200mg/kg | 6<br>400mg/kg | 7<br>800mg/kg | 8<br>1600mg/kg |
|----------------|------------|--------------|--------------|--------------|---------------|---------------|---------------|---------------|----------------|
| Body<br>Weight | MEAN       | 204          | 199          | 206          | 195           | 205           | 188           | 178           | 166            |
|                | S.D.       | 17.1         | 17.8         | 22.2         | 8.5           | 10.0          | 20.5          | 25.1          | ---            |
|                | N          | 6            | 6            | 6            | 6             | 6             | 5             | 5             | 1              |
| Brain          | MEAN       | 1.71         | 1.72         | 1.67         | 1.73          | 1.72          | 1.73          | 1.70          | 1.64           |
|                | S.D.       | 0.082        | 0.036        | 0.076        | 0.055         | 0.083         | 0.029         | 0.137         | ---            |
|                | % BODY WT  | 0.841        | 0.866        | 0.805        | 0.891         | 0.839         | 0.929         | 0.959         | 0.988          |
|                | S.D.       | 0.061        | 0.072        | 0.071        | 0.027         | 0.064         | 0.107         | 0.064         | ---            |
|                | N          | 6            | 6            | 6            | 6             | 6             | 5             | 5             | 1              |
| Adrenals       | MEAN       | 0.071        | 0.063        | 0.065        | 0.075         | 0.072         | 0.079         | 0.068         | 0.080          |
|                | S.D.       | 0.008        | 0.011        | 0.016        | 0.010         | 0.008         | 0.009         | 0.006         | ---            |
|                | % BODY WT  | 0.035        | 0.032        | 0.031        | 0.038         | 0.035         | 0.042         | 0.039         | 0.048          |
|                | S.D.       | 0.003        | 0.006        | 0.007        | 0.005         | 0.005         | 0.006         | 0.006         | ---            |
|                | % BRAIN WT | 4.14         | 3.69         | 3.91         | 4.31          | 4.20          | 4.53          | 4.04          | 4.88           |
|                | S.D.       | 0.4          | 0.7          | 1.0          | 0.7           | 0.6           | 0.4           | 0.4           | ---            |
| Kidneys        | MEAN       | 1.68         | 1.68         | 1.74         | 1.67          | 1.75          | 1.64          | 1.71          | 1.75           |
|                | S.D.       | 0.233        | 0.194        | 0.164        | 0.156         | 0.191         | 0.209         | 0.177         | ---            |
|                | % BODY WT  | 0.821        | 0.850        | 0.825        | 0.859         | 0.856         | 0.872         | 0.974         | 1.054          |
|                | S.D.       | 0.061        | 0.115        | 0.057        | 0.080         | 0.094         | 0.039         | 0.157         | ---            |
|                | % BRAIN WT | 98.07        | 98.12        | 103.56       | 96.46         | 102.10        | 94.87         | 101.09        | 106.71         |
|                | S.D.       | 10.9         | 10.6         | 6.8          | 8.6           | 9.8           | 11.5          | 10.6          | ---            |
| Ovaries        | MEAN       | 0.121        | 0.108        | 0.117        | 0.101         | 0.111         | 0.120         | 0.111         | 0.080          |
|                | S.D.       | 0.026        | 0.009        | 0.009        | 0.015         | 0.011         | 0.024         | 0.012         | ---            |
|                | % BODY WT  | 0.059        | 0.054        | 0.057        | 0.052         | 0.054         | 0.063         | 0.063         | 0.048          |
|                | S.D.       | 0.009        | 0.005        | 0.004        | 0.008         | 0.003         | 0.010         | 0.013         | ---            |
|                | % BRAIN WT | 7.01         | 6.27         | 7.00         | 5.87          | 6.45          | 6.89          | 6.57          | 4.88           |
|                | S.D.       | 1.2          | 0.4          | 0.5          | 1.0           | 0.7           | 1.3           | 0.9           | ---            |
| Liver          | MEAN       | 9.82         | 9.30         | 9.98         | 9.03          | 10.05         | 9.17          | 8.81          | 9.17           |
|                | S.D.       | 1.008        | 0.984        | 1.363        | 0.591         | 1.133         | 1.160         | 1.774         | ---            |
|                | % BODY WT  | 4.801        | 4.665        | 4.841        | 4.643         | 4.892         | 4.859         | 4.927         | 5.524          |
|                | S.D.       | 0.145        | 0.313        | 0.230        | 0.247         | 0.361         | 0.167         | 0.573         | ---            |
|                | % BRAIN WT | 573.66       | 541.50       | 596.11       | 521.67        | 587.19        | 592.02        | 517.17        | 559.15         |
|                | S.D.       | 51.2         | 55.1         | 73.4         | 35.6          | 75.8          | 64.6          | 82.5          | ---            |

\* Indicates significance at the 0.05 level.

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APPENDIX J

90-DAY FOOD CONSUMPTION OF  
MALE AND FEMALE RATS



90-DAY TCM STUDY #75-51-0743-88(2)  
SUMMARY OF FOOD CONSUMPTION (GRAMS)  
FEMALE RATS

| WEEK | GROUP | 1<br>Water | 2<br>Triton-X | 3<br>30mg/kg | 4<br>150mg/kg | 5<br>300mg/kg |
|------|-------|------------|---------------|--------------|---------------|---------------|
| 1    | MEAN  | 143        | 144           | 142          | 137           | 135           |
|      | S.D.  | 8.4        | 16.6          | 10.8         | 12.5          | 14.8          |
|      | N     | 10         | 10            | 10           | 10            | 9             |
| 2    | MEAN  | 149        | 149           | 153          | 148           | 145           |
|      | S.D.  | 11.6       | 18.5          | 10.9         | 17.5          | 17.0          |
|      | N     | 10         | 10            | 10           | 10            | 9             |
| 3    | MEAN  | 151        | 152           | 152          | 153           | 147           |
|      | S.D.  | 13.1       | 13.4          | 14.8         | 8.2           | 14.6          |
|      | N     | 10         | 10            | 10           | 10            | 8             |
| 4    | MEAN  | 158        | 154           | 154          | 153           | 155           |
|      | S.D.  | 13.4       | 16.9          | 14.2         | 9.1           | 18.5          |
|      | N     | 10         | 10            | 10           | 10            | 7             |
| 5    | MEAN  | 161        | 159           | 161          | 161           | 169           |
|      | S.D.  | 12.8       | 20.1          | 16.7         | 10.3          | 16.6          |
|      | N     | 10         | 10            | 10           | 10            | 7             |
| 6    | MEAN  | 160        | 159           | 163          | 163           | 164           |
|      | S.D.  | 16.9       | 17.3          | 20.7         | 17.7          | 30.4          |
|      | N     | 10         | 10            | 10           | 10            | 7             |
| 7    | MEAN  | 161        | 158           | 164          | 158           | 142           |
|      | S.D.  | 12.8       | 19.8          | 24.0         | 27.8          | 22.8          |
|      | N     | 10         | 10            | 10           | 10            | 7             |
| 8    | MEAN  | 170        | 161           | 172          | 160           | 137*          |
|      | S.D.  | 13.4       | 16.3          | 23.1         | 25.9          | 37.9          |
|      | N     | 10         | 10            | 10           | 9             | 7             |
| 9    | MEAN  | 160        | 158           | 155          | 163           | 149           |
|      | S.D.  | 13.0       | 20.1          | 14.8         | 19.2          | 25.6          |
|      | N     | 10         | 10            | 10           | 7             | 10            |
| 10   | MEAN  | 165        | 162           | 164          | 160           | 153           |
|      | S.D.  | 18.6       | 20.4          | 24.6         | 19.6          | 21.4          |
|      | N     | 10         | 10            | 10           | 7             | 7             |
| 11   | MEAN  | 167        | 164           | 164          | 159           | 148           |
|      | S.D.  | 11.3       | 19.0          | 31.2         | 17.2          | 37.7          |
|      | N     | 10         | 10            | 10           | 7             | 7             |
| 12   | MEAN  | 150        | 151           | 148          | 149           | 131           |
|      | S.D.  | 11.3       | 15.6          | 27.9         | 14.7          | 33.8          |
|      | N     | 10         | 10            | 10           | 7             | 7             |
| 13   | MEAN  | 155        | 144           | 147          | 145           | 134           |
|      | S.D.  | 15.7       | 15.1          | 25.4         | 19.0          | 21.2          |
|      | N     | 8          | 10            | 10           | 7             | 6             |

\* Indicates significance at the 0.05 level.

90-DAY TCM STUDY #75-51-0743-88 (2)  
SUMMARY OF FOOD CONSUMPTION (GRAMS)  
MALE RATS

| WEEK | GROUP | 1<br>Water | 2<br>Triton-X | 3<br>30mg/kg | 4<br>150mg/kg | 5<br>300mg/kg |
|------|-------|------------|---------------|--------------|---------------|---------------|
| 1    | MEAN  | 187        | 184           | 163          | 199           | 183           |
|      | S.D.  | 26.0       | 12.7          | 45.7         | 42.0          | 13.5          |
|      | N     | 10         | 10            | 10           | 10            | 10            |
| 2    | MEAN  | 206        | 209           | 199          | 202           | 198           |
|      | S.D.  | 26.5       | 27.1          | 16.4         | 22.8          | 15.1          |
|      | N     | 10         | 10            | 10           | 10            | 10            |
| 3    | MEAN  | 209        | 212           | 203          | 207           | 214           |
|      | S.D.  | 25.8       | 16.7          | 25.5         | 32.5          | 18.9          |
|      | N     | 10         | 10            | 10           | 10            | 9             |
| 4    | MEAN  | 222        | 226           | 214          | 225           | 224           |
|      | S.D.  | 29.3       | 20.0          | 24.3         | 26.4          | 29.2          |
|      | N     | 10         | 10            | 10           | 10            | 9             |
| 5    | MEAN  | 222        | 223           | 213          | 226           | 221           |
|      | S.D.  | 33.7       | 20.9          | 26.0         | 31.7          | 31.4          |
|      | N     | 10         | 10            | 10           | 10            | 8             |
| 6    | MEAN  | 227        | 235           | 222          | 235           | 212           |
|      | S.D.  | 36.6       | 20.2          | 23.7         | 42.2          | 47.3          |
|      | N     | 10         | 10            | 10           | 10            | 8             |
| 7    | MEAN  | 228        | 237           | 221          | 240           | 214           |
|      | S.D.  | 36.5       | 21.8          | 25.6         | 39.3          | 45.1          |
|      | N     | 10         | 10            | 10           | 10            | 7             |
| 8    | MEAN  | 236        | 243           | 227          | 241           | 238           |
|      | S.D.  | 33.4       | 21.9          | 27.1         | 30.0          | 18.8          |
|      | N     | 10         | 10            | 10           | 10            | 7             |
| 9    | MEAN  | 229        | 241           | 191          | 229           | 221           |
|      | S.D.  | 36.1       | 25.2          | 47.7         | 29.0          | 49.1          |
|      | N     | 10         | 10            | 10           | 10            | 7             |
| 10   | MEAN  | 227        | 216           | 216          | 231           | 230           |
|      | S.D.  | 39.6       | 31.0          | 31.0         | 30.5          | 38.2          |
|      | N     | 10         | 10            | 10           | 10            | 6             |
| 11   | MEAN  | 229        | 231           | 220          | 231           | 209           |
|      | S.D.  | 37.5       | 20.0          | 31.2         | 30.5          | 40.9          |
|      | N     | 10         | 10            | 10           | 10            | 6             |
| 12   | MEAN  | 226        | 226           | 213          | 221           | 204           |
|      | S.D.  | 40.6       | 18.1          | 29.4         | 36.9          | 24.7          |
|      | N     | 10         | 10            | 10           | 10            | 10            |
| 13   | MEAN  | 214        | 220           | 200          | 204           | 201           |
|      | S.D.  | 39.8       | 21.4          | 24.9         | 51.6          | 19.5          |
|      | N     | 10         | 10            | 10           | 10            | 6             |

\* Indicates significance at the 0.05 level.

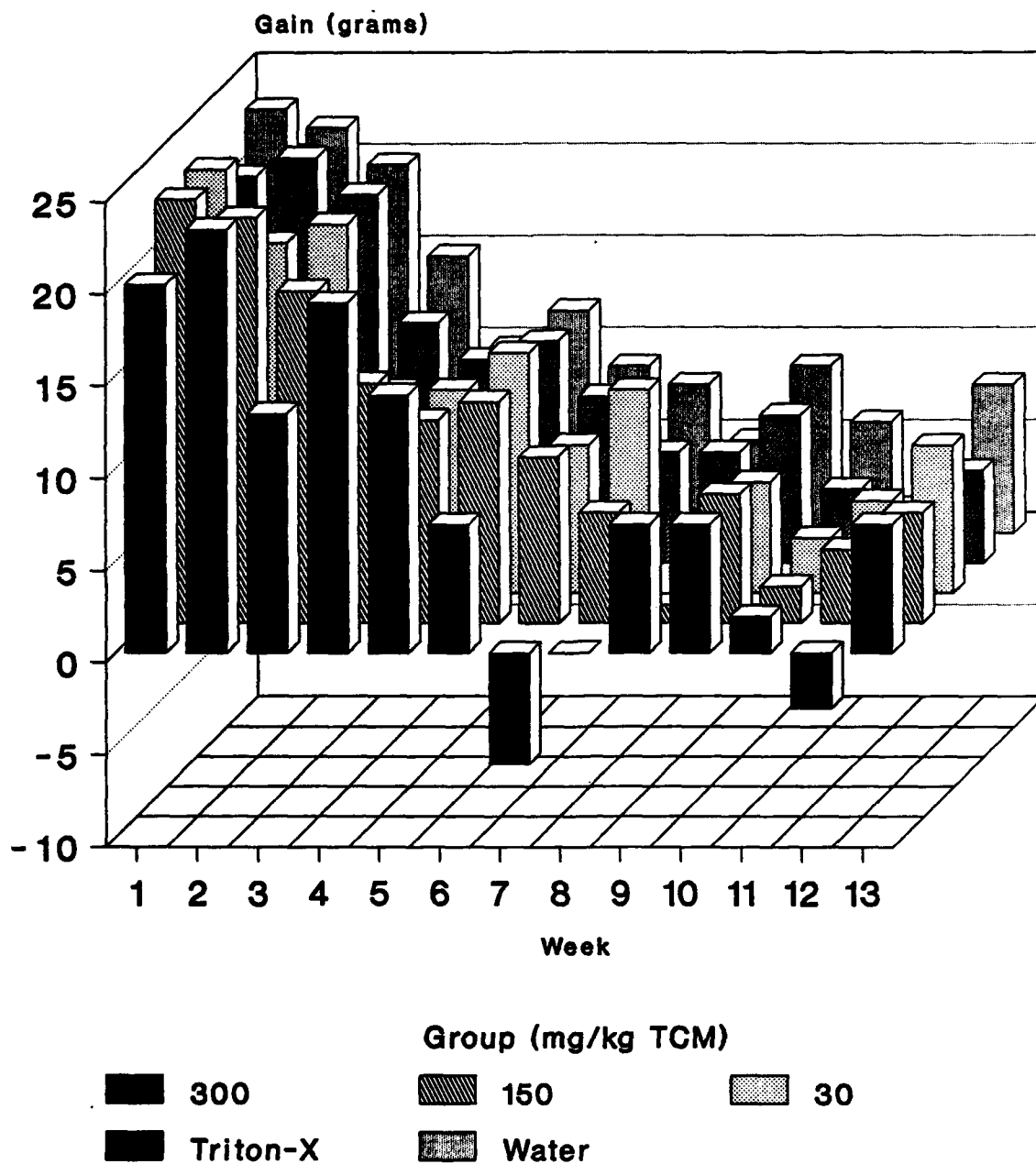
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APPENDIX K

90-DAY WEIGHT GAINS/LOSS FOR  
MALE AND FEMALE RATS

# 90-DAY TCM STUDY #75-51-0743-88

## WEIGHT GAINS - FEMALE RATS



90-DAY TCM STUDY #75-51-0743-88(2)  
SUMMARY OF BODY WEIGHT GAINS (GRAMS)  
FEMALE RATS

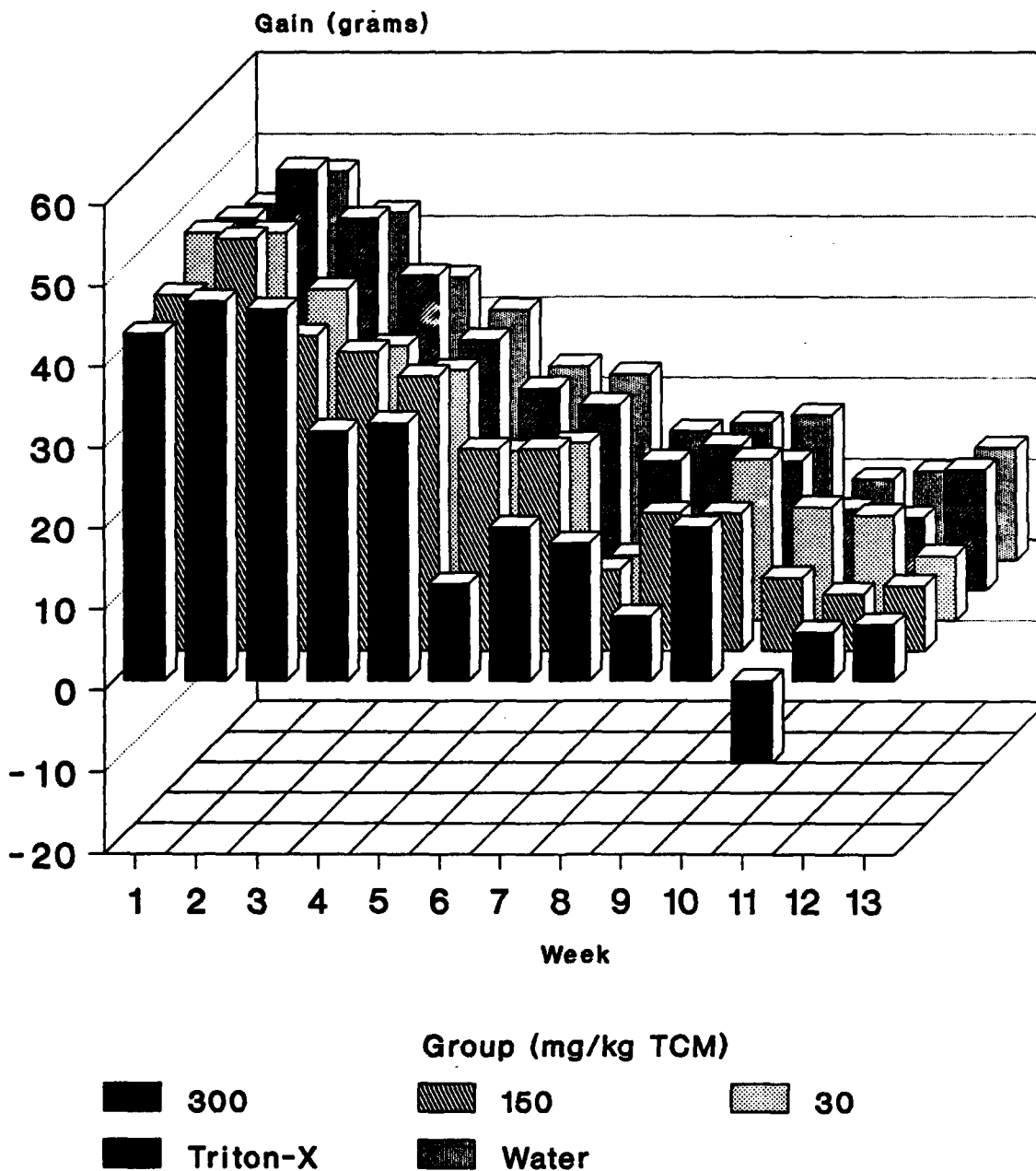
| WEEK       | GROUP | 1<br>Water | 2<br>Triton-X | 3<br>30mg/kg | 4<br>150mg/kg | 5<br>300mg/kg |
|------------|-------|------------|---------------|--------------|---------------|---------------|
| 1          | MEAN  | 23         | 21            | 23           | 23            | 20            |
|            | S.D.  | 6.5        | 5.2           | 5.0          | 4.6           | 8.2           |
|            | N     | 10         | 10            | 10           | 10            | 9             |
| 2          | MEAN  | 22         | 22            | 19           | 22            | 23            |
|            | S.D.  | 4.6        | 7.5           | 5.3          | 7.0           | 5.1           |
|            | N     | 10         | 10            | 10           | 10            | 9             |
| 3          | MEAN  | 20         | 20            | 20           | 18            | 13            |
|            | S.D.  | 5.6        | 5.0           | 8.4          | 5.1           | 10.8          |
|            | N     | 10         | 10            | 10           | 10            | 8             |
| 4          | MEAN  | 15         | 13            | 11           | 13            | 19            |
|            | S.D.  | 4.4        | 4.7           | 5.7          | 5.0           | 7.4           |
|            | N     | 10         | 10            | 10           | 10            | 7             |
| 5          | MEAN  | 10         | 11            | 11           | 11            | 14            |
|            | S.D.  | 2.9        | 3.6           | 4.0          | 3.7           | 5.1           |
|            | N     | 10         | 10            | 10           | 10            | 7             |
| 6          | MEAN  | 12         | 12            | 13           | 12            | 7             |
|            | S.D.  | 6.8        | 5.8           | 4.0          | 6.6           | 10.1          |
|            | N     | 10         | 10            | 10           | 10            | 7             |
| 7          | MEAN  | 9          | 9             | 8            | 6             | -6*           |
|            | S.D.  | 3.1        | 5.5           | 7.5          | 11.9          | 14.6          |
|            | N     | 10         | 10            | 10           | 10            | 7             |
| 8          | MEAN  | 8          | 6             | 11           | 1             | 0             |
|            | S.D.  | 6.2        | 4.0           | 3.6          | 16.8          | 17.8          |
|            | N     | 10         | 10            | 10           | 9             | 7             |
| 9          | MEAN  | 5          | 6             | 3            | 6             | 7             |
|            | S.D.  | 7.4        | 5.3           | 5.6          | 8.7           | 9.4           |
|            | N     | 10         | 10            | 10           | 7             | 10            |
| 10         | MEAN  | 9          | 8             | 6            | 7             | 7             |
|            | S.D.  | 3.8        | 5.2           | 5.4          | 3.2           | 4.5           |
|            | N     | 10         | 10            | 10           | 7             | 7             |
| 11         | MEAN  | 6          | 4             | 3            | 2             | 2             |
|            | S.D.  | 2.7        | 4.9           | 13.7         | 6.3           | 14.5          |
|            | N     | 10         | 10            | 10           | 7             | 7             |
| 12         | MEAN  | 2          | 3             | 5            | 4             | -3            |
|            | S.D.  | 3.7        | 3.4           | 8.6          | 7.0           | 12.2          |
|            | N     | 10         | 10            | 10           | 7             | 7             |
| 13         | MEAN  | 8          | 5             | 8            | 6             | 7             |
|            | S.D.  | 6.8        | 3.1           | 3.5          | 7.1           | 5.4           |
|            | N     | 8          | 10            | 10           | 7             | 6             |
| TOTAL GAIN | MEAN  | 150        | 140           | 141          | 143           | 127           |
|            | S.D.  | 18.9       | 24.2          | 30.1         | 29.1          | 14.5          |
|            | N     | 8          | 10            | 10           | 7             | 6             |

\* Indicates significance at the 0.05 level.

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# 90-DAY TCM STUDY #75-51-0743-88

## WEIGHT GAINS - MALE RATS



90-DAY TCM STUDY #75-51-0743-88(2)  
SUMMARY OF BODY WEIGHT GAINS (GRAMS)  
MALE RATS

| WEEK       | GROUP | 1<br>Water | 2<br>Triton-X | 3<br>30mg/kg | 4<br>150mg/kg | 5<br>300mg/kg |
|------------|-------|------------|---------------|--------------|---------------|---------------|
| 1          | MEAN  | 44         | 46            | 48           | 44            | 43            |
|            | S.D.  | 8.5        | 8.7           | 5.6          | 6.8           | 9.5           |
|            | N     | 10         | 10            | 10           | 10            | 9             |
| 2          | MEAN  | 48         | 52            | 48           | 51            | 47            |
|            | S.D.  | 9.5        | 10.0          | 10.3         | 8.5           | 6.7           |
|            | N     | 10         | 10            | 10           | 10            | 9             |
| 3          | MEAN  | 43         | 46            | 41           | 39            | 46            |
|            | S.D.  | 9.4        | 9.0           | 13.5         | 15.0          | 10.6          |
|            | N     | 10         | 10            | 10           | 10            | 8             |
| 4          | MEAN  | 35         | 39            | 34           | 37            | 31            |
|            | S.D.  | 8.3        | 8.7           | 9.2          | 6.3           | 14.4          |
|            | N     | 10         | 10            | 10           | 10            | 7             |
| 5          | MEAN  | 31         | 31            | 31           | 34            | 32            |
|            | S.D.  | 6.3        | 6.2           | 5.2          | 7.4           | 9.2           |
|            | N     | 10         | 10            | 10           | 10            | 7             |
| 6          | MEAN  | 24         | 25            | 21           | 25            | 12            |
|            | S.D.  | 7.3        | 6.5           | 4.6          | 12.7          | 22.1          |
|            | N     | 10         | 10            | 10           | 10            | 7             |
| 7          | MEAN  | 23         | 23            | 22           | 25            | 19            |
|            | S.D.  | 5.6        | 5.1           | 8.7          | 7.8           | 28.5          |
|            | N     | 10         | 10            | 10           | 10            | 7             |
| 8          | MEAN  | 16         | 16            | 8            | 10            | 17            |
|            | S.D.  | 8.0        | 5.4           | 11.9         | 9.8           | 8.7           |
|            | N     | 10         | 10            | 10           | 9             | 7             |
| 9          | MEAN  | 17         | 18            | 7            | 17            | 8             |
|            | S.D.  | 5.4        | 4.3           | 21.2         | 11.1          | 24.4          |
|            | N     | 10         | 10            | 10           | 7             | 10            |
| 10         | MEAN  | 18         | 16            | 20           | 17            | 19            |
|            | S.D.  | 3.7        | 4.5           | 13.3         | 5.7           | 7.2           |
|            | N     | 10         | 10            | 10           | 7             | 7             |
| 11         | MEAN  | 10         | 10            | 14           | 9             | -10*          |
|            | S.D.  | 5.3        | 4.3           | 8.5          | 10.9          | 14.5          |
|            | N     | 10         | 10            | 10           | 7             | 7             |
| 12         | MEAN  | 11         | 9             | 13           | 7             | 6             |
|            | S.D.  | 4.7        | 4.1           | 5.8          | 8.8           | 10.6          |
|            | N     | 10         | 10            | 10           | 7             | 7             |
| 13         | MEAN  | 14         | 15            | 8            | 8             | 7             |
|            | S.D.  | 7.6        | 6.1           | 10.0         | 20.4          | 23.2          |
|            | N     | 8          | 10            | 10           | 7             | 6             |
| TOTAL GAIN | MEAN  | 332        | 346           | 315          | 332           | 284           |
|            | S.D.  | 61.7       | 54.0          | 56.6         | 52.9          | 47.2          |
|            | N     | 8          | 10            | 10           | 7             | 6             |

\* Indicates significance at the 0.05 level.

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APPENDIX L

90-DAY CLINICAL CHEMISTRY VALUES  
FOR MALE AND FEMALE RATS



90-DAY TCM STUDY #75-51-0743-88(2)  
CLINICAL CHEMISTRY SUMMARY  
FEMALE RATS

| TEST                | GROUP | 1<br>Water | 2<br>Triton-X | 3<br>30mg/kg | 4<br>150mg/kg | 5<br>300mg/kg |
|---------------------|-------|------------|---------------|--------------|---------------|---------------|
| ALK. PHOS.<br>IU/L  | MEAN  | 196.0      | 173.9         | 173.8        | 277.8         | 198.6         |
|                     | S.D.  | 56.7       | 57.2          | 64.0         | 115.4         | 80.8          |
|                     | N     | 10         | 10            | 10           | 7             | 6             |
| SGOT<br>IU/L        | MEAN  | 68.1       | 89.8          | 90.8         | 87.8          | 84.6          |
|                     | S.D.  | 8.9        | 25.9          | 24.3         | 21.5          | 19.4          |
|                     | N     | 10         | 10            | 10           | 7             | 6             |
| SGPT<br>IU/L        | MEAN  | 36.7       | 50.6          | 46.0         | 50.4          | 41.9          |
|                     | S.D.  | 5.4        | 22.1          | 14.1         | 10.7          | 14.7          |
|                     | N     | 10         | 10            | 10           | 7             | 6             |
| GLUCOSE<br>IU/L     | MEAN  | 146.2      | 134.4         | 139.4        | 127.9         | 131.0         |
|                     | S.D.  | 32.1       | 15.9          | 36.3         | 13.6          | 19.4          |
|                     | N     | 10         | 10            | 10           | 7             | 6             |
| TOT. BILI.<br>MG/DL | MEAN  | 1.1        | 1.1           | 1.0          | 0.9           | 0.9           |
|                     | S.D.  | 0.6        | 0.4           | 0.3          | 0.2           | 0.4           |
|                     | N     | 10         | 10            | 10           | 7             | 6             |
| BUN<br>MG/DL        | MEAN  | 21.4       | 22.3          | 24.1         | 21.4          | 21.2          |
|                     | S.D.  | 3.5        | 2.0           | 5.0          | 2.4           | 3.7           |
|                     | N     | 10         | 10            | 10           | 7             | 6             |
| TOT. PROT.<br>G/DL  | MEAN  | 8.8        | 8.8           | 8.7          | 8.4           | 8.2           |
|                     | S.D.  | 0.6        | 0.6           | 0.7          | 0.6           | 0.7           |
|                     | N     | 10         | 10            | 10           | 7             | 6             |
| CALCIUM<br>MG/DL    | MEAN  | 12.0       | 11.5          | 11.5         | 10.9*         | 11.2*         |
|                     | S.D.  | 0.7        | 0.4           | 0.8          | 0.5           | 0.5           |
|                     | N     | 10         | 10            | 10           | 7             | 6             |

\* Indicates significance at the 0.05 level.

ALK. PHOS. - Alkaline Phosphatase  
SGOT - Serum Glutamic Oxaloacetic Transaminase  
SGPT - Serum Glutamic Pyruvic Transaminase  
TOT. BILI. - Total Bilirubin  
BUN - Blood Urea Nitrogen  
TOT. PROT. - Total Protein

90-DAY TCM STUDY #75-51-0743-88 (2)  
CLINICAL CHEMISTRY SUMMARY  
MALE RATS

| TEST                | GROUP | 1<br>Water | 2<br>Triton-X | 3<br>30mg/kg | 4<br>150mg/kg | 5<br>300mg/kg |
|---------------------|-------|------------|---------------|--------------|---------------|---------------|
| ALK. PHOS.<br>IU/L  | MEAN  | 254.8      | 284.2         | 258.9        | 245.9         | 169.4         |
|                     | S.D.  | 72.4       | 86.1          | 107.3        | 75.4          | 34.4          |
|                     | N     | 10         | 10            | 9            | 10            | 6             |
| SGOT<br>IU/L        | MEAN  | 94.2       | 86.1          | 90.7         | 89.7          | 77.6          |
|                     | S.D.  | 18.2       | 19.7          | 16.9         | 33.3          | 13.1          |
|                     | N     | 10         | 10            | 9            | 10            | 6             |
| SGPT<br>IU/L        | MEAN  | 42.9       | 47.9          | 47.9         | 48.5          | 47.5          |
|                     | S.D.  | 7.4        | 10.2          | 10.3         | 6.5           | 8.8           |
|                     | N     | 10         | 10            | 9            | 10            | 6             |
| GLUCOSE<br>IU/L     | MEAN  | 119.1      | 131.4         | 130.9        | 150.3*        | 117.4         |
|                     | S.D.  | 17.1       | 16.8          | 20.8         | 38.2          | 5.5           |
|                     | N     | 10         | 10            | 9            | 10            | 6             |
| TOT. BILI.<br>MG/DL | MEAN  | 0.8        | 0.7           | 0.8          | 0.6           | 0.6           |
|                     | S.D.  | 0.4        | 0.1           | 0.2          | 0.1           | 0.2           |
|                     | N     | 7          | 6             | 4            | 5             | 4             |
| BUN<br>MG/DL        | MEAN  | 24.3       | 25.1          | 24.0         | 23.3          | 23.5          |
|                     | S.D.  | 5.0        | 2.9           | 3.6          | 2.3           | 3.4           |
|                     | N     | 10         | 10            | 9            | 10            | 6             |
| TOT. PROT.<br>G/DL  | MEAN  | 8.6        | 8.6           | 8.5          | 8.1           | 7.7*          |
|                     | S.D.  | 0.5        | 0.5           | 0.6          | 0.5           | 0.7           |
|                     | N     | 10         | 10            | 9            | 10            | 6             |
| CALCIUM<br>MG/DL    | MEAN  | 10.6       | 10.8          | 10.9         | 10.7          | 10.3          |
|                     | S.D.  | 0.6        | 0.7           | 0.5          | 0.8           | 0.5           |
|                     | N     | 10         | 10            | 9            | 10            | 6             |

\* Indicates significance at the 0.05 level.

ALK. PHOS. - Alkaline Phosphatase  
SGOT - Serum Glutamic Oxaloacetic Transaminase  
SGPT - Serum Glutamic Pyruvic Transaminase  
TOT. BILI. - Total Bilirubin  
BUN - Blood Urea Nitrogen  
TOT. PROT. - Total Protein

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APPENDIX M

HEMATOLOGY VALUES FOR  
MALE AND FEMALE RATS

# ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - HEMOGLOBIN (g/dL)

| ANIMAL #    | GROUPS                                       |     |     |     |         |        |        |        |       |       | GRAND TOTALS | SUM OF SQUARES |         |
|-------------|----------------------------------------------|-----|-----|-----|---------|--------|--------|--------|-------|-------|--------------|----------------|---------|
|             | *DATA*                                       |     |     |     |         |        |        |        |       |       |              |                |         |
|             | * control veh cont 30mg/kg 150mg/kg 300mg/kg |     |     |     |         |        |        |        |       |       |              |                |         |
|             | 1                                            | 2   | 3   | 4   | 5       | 6      | 7      | 8      | 9     | 10    |              |                |         |
| 487         | 474                                          | 475 | 480 | 478 | * 14.9  | 15.2   | 14.7   | 15.7   | 15.0  |       | 1140.63      |                |         |
| 495         | 482                                          | 476 | 481 | 479 | * 14.7  | 15.5   | 15.2   | 15.5   | 15.4  |       | 1164.79      |                |         |
| 503         | 489                                          | 477 | 483 | 484 | * 15.3  | 15.3   | 16.0   | 14.9   | 14.0  |       | 1142.19      |                |         |
| 504         | 492                                          | 486 | 485 | 490 | * 16.2  | 15.1   | 15.8   | 15.3   | 14.4  |       | 1181.54      |                |         |
| 509         | 494                                          | 491 | 493 | 519 | * 15.7  | 14.5   | 16.3   | 14.2   | 15.1  |       | 1152.08      |                |         |
| 510         | 498                                          | 500 | 499 | 525 | * 14.5  | 15.4   | 14.9   | 16.1   | 15.9  |       | 1181.44      |                |         |
| 522         | 501                                          | 502 | 507 |     | * 15.1  | 15.1   | 15.3   | 15.3   |       |       | 924.20       |                |         |
| 524         | 511                                          | 516 |     |     | * 15.2  | 15.2   | 15.5   |        |       |       | 702.33       |                |         |
| 526         | 512                                          | 517 |     |     | * 15.0  | 15.7   | 14.8   |        |       |       | 690.53       |                |         |
| 527         | 513                                          | 521 |     |     | * 15.8  | 16.0   | 14.6   |        |       |       | 718.80       |                |         |
| -----       |                                              |     |     |     |         |        |        |        |       |       |              |                |         |
| Totals      |                                              |     |     |     | 152.40  | 153.00 | 153.10 | 107.00 | 89.80 | 0.00  | 0.00         | 655.30         | 9998.53 |
| -----       |                                              |     |     |     |         |        |        |        |       |       |              |                |         |
| Observation |                                              |     |     |     |         |        |        |        |       |       |              |                |         |
|             |                                              |     |     |     | 10.00   | 10.00  | 10.00  | 7.00   | 6.00  | 1.00  | 1.00         |                |         |
|             |                                              |     |     |     | Mean    | 15.24  | 15.30  | 15.31  | 15.29 | 14.97 | ERR          | ERR            |         |
|             |                                              |     |     |     | Std Dev | 0.59   | 0.32   | 0.59   | 0.61  | 0.62  | ERR          | ERR            |         |

# of Group 5

## ANALYSIS OF VARIANCE TABLE

| Source         | Sum of Squares | Deg. of Freedom | Mean Square | F Ratio |
|----------------|----------------|-----------------|-------------|---------|
| Between Groups | 0.55           | 4               | 0.14        | 0.45    |
| Within Groups  | 11.51          | 38              | 0.30        |         |
| Totals         | 12.06          | 42              |             |         |

F-table Lookup (num. 4, denom. 38)  
F RATIO .05 = 2.62  
F RATIO .01 = 3.86

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

# ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - HEMOGLOBIN (g/dL)

| ANIMAL #     | GROUPS                                       |        |        |        |       |      |      |      |      |      | GRAND TOTALS | SUM OF SQUARES |
|--------------|----------------------------------------------|--------|--------|--------|-------|------|------|------|------|------|--------------|----------------|
|              | 1                                            | 2      | 3      | 4      | 5     | 6    | 7    | 8    | 9    | 10   |              |                |
|              | *DATA                                        |        |        |        |       |      |      |      |      |      |              |                |
|              | * control veh cont 30mg/kg 150mg/kg 300mg/kg |        |        |        |       |      |      |      |      |      |              |                |
| 379          | 387                                          | 381    | 382    | 383    |       |      |      |      |      |      |              | 1033.12        |
| 386          | 389                                          | 400    | 388    | 385    |       |      |      |      |      |      |              | 1123.14        |
| 396          | 395                                          | 404    | 391    | 399    |       |      |      |      |      |      |              | 1093.51        |
| 402          | 397                                          | 405    | 392    | 409    |       |      |      |      |      |      |              | 1189.51        |
| 403          | 401                                          | 413    | 398    | 414    |       |      |      |      |      |      |              | 1108.10        |
| 406          | 408                                          | 425    | 419    | 415    |       |      |      |      |      |      |              | 1226.97        |
| 407          | 411                                          | 427    | 421    |        |       |      |      |      |      |      |              | 1004.94        |
| 410          | 416                                          | 428    | 423    |        |       |      |      |      |      |      |              | 928.19         |
| 420          | 418                                          | 429    | 424    |        |       |      |      |      |      |      |              | 912.58         |
| 422          | 426                                          | 432    | 433    |        |       |      |      |      |      |      |              | 980.18         |
| Totals       | 153.60                                       | 152.60 | 152.30 | 152.60 | 86.50 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 697.60       | 10600.24       |
| Observation  | 10.00                                        | 10.00  | 10.00  | 10.00  | 6.00  | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 46.00        |                |
| Mean         | 15.36                                        | 15.26  | 15.23  | 15.26  | 14.42 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 15.17        |                |
| Std Dev      | 0.50                                         | 0.46   | 0.59   | 0.72   | 0.87  | ERR  | ERR  | ERR  | ERR  | ERR  |              |                |
| # of Group 5 |                                              |        |        |        |       |      |      |      |      |      |              |                |

## ANALYSIS OF VARIANCE TABLE

| Sum of         |         | Deg. of |        | Mean    |  |
|----------------|---------|---------|--------|---------|--|
| Source         | Squares | Freedom | Square | F Ratio |  |
| Between Groups | 3.96    | 4       | 0.99   | 2.39    |  |
| Within Groups  | 17.02   | 41      | 0.42   |         |  |
| Totals         | 20.98   | 45      |        |         |  |

F-table Lookup (num. 4, denom. 41)  
 F RATIO .05 = 2.60  
 F RATIO .01 = 3.82

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
 : AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

# ANALYSIS OF VARIANCE

90-DAY TOX STUDY NO. 75-51-0743-88(2) FEMALE RATS - HEMATOCRIT (%)

| ANIMAL # | GROUPS                                       |     |     |     |   |   |   |   |   |    | GRAND TOTALS | SUM OF SQUARES |
|----------|----------------------------------------------|-----|-----|-----|---|---|---|---|---|----|--------------|----------------|
|          | *DATA                                        |     |     |     |   |   |   |   |   |    |              |                |
|          | 1                                            | 2   | 3   | 4   | 5 | 6 | 7 | 8 | 9 | 10 |              |                |
|          | * control veh cont 30mg/kg 150mg/kg 300mg/kg |     |     |     |   |   |   |   |   |    |              |                |
| 487      | 474                                          | 475 | 480 | 478 |   |   |   |   |   |    | 8572.21      |                |
| 495      | 482                                          | 476 | 481 | 479 |   |   |   |   |   |    | 8941.72      |                |
| 503      | 489                                          | 477 | 483 | 484 |   |   |   |   |   |    | 8837.04      |                |
| 504      | 492                                          | 486 | 485 | 490 |   |   |   |   |   |    | 9286.39      |                |
| 509      | 494                                          | 491 | 493 | 519 |   |   |   |   |   |    | 8907.74      |                |
| 510      | 498                                          | 500 | 499 | 525 |   |   |   |   |   |    | 9795.07      |                |
| 522      | 501                                          | 502 | 507 |     |   |   |   |   |   |    | 7553.63      |                |
| 524      | 511                                          | 516 |     |     |   |   |   |   |   |    | 6006.34      |                |
| 526      | 512                                          | 517 |     |     |   |   |   |   |   |    | 6064.24      |                |
| 527      | 513                                          | 521 |     |     |   |   |   |   |   |    | 6366.13      |                |

2.4

## ANALYSIS OF VARIANCE TABLE

| Source         | Sum of Squares | Deg. of Freedom | Mean Square | F Ratio |
|----------------|----------------|-----------------|-------------|---------|
| Between Groups | 28.59          | 4               | 7.15        | 1.48    |
| Within Groups  | 183.15         | 38              | 4.82        |         |
| Totals         | 211.74         | 42              |             |         |

F-table Lookup (num. 4, denom. 38)  
F RATIO .05 = 2.62  
F RATIO .01 = 3.86

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

# ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - HEMATOCRIT (X)

| ANIMAL #     | GROUPS                                       |        |        |        |        |      |      |      |      |      | GRAND TOTALS | SUM OF SQUARES |
|--------------|----------------------------------------------|--------|--------|--------|--------|------|------|------|------|------|--------------|----------------|
|              | 1                                            | 2      | 3      | 4      | 5      | 6    | 7    | 8    | 9    | 10   |              |                |
|              | *DATA                                        |        |        |        |        |      |      |      |      |      |              |                |
|              | * control veh cont 30mg/kg 150mg/kg 300mg/kg |        |        |        |        |      |      |      |      |      |              |                |
| 379          | 387                                          | 381    | 382    | 383    |        |      |      |      |      |      |              | 9331.31        |
| 386          | 389                                          | 400    | 388    | 385    |        |      |      |      |      |      |              | 10070.14       |
| 396          | 395                                          | 404    | 391    | 399    |        |      |      |      |      |      |              | 9960.97        |
| 402          | 397                                          | 405    | 392    | 409    |        |      |      |      |      |      |              | 11251.59       |
| 403          | 401                                          | 413    | 398    | 414    |        |      |      |      |      |      |              | 10375.67       |
| 406          | 408                                          | 425    | 419    | 415    |        |      |      |      |      |      |              | 11314.74       |
| 407          | 411                                          | 427    | 421    |        |        |      |      |      |      |      |              | 9305.39        |
| 410          | 416                                          | 428    | 423    |        |        |      |      |      |      |      |              | 8715.86        |
| 420          | 418                                          | 429    | 424    |        |        |      |      |      |      |      |              | 8486.70        |
| 422          | 426                                          | 432    | 433    |        |        |      |      |      |      |      |              | 8834.73        |
| Totals       | 467.90                                       | 463.10 | 460.50 | 459.80 | 265.90 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 2117.20      | 97647.10       |
| Observation  | 10.00                                        | 10.00  | 10.00  | 10.00  | 6.00   | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 46.00        |                |
| Mean         | 46.79                                        | 46.31  | 46.05  | 45.98  | 44.32  | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 46.03        |                |
| Std Dev      | 1.81                                         | 1.47   | 1.63   | 2.26   | 2.92   | ERR  | ERR  | ERR  | ERR  | ERR  | ERR          |                |
| # of Group 5 |                                              |        |        |        |        |      |      |      |      |      |              |                |

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## ANALYSIS OF VARIANCE TABLE

| Source         | Sum of Squares | Deg. of Freedom | Mean Square | F Ratio |
|----------------|----------------|-----------------|-------------|---------|
| Between Groups | 24.20          | 4               | 6.05        | 1.41    |
| Within Groups  | 176.47         | 41              | 4.30        |         |
| Totals         | 200.67         | 45              |             |         |

F-table Lookup (num. 4, denom. 41)  
F RATIO .05 = 2.60  
F RATIO .01 = 3.82

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

# ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - RED BLOOD CELLS (10E+6/ $\mu$ L)

| ANIMAL #    | GROUPS                                       |     |     |     |   |   |   |   |   |    | GRAND TOTALS | SUM OF SQUARES |
|-------------|----------------------------------------------|-----|-----|-----|---|---|---|---|---|----|--------------|----------------|
|             | 1                                            | 2   | 3   | 4   | 5 | 6 | 7 | 8 | 9 | 10 |              |                |
|             | * DATA                                       |     |     |     |   |   |   |   |   |    |              |                |
|             | * control veh cont 30mg/kg 150mg/kg 300mg/kg |     |     |     |   |   |   |   |   |    |              |                |
| 487         | 474                                          | 475 | 480 | 478 |   |   |   |   |   |    |              | 287.67         |
| 495         | 482                                          | 476 | 481 | 479 |   |   |   |   |   |    |              | 298.14         |
| 503         | 489                                          | 477 | 483 | 484 |   |   |   |   |   |    |              | 299.95         |
| 504         | 492                                          | 486 | 485 | 490 |   |   |   |   |   |    |              | 304.94         |
| 509         | 494                                          | 491 | 493 | 519 |   |   |   |   |   |    |              | 288.67         |
| 510         | 498                                          | 500 | 499 | 525 |   |   |   |   |   |    |              | 326.11         |
| 522         | 501                                          | 502 | 507 |     |   |   |   |   |   |    |              | 245.07         |
| 524         | 511                                          | 516 |     |     |   |   |   |   |   |    |              | 196.97         |
| 526         | 512                                          | 517 |     |     |   |   |   |   |   |    |              | 202.22         |
| 527         | 513                                          | 521 |     |     |   |   |   |   |   |    |              | 202.14         |
| Totals      |                                              |     |     |     |   |   |   |   |   |    | 337.20       | 2651.88        |
| Observation |                                              |     |     |     |   |   |   |   |   |    | 1.00         | 43.00          |
| Mean        |                                              |     |     |     |   |   |   |   |   |    | 0.00         | 7.84           |
| Std Dev     |                                              |     |     |     |   |   |   |   |   |    | ERR          | ERR            |

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## ANALYSIS OF VARIANCE TABLE

| Source         | Sum of Squares | Deg. of Freedom | Mean Square | F Ratio |
|----------------|----------------|-----------------|-------------|---------|
| Between Groups | 0.62           | 4               | 0.16        | 0.85    |
| Within Groups  | 6.98           | 38              | 0.18        |         |
| Totals         | 7.60           | 42              |             |         |

F-table Lookup (num. 4, denom. 38)  
 F RATIO .05 = 2.62  
 F RATIO .01 = 3.86

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
 : AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.



# ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - RED BLOOD CELLS (10E+6/ $\mu$ L)

| ANIMAL #     | GROUPS                                       |       |       |       |       |      |      |      |      |      | GRAND TOTALS | SUM OF SQUARES |
|--------------|----------------------------------------------|-------|-------|-------|-------|------|------|------|------|------|--------------|----------------|
|              | 1                                            | 2     | 3     | 4     | 5     | 6    | 7    | 8    | 9    | 10   |              |                |
|              | *DATA                                        |       |       |       |       |      |      |      |      |      |              |                |
|              | * control veh cont 30mg/kg 150mg/kg 300mg/kg |       |       |       |       |      |      |      |      |      |              |                |
| 379          | 387                                          | 381   | 382   | 383   |       |      |      |      |      |      |              | 343.92         |
| 386          | 389                                          | 400   | 388   | 385   |       |      |      |      |      |      |              | 366.91         |
| 396          | 395                                          | 404   | 391   | 399   |       |      |      |      |      |      |              | 350.42         |
| 402          | 397                                          | 405   | 392   | 409   |       |      |      |      |      |      |              | 381.40         |
| 403          | 401                                          | 413   | 398   | 414   |       |      |      |      |      |      |              | 355.15         |
| 406          | 408                                          | 425   | 419   | 415   |       |      |      |      |      |      |              | 407.91         |
| 407          | 411                                          | 427   | 421   |       |       |      |      |      |      |      |              | 319.15         |
| 410          | 416                                          | 428   | 423   |       |       |      |      |      |      |      |              | 326.31         |
| 420          | 418                                          | 429   | 424   |       |       |      |      |      |      |      |              | 294.19         |
| 422          | 426                                          | 432   | 433   |       |       |      |      |      |      |      |              | 317.54         |
| Totals       | 88.60                                        | 87.80 | 87.90 | 85.60 | 48.50 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 398.40       | 3462.90        |
| Observation  | 10.00                                        | 10.00 | 10.00 | 10.00 | 6.00  | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 46.00        |                |
| Mean         | 8.86                                         | 8.78  | 8.79  | 8.56  | 8.08  | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 8.66         |                |
| Std Dev      | 0.42                                         | 0.46  | 0.53  | 0.63  | 0.42  | ERR  | ERR  | ERR  | ERR  | ERR  | ERR          |                |
| # of Group 5 |                                              |       |       |       |       |      |      |      |      |      |              |                |

## ANALYSIS OF VARIANCE TABLE

| Source         | Sum of Squares | Deg. of Freedom | Mean Square | F Ratio |
|----------------|----------------|-----------------|-------------|---------|
| Between Groups | 2.81           | 4               | 0.70        | 3.00    |
| Within Groups  | 9.60           | 41              | 0.23        |         |
| Totals         | 12.41          | 45              |             |         |

F-table Lookup (num. 4, denom. 41)  
 F RATIO .05 = 2.60  
 F RATIO .01 = 3.82

CONCLUSIONS: AVERAGES ARE SIGNIFICANTLY DIFFERENT AT .05 LEVEL. \*  
 ; AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

# ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - MEAN CELL VOLUME (FL)

| ANIMAL #    | GROUPS                                       |        |        |        |        |      |      |      |      |      | GRAND TOTALS | SUM OF SQUARES |
|-------------|----------------------------------------------|--------|--------|--------|--------|------|------|------|------|------|--------------|----------------|
|             | 1                                            | 2      | 3      | 4      | 5      | 6    | 7    | 8    | 9    | 10   |              |                |
|             | *DATA*                                       |        |        |        |        |      |      |      |      |      |              |                |
|             | * control veh cont 30mg/kg 150mg/kg 300mg/kg |        |        |        |        |      |      |      |      |      |              |                |
| 1           | 487                                          | 474    | 475    | 480    | 478    |      |      |      |      |      |              | 14919.00       |
| 2           | 495                                          | 482    | 476    | 481    | 479    |      |      |      |      |      |              | 15131.00       |
| 3           | 503                                          | 489    | 477    | 483    | 484    |      |      |      |      |      |              | 14691.00       |
| 4           | 504                                          | 492    | 486    | 485    | 490    |      |      |      |      |      |              | 15240.00       |
| 5           | 509                                          | 494    | 491    | 493    | 519    |      |      |      |      |      |              | 15458.00       |
| 6           | 510                                          | 498    | 500    | 499    | 525    |      |      |      |      |      |              | 15135.00       |
| 7           | 522                                          | 501    | 502    | 507    |        |      |      |      |      |      |              | 12326.00       |
| 8           | 524                                          | 511    | 516    |        |        |      |      |      |      |      |              | 9186.00        |
| 9           | 526                                          | 512    | 517    |        |        |      |      |      |      |      |              | 9077.00        |
| 10          | 527                                          | 513    | 521    |        |        |      |      |      |      |      |              | 9523.00        |
| Totals      | 555.00                                       | 550.00 | 551.00 | 390.00 | 324.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 2370.00      | 130686.00      |
| Observation | 10.00                                        | 10.00  | 10.00  | 7.00   | 6.00   | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 43.00        |                |
| Mean        | 55.50                                        | 55.00  | 55.10  | 55.71  | 54.00  | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 55.12        |                |
| Std Dev     | 0.94                                         | 1.15   | 0.90   | 1.12   | 1.29   | ERR  | ERR  | ERR  | ERR  | ERR  | ERR          |                |
| # of Group  | 5                                            | 5      |        |        |        |      |      |      |      |      |              |                |

## ANALYSIS OF VARIANCE TABLE

| Source         | Squares | Deg. of Freedom | Mean Square | F Ratio |
|----------------|---------|-----------------|-------------|---------|
| Between Groups | 11.59   | 4               | 2.90        | 2.25    |
| Within Groups  | 48.83   | 38              | 1.28        |         |
| Totals         | 60.42   | 42              |             |         |

F-table Lookup (num. 4, denom. 38)  
F RATIO .05 = 2.62  
F RATIO .01 = 3.86

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

# ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - MEAN CELL VOLUME (IL)

| ANIMAL # | GROUPS |     |     |     |   |   |   |   |   |    | *DATA | GROUPS    |     |      |         |          | GRAND TOTALS | SUM OF SQUARES |          |
|----------|--------|-----|-----|-----|---|---|---|---|---|----|-------|-----------|-----|------|---------|----------|--------------|----------------|----------|
|          | 1      | 2   | 3   | 4   | 5 | 6 | 7 | 8 | 9 | 10 |       | * control | veh | cont | 30mg/kg | 150mg/kg |              |                | 300mg/kg |
|          |        |     |     |     |   |   |   |   |   |    |       |           |     |      |         |          |              |                |          |
| 379      | 387    | 381 | 382 | 383 |   |   |   |   |   |    | *     | 51        | 52  | 49   | 55      | 54       | 13647.00     |                |          |
| 386      | 389    | 400 | 388 | 385 |   |   |   |   |   |    | *     | 51        | 52  | 51   | 54      | 55       | 13847.00     |                |          |
| 396      | 395    | 404 | 391 | 399 |   |   |   |   |   |    | *     | 54        | 53  | 51   | 55      | 54       | 14267.00     |                |          |
| 402      | 397    | 405 | 392 | 409 |   |   |   |   |   |    | *     | 54        | 54  | 57   | 55      | 57       | 15355.00     |                |          |
| 403      | 401    | 413 | 398 | 414 |   |   |   |   |   |    | *     | 57        | 56  | 54   | 52      | 52       | 14709.00     |                |          |
| 406      | 408    | 425 | 419 | 415 |   |   |   |   |   |    | *     | 54        | 51  | 51   | 51      | 57       | 13968.00     |                |          |
| 407      | 411    | 427 | 421 |     |   |   |   |   |   |    | *     | 54        | 53  | 52   | 57      |          | 11678.00     |                |          |
| 410      | 416    | 428 | 423 |     |   |   |   |   |   |    | *     | 51        | 55  | 48   | 53      |          | 10739.00     |                |          |
| 420      | 418    | 429 | 424 |     |   |   |   |   |   |    | *     | 52        | 53  | 54   | 55      |          | 11454.00     |                |          |
| 422      | 426    | 432 | 433 |     |   |   |   |   |   |    | *     | 51        | 52  | 56   | 53      |          | 11250.00     |                |          |

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## ANALYSIS OF VARIANCE TABLE

| Source         | Sum of Squares | Deg. of Freedom | Mean Square | F Ratio |
|----------------|----------------|-----------------|-------------|---------|
| Between Groups | 31.01          | 4               | 7.75        | 1.76    |
| Within Groups  | 180.73         | 41              | 4.41        |         |
| Totals         | 211.74         | 45              |             |         |

F-table Lookup (num. 4, denom. 41)  
F RATIO .05 = 2.60  
F RATIO .01 = 3.82

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

# ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) FEMALE RATS - WHITE BLOOD CELLS (10E+3/ $\mu$ L)

| ANIMAL #     | GROUPS                                       |       |       |       |       |      |      |      |      |      | GRAND TOTALS | SUM OF SQUARES |
|--------------|----------------------------------------------|-------|-------|-------|-------|------|------|------|------|------|--------------|----------------|
|              | 1                                            | 2     | 3     | 4     | 5     | 6    | 7    | 8    | 9    | 10   |              |                |
|              | *DATA*                                       |       |       |       |       |      |      |      |      |      |              |                |
|              | * control veh cont 30mg/kg 150mg/kg 300mg/kg |       |       |       |       |      |      |      |      |      |              |                |
| 487          | 474                                          | 475   | 480   | 478   |       |      |      |      |      |      |              | 271.96         |
| 495          | 482                                          | 476   | 481   | 479   |       |      |      |      |      |      |              | 272.77         |
| 503          | 489                                          | 477   | 483   | 484   |       |      |      |      |      |      |              | 295.42         |
| 504          | 492                                          | 486   | 485   | 490   |       |      |      |      |      |      |              | 484.00         |
| 509          | 494                                          | 491   | 493   | 519   |       |      |      |      |      |      |              | 456.63         |
| 510          | 498                                          | 500   | 499   | 525   |       |      |      |      |      |      |              | 665.40         |
| 522          | 501                                          | 502   | 507   |       |       |      |      |      |      |      |              | 238.70         |
| 524          | 511                                          | 516   |       |       |       |      |      |      |      |      |              | 468.26         |
| 526          | 512                                          | 517   |       |       |       |      |      |      |      |      |              | 176.40         |
| 527          | 513                                          | 521   |       |       |       |      |      |      |      |      |              | 343.61         |
| Totals       | 97.90                                        | 80.00 | 83.40 | 60.90 | 53.50 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 375.70       | 3673.15        |
| Observation  | 10.00                                        | 10.00 | 10.00 | 7.00  | 6.00  | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 43.00        |                |
| Mean         | 9.79                                         | 8.00  | 8.34  | 8.70  | 8.92  | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 8.74         |                |
| Std Dev      | 1.57                                         | 2.84  | 1.64  | 1.66  | 5.07  | ERR  | ERR  | ERR  | ERR  | ERR  | ERR          |                |
| # of Group 5 |                                              |       |       |       |       |      |      |      |      |      |              |                |

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## ANALYSIS OF VARIANCE TABLE

| Source         | Sum of Squares | Deg. of Freedom | Mean Square | F Ratio |
|----------------|----------------|-----------------|-------------|---------|
| Between Groups | 18.30          | 4               | 4.57        | 0.47    |
| Within Groups  | 372.28         | 38              | 9.80        |         |
| Totals         | 390.58         | 42              |             |         |

F-table Lookup (num. 4, denom. 38)  
F RATIO .05 = 2.62  
F RATIO .01 = 3.86

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

# ANALYSIS OF VARIANCE

90-DAY TCM STUDY NO. 75-51-0743-88(2) MALE RATS - WHITE BLOOD CELLS (10E+3/ $\mu$ L)

| ANIMAL #     | GROUPS                                       |        |        |        |       |      |      |      |      |      | GRAND TOTALS | SUM OF SQUARES |
|--------------|----------------------------------------------|--------|--------|--------|-------|------|------|------|------|------|--------------|----------------|
|              | 1                                            | 2      | 3      | 4      | 5     | 6    | 7    | 8    | 9    | 10   |              |                |
|              | *DATA                                        |        |        |        |       |      |      |      |      |      |              |                |
|              | * control veh cont 30mg/kg 150mg/kg 300mg/kg |        |        |        |       |      |      |      |      |      |              |                |
| 379          | 387                                          | 381    | 382    | 383    |       |      |      |      |      |      |              | 795.70         |
| 386          | 389                                          | 400    | 388    | 385    |       |      |      |      |      |      |              | 931.67         |
| 396          | 395                                          | 404    | 391    | 399    |       |      |      |      |      |      |              | 944.61         |
| 402          | 397                                          | 405    | 392    | 409    |       |      |      |      |      |      |              | 1382.07        |
| 403          | 401                                          | 413    | 398    | 414    |       |      |      |      |      |      |              | 938.84         |
| 406          | 408                                          | 425    | 419    | 415    |       |      |      |      |      |      |              | 926.38         |
| 407          | 411                                          | 427    | 421    |        |       |      |      |      |      |      |              | 1446.22        |
| 410          | 416                                          | 428    | 423    |        |       |      |      |      |      |      |              | 588.33         |
| 420          | 418                                          | 429    | 424    |        |       |      |      |      |      |      |              | 653.67         |
| 422          | 426                                          | 432    | 433    |        |       |      |      |      |      |      |              | 654.98         |
| Totals       | 130.70                                       | 149.70 | 123.20 | 148.10 | 75.40 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 627.10       | 9262.47        |
| Observation  | 10.00                                        | 10.00  | 10.00  | 10.00  | 6.00  | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 46.00        |                |
| Mean         | 13.07                                        | 14.97  | 12.32  | 14.81  | 12.57 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 13.63        |                |
| Std Dev      | 2.21                                         | 4.55   | 2.06   | 2.90   | 4.29  | ERR  | ERR  | ERR  | ERR  | ERR  | ERR          |                |
| # of Group 5 |                                              |        |        |        |       |      |      |      |      |      |              |                |

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## ANALYSIS OF VARIANCE TABLE

| Source         | Sum of Squares | Deg. of Freedom | Mean Square | F Ratio |
|----------------|----------------|-----------------|-------------|---------|
| Between Groups | 58.96          | 4               | 14.74       | 0.92    |
| Within Groups  | 654.50         | 41              | 15.96       |         |
| Totals         | 713.46         | 45              |             |         |

F-table Lookup (num. 4, denom. 41)  
F RATIO .05 = 2.60  
F RATIO .01 = 3.82

CONCLUSIONS: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .05 LEVEL.  
: AVERAGES ARE NOT SIGNIFICANTLY DIFFERENT AT .01 LEVEL.

Phase 2, Toxicological Study No. 75-51-0743-88(2), 3 Aug 88 -  
17 Jan 89

APPENDIX N

90-DAY SUMMARY OF ORGAN WEIGHTS FOR  
MALE AND FEMALE RATS

90-DAY TCM STUDY #75-51-0743-88(2)  
SUMMARY OF ORGAN WEIGHTS (GRAMS)  
FEMALE RATS

| ORGAN       | GROUP                                                        | 1<br>Water                                                | 2<br>Triton-X                                             | 3<br>30mg/kg                                               | 4<br>150mg/kg                                            | 5<br>300mg/kg                                              |
|-------------|--------------------------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------|----------------------------------------------------------|------------------------------------------------------------|
| Body Weight | MEAN<br>S.D.<br>N                                            | 311<br>26.1<br>10                                         | 301<br>25.7<br>10                                         | 300<br>35.0<br>10                                          | 303<br>28.0<br>7                                         | 286<br>21.5<br>5                                           |
| Brain       | MEAN<br>S.D.<br>% BODY WT<br>S.D.<br>N                       | 1.91<br>0.087<br>0.62<br>0.044<br>10                      | 1.88<br>0.070<br>0.63<br>0.060<br>10                      | 1.81<br>0.354<br>0.60<br>0.115<br>10                       | 1.96<br>0.055<br>0.65<br>0.078<br>7                      | 1.90<br>0.043<br>0.67<br>0.054<br>5                        |
| Adrenals    | MEAN<br>S.D.<br>% BODY WT<br>S.D.<br>% BRAIN WT<br>S.D.<br>N | 0.080<br>0.015<br>0.026<br>0.005<br>4.208<br>0.845<br>10  | 0.078<br>0.018<br>0.026<br>0.006<br>4.145<br>0.877<br>10  | 0.079<br>0.018<br>0.026<br>0.005<br>4.696<br>2.167<br>10   | 0.084<br>0.009<br>0.028<br>0.002<br>4.266<br>0.539<br>7  | 0.085<br>0.027<br>0.029<br>0.008<br>4.479<br>1.545<br>5    |
| Kidneys     | MEAN<br>S.D.<br>% BODY WT<br>S.D.<br>% BRAIN WT<br>S.D.<br>N | 2.15<br>0.183<br>0.69<br>0.055<br>112.08<br>7.543<br>10   | 2.22<br>0.274<br>0.74<br>0.099<br>117.83<br>11.965<br>10  | 2.23<br>0.388<br>0.74<br>0.079<br>130.08<br>45.717<br>10   | 2.26<br>0.120<br>0.75<br>0.052<br>115.07<br>8.095<br>7   | 2.19<br>0.212<br>0.77<br>0.085<br>115.24<br>9.237<br>5     |
| Ovaries     | MEAN<br>S.D.<br>% BODY WT<br>S.D.<br>% BRAIN WT<br>S.D.<br>N | 0.14<br>0.019<br>0.04<br>0.009<br>7.08<br>1.138<br>10     | 0.14<br>0.038<br>0.05<br>0.010<br>7.28<br>1.911<br>10     | 0.12<br>0.027<br>0.04<br>0.009<br>7.46<br>4.200<br>10      | 0.15<br>0.014<br>0.05<br>0.006<br>7.43<br>0.738<br>7     | 0.28<br>0.339<br>0.10<br>0.129<br>14.87<br>17.623<br>5     |
| Liver       | MEAN<br>S.D.<br>% BODY WT<br>S.D.<br>% BRAIN WT<br>S.D.<br>N | 10.45<br>1.452<br>3.35<br>0.301<br>546.57<br>73.138<br>10 | 10.60<br>1.131<br>3.53<br>0.295<br>565.14<br>61.919<br>10 | 10.87<br>1.925<br>3.61<br>0.376<br>629.45<br>198.179<br>10 | 11.20<br>1.437<br>3.69<br>0.245<br>571.89<br>82.977<br>7 | 11.18<br>0.612<br>3.92 *<br>0.300<br>589.24<br>46.163<br>5 |
| Spleen      | MEAN<br>S.D.<br>% BODY WT<br>S.D.<br>% BRAIN WT<br>S.D.<br>N | 0.55<br>0.093<br>0.18<br>0.031<br>28.84<br>4.662<br>10    | 0.53<br>0.078<br>0.18<br>0.035<br>28.03<br>4.146<br>10    | 0.54<br>0.066<br>0.18<br>0.019<br>31.36<br>9.473<br>10     | 0.60<br>0.068<br>0.20<br>0.020<br>30.47<br>3.875<br>7    | 0.53<br>0.051<br>0.19<br>0.029<br>28.09<br>2.452<br>5      |

\* Indicates significance at the 0.05 level.

90-DAY TCM STUDY #75-51-0743-88(2)  
SUMMARY OF ORGAN WEIGHTS (GRAMS)  
MALE RATS

| ORGAN       | GROUP      | 1<br>Water | 2<br>Triton-X | 3<br>30mg/kg | 4<br>150mg/kg | 5<br>300mg/kg |
|-------------|------------|------------|---------------|--------------|---------------|---------------|
| Body Weight | MEAN       | 529        | 534           | 507          | 514           | 477           |
|             | S.D.       | 69.4       | 65.8          | 62.9         | 53.7          | 46.6          |
|             | N          | 10         | 10            | 10           | 10            | 10            |
| Brain       | MEAN       | 2.00       | 1.97          | 1.96         | 1.97          | 2.00          |
|             | S.D.       | 0.061      | 0.078         | 0.055        | 0.065         | 0.074         |
|             | % BODY WT  | 0.38       | 0.37          | 0.39         | 0.39          | 0.42          |
|             | S.D.       | 0.055      | 0.037         | 0.044        | 0.034         | 0.044         |
|             | N          | 10         | 9             | 10           | 10            | 6             |
| Adrenals    | MEAN       | 0.065      | 0.061         | 0.062        | 0.069         | 0.069         |
|             | S.D.       | 0.011      | 0.021         | 0.009        | 0.010         | 0.022         |
|             | % BODY WT  | 0.01       | 0.01          | 0.01         | 0.01          | 0.01          |
|             | S.D.       | 0.002      | 0.003         | 0.003        | 0.003         | 0.004         |
|             | % BRAIN WT | 3.25       | 3.07          | 3.15         | 3.52          | 3.44          |
|             | S.D.       | 0.610      | 0.979         | 0.447        | 0.494         | 1.115         |
| Kidneys     | MEAN       | 3.49       | 3.65          | 3.46         | 3.55          | 3.34          |
|             | S.D.       | 0.406      | 0.563         | 0.368        | 0.274         | 0.432         |
|             | % BODY WT  | 0.67       | 0.68          | 0.69         | 0.70          | 0.70          |
|             | S.D.       | 0.081      | 0.064         | 0.070        | 0.079         | 0.29          |
|             | % BRAIN WT | 175.09     | 184.77        | 176.56       | 180.39        | 166.77        |
|             | S.D.       | 21.789     | 25.208        | 18.506       | 12.106        | 21.848        |
| Testes      | MEAN       | 3.53       | 3.40          | 3.46         | 3.45          | 3.33          |
|             | S.D.       | 0.30       | 0.139         | 0.305        | 0.237         | 0.180         |
|             | % BODY WT  | 0.67       | 0.64          | 0.69         | 0.68          | 0.70          |
|             | S.D.       | 0.069      | 0.066         | 0.102        | 0.073         | 0.088         |
|             | % BRAIN WT | 176.86     | 172.54        | 176.31       | 175.46        | 166.11        |
|             | S.D.       | 15.831     | 3.811         | 15.000       | 11.827        | 9.212         |
| Liver       | MEAN       | 20.42      | 21.09         | 18.09        | 20.24         | 17.81         |
|             | S.D.       | 4.410      | 5.438         | 3.241        | 3.592         | 2.849         |
|             | % BODY WT  | 3.83       | 3.90          | 3.55         | 3.92          | 3.72          |
|             | S.D.       | 0.386      | 0.620         | 0.256        | 0.500         | 0.395         |
|             | % BRAIN WT | 1027.49    | 1063.92       | 923.26       | 1027.42       | 888.80        |
|             | S.D.       | 251.134    | 244.672       | 165.451      | 186.092       | 145.690       |
| Spleen      | MEAN       | 0.79       | 0.86          | 0.86         | 0.81          | 0.70          |
|             | S.D.       | 0.168      | 0.190         | 0.109        | 0.129         | 0.142         |
|             | % BODY WT  | 0.15       | 0.16          | 0.17         | 0.16          | 0.15          |
|             | S.D.       | 0.028      | 0.019         | 0.019        | 0.030         | 0.029         |
|             | % BRAIN WT | 39.47      | 43.17         | 43.68        | 41.51         | 34.92         |
|             | S.D.       | 8.702      | 8.194         | 5.086        | 7.175         | 6.958         |

\* Indicates significance at the 0.05 level.