# 14-DAY TOXICITY STUDY OF CuATSM/$H_2$ATSM (NSC-D729307) IN RABBITS

**FINAL REPORT**

**IITRI Project No. 2073-002-003**
**NCI Contract No. N01-CM-42202**

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**Developmental Therapeutics Program**
**Division of Cancer Treatment and Diagnosis**
**National Cancer Institute (NCI)**
**National Institutes of Health**
**Bethesda, MD 20892**

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**Study Initiation Date:** **May 13, 2004**
**Study Completion Date:** **December 21, 2004**

## 14-DAY TOXICITY STUDY OF CuATSM/$H_2$ATSM (NSC-D729307) IN RABBITS

## ABSTRACT

Male and female New Zealand White rabbits (8/sex/group) were dosed intravenously twice a day for 14 consecutive days to determine the target organ toxicity of CuATSM/$H_2$ATSM (NSC-D729307). Three rabbits/sex/group were retained for an additional 15 days to determine the reversibility of any toxicity. Rabbits in the treatment groups were administered the test article at doses of 0.030 and 0.060 (Groups 2 and 3, respectively) mg/kg/day based on each animal's most recent body weight. Rabbits in the control group (Group 1) received injections of vehicle (0.3% dimethyl sulfoxide, 7% ethanol and 92.7% saline) only.

All rabbits were evaluated for mortality/moribundity, clinical signs, body weights and weight gains during the treatment and recovery periods. Blood for clinical pathology (hematology and clinical chemistry) determinations was collected on Days 8, 15 and 29. Five rabbits/sex/group were sacrificed on Day 15 and the recovery animals (3/sex/group) were sacrificed on Day 29. Tissues were collected and examined grossly, and selected organs were weighed at the terminal and recovery necropsies. Tissues from animals in the control and high dose (0.060 mg/kg/day) groups sacrificed on Day 15 were evaluated histopathologically.

Intravenous injection of CuATSM/$H_2$ATSM (NSC-D729307) at dose levels of 0.030 and 0.060 mg/kg/day to male and female rabbits for 14 days resulted in no premature or unscheduled deaths. No adverse clinical signs were observed, and no treatment-related effects on body weight, weight gain, clinical chemistry, or absolute and relative organ weights were seen. Modest changes in hematology parameters occurred, but were not considered toxicologically significant. No drug-related gross lesions were observed in any male or female rabbit, and no drug-related histopathological effects were observed in either male or female rabbits in the high dose group at the end of the 14-day dosing period. Thus, no target organ toxicity was identified in this study and the no-observed-effect level (NOEL) was 0.060 mg/kg/day.

## COMPREHENSIVE SUMMARY

| | |
|---|---|
| Title: | 14-Day Toxicity Study of CuATSM/$H_2$ATSM (NSC-D729307) in Rabbits |
| Species: | New Zealand White rabbits |
| Sex: | Male and female |
| Age: | Approximately 6 months at arrival |
| Body Weight: | 3.05 kg to 3.34 kg (females) and from 3.00 kg to 3.37 kg (males) at arrival |
| Dose Groups: | 0.00, 0.030 and 0.060 mg/kg/day (Groups 1-3, respectively) |
| Dose Schedule: | Twice daily for 14 consecutive days |
| Number of Animals: | 48 [30 (5/sex/group; terminal necropsy) + 18 (3/sex/group; recovery necropsy)] |
| Dose Route: | Intravenous |
| Test Article: | Copper-diacetyl-bis($N^4$-methylthiosemicarbazone)/diacetyl-bis($N^4$-methylthiosemicarbazone) (CuATSM/$H_2$ATSM; NSC-D729307) |
| Control Articles: | dimethyl sulfoxide (DMSO), ethanol (100%) and saline (0.9% sodium chloride for injection USP); formulated at 0.3%, 7% and 92.7%, respectively |

**RESULTS:**

| | |
|---|---|
| Mortality: | No animals died prematurely during the study. |
| Clinical Observations: | All rabbits in all groups were clinically normal at all observation times. |
| Body Weights and Body Weight Gains: | No treatment-related effects on mean body weight or weight gain were observed during the treatment period or at the end of the recovery period for either sex. |
| Hematology: | No toxicologically significant effects on any hematology parameter were observed during the dosing period or at the end of the recovery period. |
| Clinical Chemistry: | No treatment-related effects on any clinical chemistry parameter were observed during the dosing period or at the end of the recovery period. |
| Organ Weights: | No treatment-related effects on absolute or relative organ weight were observed for either males or females at the terminal or recovery necropsies. |
| Gross Necropsy: | No drug-related gross lesions were observed in any male or female rabbit. |
| Histopathology: | No drug-related histopathological effects were observed in either male or female rabbits administered CuATSM/$H_2$ATSM at 0.060 mg/kg/day which were sacrificed at the end of the 14-day dosing period. |
| **CONCLUSIONS:** | No organ specific toxicity was identified in this study. The no-observed-effect level (NOEL) was 0.060 mg/kg/day of CuATSM/$H_2$ATSM. |

## 14-DAY TOXICITY STUDY OF CuATSM/$H_2$ATSM (NSC-D729307) IN RABBITS

Study Initiation Date: May 13, 2004
Experimental Initiation Date: May 14, 2004
Experimental Termination Date: June 11, 2004

## FOREWORD

This report describes a 14-day toxicity study conducted by IIT Research Institute (IITRI) for the National Cancer Institute (NCI). The NCI Project Officer for the study was Elizabeth R. Glaze, Ph.D.

William D. Johnson, Ph.D., D.A.B.T., served as Study Director and was responsible for the overall conduct of the study. David L. McCormick, Ph.D., D.A.B.T., Vice President and Director, Life Sciences Group, served as Principal Investigator. J. Brooks Harder, D.V.M., IITRI staff veterinarian, was responsible for animal care. Mary Ann Cahill, B.S., M.T. (A.S.C.P.), was responsible for the clinical pathology evaluations. Carol J. Detrisac, D.V.M., Ph.D., D.A.C.V.P., of Pathology Associates Division of Charles River Laboratories, Inc., Chicago, IL, supervised the gross necropsies and performed the microscopic tissue examinations. Glenn B. Miller, M.S., C.Q.M., Manager, Quality Assurance, was responsible for the IITRI quality assurance program.

William D. Johnson 12-21-04

William D. Johnson, Ph.D., D.A.B.T. Date
Study Director
Life Sciences Group

12/21/04

David L. McCormick, Ph.D., D.A.B.T. Date
Principal Investigator
Vice President and Director
Life Sciences Group

## 14-DAY TOXICITY STUDY OF CuATSM/$H_2$ATSM (NSC-D729307) IN RABBITS

### GLP COMPLIANCE STATEMENT

This study was conducted in accordance with the U.S. Food and Drug Administration (FDA) Good Laboratory Practice Regulations (*Code of Federal Regulations* Title 21 Part 58), with the following exception: the analysis of the test article and vehicle control dosing formulations was not performed according to Good Laboratory Practice Regulations. The study data have been reviewed, and the information contained in this report accurately reflects and is supported by the study raw data, representing an appropriate conclusion within the context of the study design and evaluation criteria.

William D. Johnson 12-21-04

William D. Johnson, Ph.D., D.A.B.T Date
Study Director
Life Sciences Group

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## 14-DAY TOXICITY STUDY OF CuATSM/$H_2$ATSM (NSC-D729307) IN RABBITS

### I. INTRODUCTION

The objective of this study was to determine target organ toxicity of CuATSM/$H_2$ATSM (NSC-D729307) and its reversibility when given intravenously to rabbits twice daily for 14 consecutive days.

### II. MATERIALS AND METHODS

A list of abbreviations and units of measure used in this report and their definitions is given in Table 1. The study protocol, a protocol amendment and a protocol deviation are included as Appendix A.

A. Test and Control Articles: The test article, copper-diacetyl-bis($N^4$-methylthiosemicarbazone)/diacetyl-bis($N^4$-methylthiosemicarbazone) [CuATSM/$H_2$ATSM (NSC-D729307)], a blue-gray powder, was received October 9, 2003 in an amber glass vial. The test article was stored at room temperature (approximately 20-25EC). The identity, strength, quality, stability and purity, as well as documentation of methods of synthesis, fabrication or derivation of the bulk test article, were the responsibility of the Sponsor. Compound data sheets for the test article are included in Appendix E. A reserve sample of the test article was retained at IITRI.

The three vehicle control articles (all clear, colorless liquids) were dimethyl sulfoxide (DMSO), ethanol (100%) and saline (0.9% sodium chloride for injection USP). DMSO (Sigma-Aldrich, St. Louis, MO; lot number 033K0640) was received October 28, 2003 in an amber glass bottle; ethanol (Pharmco Products, Inc., Brookfield, CT; lot number PS5520) was received in September 2003; and saline (Baxter Healthcare Corp., Deerfield, IL; lot number C604942) was received March 16, 2004 in 24 bags (each containing 500 ml). The vehicle control articles were stored at room temperature (approximately 20-25EC). Certificates of analysis for the vehicle control articles are included in Appendix E.

B. Test Article and Vehicle Dose Formulation Preparation: The test article was dissolved in DMSO to produce a stock solution, which was further diluted with DMSO (0.015 mg/mL formulation only) and then with ethanol and saline to produce a dosing solution with final concentrations of test article, DMSO, ethanol and saline of 0.015 or 0.030 mg/mL, 0.3%

(v/v), 7% (v/v) and 92.7% (v/v), respectively. The test article and vehicle control dosing formulations were stored at room temperature (approximately 20 to 25EC) when not in use.

The dose formulation target concentrations were 0.015 and 0.030 mg/mL for the low and high dose groups, respectively. The test article stock solution and each vehicle control and test article dosing formulation were prepared and used daily. Samples of the test article and vehicle control dosing formulations were obtained on study days 1, 8 and 14 and stored frozen until shipment to the Sponsor-designated laboratory (University of Alabama at Birmingham, Department of Pharmacology and Toxicology, Birmingham, AL, 35294-0019) for dose concentration analysis. Samples from the test article dosing formulations (top, middle and bottom portion) used on Day 1 were collected for homogeneity analysis and stored frozen and shipped to the Sponsor-designated laboratory for analysis.

C. Animals, Housing and Diet: Twenty-six (26) male and 26 female New Zealand White rabbits, approximately 6 months of age, were received on May 4, 2004, from Covance Research Products Inc., Kalamazoo, MI, for use in this study. The next day, the body weights of a representative sample of three animals per sex ranged from 3.05 kg to 3.34 kg (females) and from 3.00 kg to 3.37 kg (males).

Rabbits were individually housed in stainless steel cages suspended over excrement pans lined with cage liners to contain liquid and solid wastes. Rabbits were housed in accordance with standards set forth in the *Guide for Care and Use of Laboratory Animals* (National Research Council, 1996) and with U.S. Department of Agriculture (USDA) Animal Welfare Act standards (Public Law 99-198). Each rabbit was identified by a number unique to the study written on the inner ear with a nontoxic permanent marking pen. All cages were identified by project number, dose group, animal number and sex.

Animal room temperature and relative humidity (RH) values were recorded manually once a day during quarantine and twice each day during the study. During the quarantine and treatment phases of the study the animal room was maintained between 15.9-23.1°C and 35-80% RH. Brief excursions from the protocol-specified temperature (18-26°) and relative humidity (30-70%) ranges were not expected to interfere with the outcome of the study. An automatic timer was used to maintain a 12-hour light/dark cycle in the animal room.

Rabbits were provided Certified Hi-Fiber Rabbit Diet #5325 (PMI Nutrition International, Brentwood, MO) *ad libitum*, except for overnight fasts prior to scheduled necropsy. City of Chicago municipal water was available *ad libitum* via an automatic watering system throughout the study. Based on analysis reports for the diet provided by the vendor and external water analysis reports, no contaminants were known to be present in the food or water at levels expected to interfere with the outcome of the study.

D. Quarantine and Randomization: Animals were held in quarantine from May 4, 2004 to May 13, 2004. During the quarantine period, each rabbit received a detailed physical examination to ensure suitability as a test animal. No prophylactic or therapeutic treatments were administered during the quarantine period. Animals were randomized into experimental groups on May 13, 2004, using an in-house developed, computer-based body weight stratification procedure [RANSD-BAS (EXE), version 1.0].

E. Experimental Design: At randomization, 48 rabbits (8/sex/group) were assigned to two test article groups and a vehicle control group. Beginning on May 14, 2004, study animals were dosed twice daily with CuATSM/$H_2$ATSM for 14 consecutive days. Thirty (30) rabbits (5/sex/group) were euthanized on Day 15 (terminal necropsy) and 18 rabbits (3/sex/group) were observed for a 15-day recovery period and euthanized on Day 29 (recovery necropsy). The experimental design is summarized as follows:

| Group | Total CuATSM/ $H_2$ATSM Dose (mg/kg/day) | Number of Rabbits at Study Initiation | | Number of Rabbits Sacrificed | | | |
|---|---|---|---|---|---|---|---|
| | | Males | Females | Day 15 | | Day 29 | |
| | | | | Males | Females | Males | Females |
| 1 (vehicle control) | 0.00 | 8 | 8 | 5 | 5 | 3 | 3 |
| 2 | 0.030 | 8 | 8 | 5 | 5 | 3 | 3 |
| 3 | 0.060 | 8 | 8 | 5 | 5 | 3 | 3 |

F. Methods

1. Dosing Procedure and Test Article Administration: The test article was administered intravenously to each test article group rabbit twice a day for 14 days at 0.015 or 0.030 (Groups 2 and 3, respectively) mg/kg/dose based on each animal's most recent individual body weight. Rabbits in the vehicle control group received an equivalent volume of vehicle intravenously twice a day for 14 days. Daily doses were separated by approximately four hours, and all calculations for the amount of drug given to

each rabbit were verified by a second party. To reduce the possibility of masking drug effects, a uniform administration volume of 1.0 mL/kg body weight/dose was maintained by varying the volume within the appropriate concentration to accommodate individual body weights. The test article and vehicle were administered intravenously via the marginal ear vein with a sterile 5 mL plastic syringe with a 25 gauge 5/8-inch needle.

2. Moribundity/Mortality Observations: All rabbits were observed for mortality or evidence of moribundity at least once daily during quarantine and twice daily throughout the treatment and recovery periods. Mortality/moribundity checks were separated by a minimum of four hours.

3. Clinical Observations: Rabbits were observed daily during the dosing period, approximately 1-2 hours after dosing, and daily thereafter until study Day 29 (end of the recovery period).

4. Body Weights: Rabbits were weighed at receipt (random sample) and once during quarantine (at randomization). All rabbits were individually weighed on study Days 1, 5, 8 and 12, and rabbits scheduled for recovery necropsy were also weighed on Days 15 and 22. Final, non-fasted body weights were obtained on study Day 14 or 28 for terminal necropsy and recovery necropsy rabbits, respectively, and final, fasted body weights were obtained on study Day 15 or 29, respectively. Body weight data collected during the treatment and recovery periods were recorded using LABCAT (IPA Inc., Princeton, NJ, version 4.65).

5. Clinical Pathology: Blood samples for hematology and clinical chemistry parameter evaluations were obtained on study Days 8, 15 and 29. Blood was obtained from the central ear artery. Hematology and clinical chemistry data were collected and statistical analyses were performed using LABCAT (version 4.43).

   Hematological parameters evaluated using the ADVIA 120 Hematology System (Bayer Corp., Tarrytown, NY) consisted of erythrocyte count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, reticulocyte count (absolute and relative) and total and differential (absolute and relative) white blood cell counts.

The following clinical chemistry parameters were evaluated using a Beckman Synchron LX20 analyzer (Beckman-Coulter Incorporated, Brea, CA): blood urea nitrogen, serum aspartate aminotransferase, serum alanine aminotransferase, alkaline phosphatase, serum glucose, creatinine, total bile acids (Days 15 and 29 only), gamma glutamyl transferase, total bilirubin, total protein, albumin, cholesterol, triglycerides, inorganic phosphorus, sodium, potassium, chloride and calcium. Globulin levels and albumin/globulin ratios were calculated from the data.

6. Necropsy: Five male and five female rabbits from each dose group were sacrificed on study Day 15 (terminal necropsy) and three male and three female rabbits were sacrificed on study Day 29 (recovery necropsy). The animals were fasted overnight, weighed, bled for clinical pathology, euthanized by sodium pentobarbital overdose and subjected to a complete necropsy. The following tissues were collected at necropsy, examined and fixed in 10% neutral buffered formalin: adrenal glands (2), aorta, bone with articular surface (femur), bone marrow (femur), brain (sections of medulla/pons, cerebellum and cerebral cortex), esophagus, gall bladder, heart, intestine [cecum, colon, duodenum, ileum, jejunum], kidneys (2), liver, lungs (infused with formalin), lymph nodes (mandibular and mesenteric), mammary gland (when present in regular abdominal skin section), ovaries (2), pancreas, parathyroid gland, pituitary gland, salivary glands (mandibular and parotid), sciatic nerve, skeletal muscle, skin (ventral abdomen and injection site), spinal cord (cervical, mid-thoracic and lumbar), spleen, stomach (cardiac, fundic and pyloric), thymus, thyroid glands, trachea, urinary bladder, uterine horn (2) and gross lesions. Also collected and examined were the testes (2) and epididymides, which were fixed in Bouin's fixative, and the eyes, which were fixed in Davidson's fixative.

   Prior to fixation, the following tissues were weighed at necropsy (paired organs were weighed together): adrenal glands, brain, gonads (testes/ovaries), heart, kidneys, liver, spleen, thymus and thyroid (with parathyroid) glands.

7. Histopathologic Evaluation: Tissues collected from the control and high dose (Group 3 – 0.060 mg/kg/day) animals sacrificed at terminal necropsy were subjected to histopathological evaluation. Tissue sections were embedded in paraffin, processed by routine histological methods, stained with hematoxylin and eosin, and evaluated microscopically by a board-certified veterinary pathologist.

G. Statistical Procedures: Statistical analysis of continuous data was performed using analysis of variance (ANOVA) followed, where appropriate, by the *post hoc* Dunnett's test for comparing multiple treatment groups to a single control. A minimum significance level of $p<0.05$ (data collected on LABCAT, except for total body weight gains for terminal animals; Day 15 body weights, Day 15 body weight gains, and total body weight gains for recovery animals, due to LABCAT program constraints) or $p\leq0.05$ [total body weight gains for terminal animals; Day 15 body weights, Day 15 body weight gains, and total body weight gains for recovery animals, and organ weight data, which were analyzed using SYSTAT software (SYSTAT Software Inc., Richmond, CA); version 10.2] was used in all comparisons.

H. Archives: All raw data generated at IITRI, specimens and a copy of the final report will be retained in the IITRI archives for a period of one year from the date of completion of the study. At that time, the Sponsor will be consulted concerning the final disposition of the archival materials. IITRI's Quality Assurance Unit will maintain a complete record of the disposition of all archival materials.

## III. RESULTS

A. Dose Formulation Analyses: Concentration and homogeneity analyses of the dosing formulations were performed by a Sponsor-designated analytical laboratory (University of Alabama at Birmingham, Department of Pharmacology and Toxicology, Birmingham, AL, 35294-0019). Results of these analyses are presented in Table 1 of Appendix C (page C-4). The test article was not detected in any of the vehicle control dose formulation samples. Analysis of the low-dose test article dose formulations showed that the samples were within 10% of the target concentration of 0.015 mg/mL (concentration range of approximately 0.014-0.015 mg/mL; 90-102% of target), with the exception of one sample that had a concentration of approximately 0.019 mg/mL (127% of target). Analysis of the high-dose test article dose formulation samples (0.030 mg/mL) showed a concentration range of approximately 0.017-0.033 (57-111% of target). Thus, the majority of the low-dose test article formulation samples were within 90-110% of the target concentration; it is unclear why the concentrations of the high-dose test article formulations were outside this range. The mean ± standard deviation concentration for the low-dose test article homogeneity samples was 0.014 ± 0.0003 mg/mL [~92% of target; relative standard deviation (R.S.D.) = 2%] and the mean ± standard deviation

concentration for the high-dose test article homogeneity samples was 0.022 ± 0.0048 mg/mL (~74% of target; R.S.D. = 22%). Thus, the low dose formulation was homogeneous (R.S.D. <10%); however, the high dose formulation was not homogeneous, which was due to the low measured concentration of the "top" portion of the sample (approximately .017 mg/mL).

B. Mortality and Clinical Observations: Clinical observation frequency is summarized in Table 2, and individual animal clinical observations are presented in Appendix B, Table 1. No rabbits died prematurely during the study, and all rabbits in all groups were described as clinically normal at all observation times.

C. Body Weights and Body Weight Gains: Body weights and body weight gains are summarized in Tables 3 and 4, respectively, and individual animal data are presented in Appendix B, Tables 2 and 3, respectively. No statistically significant effects on mean body weight or weight gain were observed during the treatment or recovery periods.

D. Clinical Pathology

1. Hematology: Hematology data are summarized in Table 5, and individual animal data are presented in Appendix B, Table 4. No statistically significant differences between the test article-treated groups and the vehicle control group were seen for any hematology parameter in male rabbits at Day 8. For female rabbits administered 0.030 and 0.060 mg/kg/day (Groups 2 and 3, respectively), relative lymphocytes were statistically significantly increased (7% and 8%, respectively) in comparison to the vehicle control group at Day 8. In addition, for Group 3 females at Day 8, relative neutrophils were statistically significantly decreased (20%) in comparison to the vehicle control group. No statistically significant differences between the test article-treated groups and the vehicle control group were seen for any hematology parameter in rabbits of either sex at Day 15. At Day 29, males administered 0.060 mg/kg/day (Group 3) exhibited a statistically significantly decreased absolute eosinophil count (42%), and male rabbits administered 0.030 mg/kg/day (Group 2) exhibited statistically significantly decreased absolute and relative eosinophil counts (32% and 41%, respectively), in comparison to the vehicle control group. At Day 29, female rabbits administered 0.030 mg/kg/day (Group 2) exhibited statistically

significantly decreased hemoglobin (10%) in comparison to the vehicle control group.

The changes seen in females on Day 8 were transient, as similar changes were not seen on Day 15, and the magnitude of the changes was modest. Hence, these changes were not considered toxicologically significant. None of the statistically significant differences seen at Day 29 were considered treatment-related, since similar changes were not seen at the end of the dosing period (Day 15).

2. Clinical Chemistry: Clinical chemistry data are summarized in Table 6, and individual animal data are presented in Appendix B, Table 5. No statistically significant differences between the test article-treated groups and the vehicle control group were seen for any clinical chemistry parameter in rabbits of either sex at Days 8 and 15, or for female rabbits at Day 29. At Day 29, male rabbits administered 0.060 mg/kg/day (Group 3) exhibited statistically significantly increased (9%) inorganic phosphorus levels, and male rabbits dosed at 0.030 mg/kg/day (Group 2) exhibited statistically significantly increased (4%) chloride, in comparison to the vehicle control group. Since similar changes were not seen at the end of the dosing period (Day 15), these increases were not considered treatment-related. For total bile acids, no statistically significant differences between the test article-treated groups and the vehicle control group were seen in rabbits of either sex at Days 15 or 29.

E. Organ Weights: Mean absolute and relative (organ-to-body weight ratios) organ weights are summarized in Tables 7 and 8, respectively, and individual animal data are presented in Appendix B, Tables 6 and 7, respectively. No statistically significant differences between the test article-treated groups and the vehicle control group were seen in absolute or relative organ weights for male rabbits at any time period. For female rabbits dosed at 0.030 and 0.060 mg/kg/day (Groups 2 and 3, respectively), statistically significant decreases in absolute and relative spleen weight in comparison to the vehicle control group were observed at terminal necropsy. Female recovery rabbits dosed at 0.030 mg/kg/day (Group 2) exhibited statistically significant increased absolute heart weight in comparison to the vehicle control group. The decrease in spleen weight seen in the female rabbits was not considered treatment-related, since no corresponding histopathological change was seen in the spleen of the high dose (0.060 mg/kg/day) group females which could account for the decreased spleen weight. The increased

absolute heart weight seen in the recovery female rabbits (Group 2) was also not considered treatment-related since no corresponding change was seen in the Group 2 females sacrificed at the end of the dosing period (Day 15) and due to the lack of a dose response.

F. Necropsy: Gross necropsy findings are summarized in Tables IIIA (Terminal Sacrifice) and IIIB (Recovery Sacrifice) of the pathology report, which is included as Appendix D. All gross lesions observed were interpreted as incidental findings typically present in rabbit toxicology studies.

G. Histopathology: A detailed pathology report is included as Appendix D. No treatment-related pathological effects were observed in the tissues examined microscopically from Group 1 (control) and Group 3 (high dose) males and females at terminal sacrifice. All histopathology findings were interpreted as incidental findings typically present in rabbit toxicology studies or related to trauma associated with repeated intravenous injection (i.e., minimal hemorrhage, edema, inflammation, and fibrin deposition/fibrosis in the injection site skin, which, in general, were present in both the control and test article-treated groups).

## IV. DISCUSSION AND CONCLUSIONS

Intravenous injection of CuATSM/$H_2$ATSM (NSC-D729307) at dose levels of 0.030 and 0.060 mg/kg/day to male and female rabbits for 14 days resulted in no premature or unscheduled deaths. No adverse clinical signs were observed, and no treatment-related effects on body weight, weight gain, clinical chemistry, or absolute and relative organ weights were seen. No toxicologically significant changes in hematology parameters were observed. No drug-related gross lesions were observed in any male or female rabbit, and no drug-related histopathological effects were observed in either male or female rabbits in the high dose group at the end of the 14-day dosing period. Thus, no organ specific toxicity was identified in this study and the no-observed-effect level (NOEL) was 0.060 mg/kg/day.

## V. QUALITY ASSURANCE STATEMENT

Study Title: 14-Day Toxicity Study of CuATSM/$H_2$ATSM (NSC-D729307) in Rabbits

Project Number: 2073-002-003

Study Director: William D. Johnson, Ph.D., D.A.B.T.

The portions of this study conducted by IITRI have been subjected to inspections and the report has been audited by the IITRI Quality Assurance Unit in accordance with the Food and Drug Administration's "Good Laboratory Practice Regulations" – "*Code of Federal Regulations* Title 21 Section 58.35." The report describes the methods and procedures used in the study and the reported results accurately reflect the raw data.

The following are the inspection dates and the dates inspection findings were reported:

| | Findings Reported To: | |
|---|---|---|
| Inspection Dates | Study Director | Management |
| May 12, 2004 | May 12, 2004 | May 12, 2004 |
| May 14, 2004 | May 17, 2004 | May 21, 2004 |
| May 26, 2004 | May 26, 2004 | June 11, 2004 |
| May 27, 2004 | May 27, 2004 | June 11, 2004 |
| May 28, 2004 | May 28, 2004 | June 16, 2004 |
| June 11, 2004 | June 14, 2004 | June 21, 2004 |
| October 20 – 22, 2004 | October 22, 2004 | October 25, 2004 |
| December 20, 2004 | December 21, 2004 | December 21, 2004 |

12-21-04

Glenn B. Miller, M.S., C.Q.M. Date
Manager, Quality Assurance

# VI. TABLES

Table 1 – Abbreviations and Units of Measure

| Abbreviation | Interpretation | Abbreviation | Interpretation |
|---|---|---|---|
| % | percent | L or l | liter |
| µL or uL | microliter ($10^{-6}$ L) | LUC | absolute large unstained cell count ($10^3$ cells/µL blood; percent) |
| A/G RATIO | albumin/globulin ratio | LYMPH | absolute lymphocytes ($10^3$ cells/µL blood; percent) |
| ALB | albumin (g/dL serum) | M | male |
| ALP | alkaline phosphatase (IU/L serum) | MCH | mean corpuscular hemoglobin (pg) |
| ALT | alanine aminotransferase (IU/L serum) | MCHC | mean corpuscular hemoglobin concentration (g/dL blood) |
| AST | aspartate aminotransferase (IU/L serum) | MCV | mean corpuscular volume (fL) |
| BASO | basophils ($10^3$ cells/µL blood; percent) | mg | milligrams ($10^{-3}$ g) |
| BUN | blood urea nitrogen (mg nitroge n/dL serum) | ml or mL | milliliter ($10^{-3}$ l) |
| CALC | calcium (mg/dL serum) | MONO | absolute monocytes ($10^3$ cells/µL blood; percent) |
| CHOL | cholesterol (mg/dL serum) | mmol | millimole |
| CL | chloride (mmol/L serum) | N | number |
| CRE | creatinine (mg/dL serum) | NA | sodium (mmol/L serum) |
| dL or dl | deciliter ($10^{-1}$ L) | NEUT | absolute neutrophils ($10^3$ cells/µL blood; percent) |
| EOS | eosinophils ($10^3$ cells/µL blood; percent) | p or P | probability |
| F | female | pg | picogram ($10^{-12}$ g) |
| fL | femtoliter ($10^{-15}$ L) | PHOS | inorganic phosphorus (mg/dL serum) |
| g | gram | PLT | platelet count ($10^3$/µL blood) |
| GGT | gamma-glutamyl transpeptidase (IU/L serum) | RBC | red blood cell count ($10^6$ cells/µL blood) |
| GLOB | globulin (g/dL blood) | RETIC | absolute reticulocyte count ($10^9$ cells/L blood; %) |
| GLUC | glucose (mg/dL serum) | SD or S.D. | standard deviation |
| GLP | Good Laboratory Practice | TBIL | total bilirubin (mg/dL serum) |
| HGB | hemoglobin (g/dL blood) | TG | triglycerides (mg/dL serum) |
| IU | international units | TP | total protein (g protein/dL serum) |
| K | potassium (mmol/L serum) | WBC | white blood cell count ($10^3$ cells/µL blood) |
| kg or Kg | kilogram ($10^3$ g) | | |

Table 2

SUMMARY OF OBSERVATION FREQUENCY@

STUDY: 2073-002-003 SEX: MALE

| DOSE:(mg/kg) | 0 | 0.030 | 0.060 |
|---|---|---|---|
| GROUP: | 1-M | 2-M | 3-M |
| Recovery Sacrifice | 3 | 3 | 3 |
| Terminal Sacrifice | 5 | 5 | 5 |
| Normal | 8 | 8 | 8 |
| Total Number of Animals | 8 | 8 | 8 |

@ Number of animals exhibiting the sign at some time during the study

Table 2 (cont.)

SUMMARY OF OBSERVATION FREQUENCY@

STUDY: 2073-002-003 SEX: FEMALE

| DOSE:(mg/kg) | 0 | 0.030 | 0.060 |
|---|---|---|---|
| GROUP: | 1-F | 2-F | 3-F |
| Recovery Sacrifice | 3 | 3 | 3 |
| Terminal Sacrifice | 5 | 5 | 5 |
| Normal | 8 | 8 | 8 |
| Total Number of Animals | 8 | 8 | 8 |

@ Number of animals exhibiting the sign at some time during the study

# 14-DAY TOXICITY STUDY OF CuATSM/$H_2$ATSM (NSC-D729307) IN RABBITS

Table 3

## SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 2073-002-003 SEX: MALE

| PERIOD | DOSE: (mg/kg) / GROUP: | 0 1-M | 0.030 2-M | 0.060 3-M |
|---|---|---|---|---|
| DAY 1 | MEAN | 3.34 | 3.34 | 3.34 |
| | S.D. | 0.175 | 0.158 | 0.137 |
| | N | 8 | 8 | 8 |
| DAY 5 | MEAN | 3.40 | 3.37 | 3.35 |
| | S.D. | 0.196 | 0.191 | 0.129 |
| | N | 8 | 8 | 8 |
| DAY 8 | MEAN | 3.39 | 3.40 | 3.38 |
| | S.D. | 0.220 | 0.190 | 0.140 |
| | N | 8 | 8 | 8 |
| DAY 12 | MEAN | 3.48 | 3.46 | 3.45 |
| | S.D. | 0.228 | 0.213 | 0.163 |
| | N | 8 | 8 | 8 |
| DAY 14 | MEAN | 3.56 | 3.55 | 3.42 |
| | S.D. | 0.227 | 0.164 | 0.183 |
| | N | 5 | 5 | 5 |

Table 3 (cont.)

**SUMMARY OF BODY WEIGHTS** (Kilograms)

STUDY: 2073-002-003 SEX: FEMALE

| PERIOD | DOSE: (mg/kg) / GROUP: | 0 / 1-F | 0.030 / 2-F | 0.060 / 3-F |
|---|---|---|---|---|
| DAY 1 | MEAN | 3.30 | 3.29 | 3.30 |
| | S.D. | 0.151 | 0.147 | 0.154 |
| | N | 8 | 8 | 8 |
| DAY 5 | MEAN | 3.35 | 3.34 | 3.32 |
| | S.D. | 0.100 | 0.151 | 0.143 |
| | N | 8 | 8 | 8 |
| DAY 8 | MEAN | 3.34 | 3.37 | 3.29 |
| | S.D. | 0.110 | 0.165 | 0.095 |
| | N | 8 | 8 | 8 |
| DAY 12 | MEAN | 3.39 | 3.38 | 3.39 |
| | S.D. | 0.121 | 0.135 | 0.121 |
| | N | 8 | 8 | 8 |
| DAY 14 | MEAN | 3.43 | 3.35 | 3.41 |
| | S.D. | 0.156 | 0.151 | 0.124 |
| | N | 5 | 5 | 5 |

Table 3 (cont.)
(Recovery)

SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 2073-002-003 SEX: MALE

| PERIOD | DOSE: (mg/kg) / GROUP: | 0 1-M | 0.030 2-M | 0.060 3-M |
|---|---|---|---|---|
| DAY 15 | MEAN | 3.47 | 3.43 | 3.60 |
| | S.D. | 0.312 | 0.330 | 0.175 |
| | N | 3 | 3 | 3 |
| DAY 22 | MEAN | 3.50 | 3.44 | 3.60 |
| | S.D. | 0.300 | 0.339 | 0.210 |
| | N | 3 | 3 | 3 |
| DAY 28 | MEAN | 3.55 | 3.50 | 3.65 |
| | S.D. | 0.283 | 0.340 | 0.242 |
| | N | 3 | 3 | 3 |

Table 3 (cont.)
(Recovery)

**SUMMARY OF BODY WEIGHTS** (Kilograms)

STUDY: 2073-002-003 SEX: FEMALE

| PERIOD | DOSE: (mg/kg) / GROUP: | 0 1-F | 0.030 2-F | 0.060 3-F |
|---|---|---|---|---|
| DAY 15 | MEAN | 3.43 | 3.54 | 3.40 |
| | S.D. | 0.125 | 0.055 | 0.155 |
| | N | 3 | 3 | 3 |
| DAY 22 | MEAN | 3.43 | 3.62 | 3.52 |
| | S.D. | 0.154 | 0.085 | 0.185 |
| | N | 3 | 3 | 3 |
| DAY 28 | MEAN | 3.47 | 3.68 | 3.58 |
| | S.D. | 0.158 | 0.130 | 0.193 |
| | N | 3 | 3 | 3 |

## 14-DAY TOXICITY STUDY OF CuATSM/$H_2$ATSM (NSC-D729307) IN RABBITS

Table 4

**SUMMARY OF WEIGHT GAINS** (Kilograms)

STUDY: 2073-002-003 SEX: MALE

| PERIOD | DOSE: (mg/kg) / GROUP: | 0 1-M | 0.030 2-M | 0.060 3-M |
|---|---|---|---|---|
| DAY 5 | MEAN | 0.06 | 0.04 | 0.01 |
| | S.D. | 0.057 | 0.076 | 0.048 |
| | N | 8 | 8 | 8 |
| DAY 8 | MEAN | -0.01 | 0.03 | 0.04 |
| | S.D. | 0.073 | 0.038 | 0.025 |
| | N | 8 | 8 | 8 |
| DAY 12 | MEAN | 0.09 | 0.06 | 0.06 |
| | S.D. | 0.035 | 0.037 | 0.029 |
| | N | 8 | 8 | 8 |
| DAY 14 | MEAN | 0.03 | 0.05 | 0.02 |
| | S.D. | 0.013 | 0.027 | 0.026 |
| | N | 5 | 5 | 5 |
| TOTAL GAIN | MEAN | 0.16 | 0.22 | 0.10 |
| | S.D. | 0.089 | 0.067 | 0.094 |
| | N | 5 | 5 | 5 |

Table 4 (cont.)

**SUMMARY OF WEIGHT GAINS** (Kilograms)

STUDY: 2073203 SEX: FEMALE

| PERIOD | DOSE: (mg/kg) GROUP: | 0 1-F | 0.030 2-F | 0.060 3-F |
|---|---|---|---|---|
| DAY 5 | MEAN | 0.05 | 0.05 | 0.01 |
| | S.D. | 0.100 | 0.056 | 0.081 |
| | N | 8 | 8 | 8 |
| DAY 8 | MEAN | -0.01 | 0.02 | -0.02 |
| | S.D. | 0.042 | 0.031 | 0.070 |
| | N | 8 | 8 | 8 |
| DAY 12 | MEAN | 0.04 | 0.01 | 0.09 |
| | S.D. | 0.052 | 0.093 | 0.037 |
| | N | 8 | 8 | 8 |
| DAY 14 | MEAN | 0.04 | 0.01 | 0.02 |
| | S.D. | 0.023 | 0.018 | 0.029 |
| | N | 5 | 5 | 5 |
| TOTAL GAIN | MEAN | 0.11 | 0.09 | 0.13 |
| | S.D. | 0.150 | 0.098 | 0.087 |
| | N | 5 | 5 | 5 |

Table 4 (cont.)
(Recovery)

**SUMMARY OF WEIGHT GAINS** (Kilograms)

STUDY: 2073-002-003 SEX: MALE

| PERIOD | DOSE: (mg/kg) / GROUP: | 0 1-M | 0.030 2-M | 0.060 3-M |
|---|---|---|---|---|
| DAY 15 | MEAN | 0.07 | 0.06 | 0.08 |
| | S.D. | 0.055 | 0.050 | 0.030 |
| | N | 3 | 3 | 3 |
| DAY 22 | MEAN | 0.02 | 0.02 | 0.00 |
| | S.D. | 0.060 | 0.067 | 0.035 |
| | N | 3 | 3 | 3 |
| DAY 28 | MEAN | 0.05 | 0.06 | 0.05 |
| | S.D. | 0.020 | 0.006 | 0.038 |
| | N | 3 | 3 | 3 |
| TOTAL GAIN # | MEAN | 0.15 | 0.13 | 0.12 |
| | S.D. | 0.046 | 0.036 | 0.101 |
| | N | 3 | 3 | 3 |

# Days 1 through 28

Table 5 (cont.)
(Recovery)

SUMMARY OF HEMATOLOGY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | %RETIC | #RETIC | %NEUT | %LYMPH | %MONO | %EOS | %BASO | %LUC |
|---|---|---|---|---|---|---|---|---|
| UNITS: | % | x10e9/L | % | % | % | % | % | % |
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| MEAN | 1.7 | 112.7 | 18.5 | 72.5 | 1.7 | 1.8 | 5.3 | 0.3 |
| SD | 0.10 | 12.40 | 2.02 | 3.73 | 1.01 | 0.15 | 1.54 | 0.06 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 1.8 | 106.1 | 20.2 | 71.8 | 1.2 | 1.7 | 4.6 | 0.4 |
| SD | 0.70 | 37.35 | 7.74 | 6.61 | 0.36 | 1.02 | 1.61 | 0.29 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 2.2 | 136.8 | 17.8 | 73.4 | 1.6 | 1.7 | 5.0 | 0.4 |
| SD | 0.40 | 29.49 | 4.75 | 4.42 | 0.87 | 0.40 | 1.88 | 0.31 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

Table 5 (cont.)
(Recovery)

SUMMARY OF HEMATOLOGY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | #NEUT | #LYMPH | #MONO | #EOS | #BASO | #LUC |
|---|---|---|---|---|---|---|
| UNITS: | x10e3/uL | x10e3/uL | x10e3/uL | x10e3/uL | x10e3/uL | x10e3/uL |
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | |
| MEAN | 1.58 | 6.24 | 0.15 | 0.15 | 0.46 | 0.02 |
| SD | 0.121 | 0.951 | 0.091 | 0.023 | 0.146 | 0.006 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 1.24 | 4.37 | 0.07 | 0.10 | 0.27 | 0.02 |
| SD | 0.540 | 0.899 | 0.029 | 0.040 | 0.044 | 0.023 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 1.31 | 5.28 | 0.12 | 0.13 | 0.35 | 0.03 |
| SD | 0.503 | 0.282 | 0.076 | 0.044 | 0.098 | 0.026 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |

Table 6

SUMMARY OF CLINICAL CHEMISTRY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: MALE
STUDY NO: 2073023

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | NA | K | CL | ALP | ALT | AST | GGT |
|---|---|---|---|---|---|---|---|
| UNITS: | mmol/L | mmol/L | mmol/L | IU/L | IU/L | IU/L | IU/L |
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | | | | | | |
| MEAN | 140 | 4.8 | 107 | 54 | 42 | 21 | 5 |
| SD | 0.7 | 0.56 | 1.3 | 18.7 | 15.4 | 2.6 | 1.8 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| MEAN | 141 | 5.0 | 108 | 54 | 38 | 20 | 6 |
| SD | 1.3 | 0.34 | 2.6 | 7.5 | 9.4 | 2.9 | 2.3 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| MEAN | 141 | 5.3 | 107 | 56 | 34 | 23 | 6 |
| SD | 3.0 | 0.80 | 2.2 | 19.0 | 11.1 | 2.1 | 1.8 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Table 6 (cont.)

SUMMARY OF CLINICAL CHEMISTRY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | TBIL | BUN | CRE | GLUC | CALC | PHOS |
|---|---|---|---|---|---|---|
| UNITS: | mg/dL | mg/dL | mg/dL | mg/dL | mg/dL | mg/dL |
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | | | | | |
| MEAN | 0.41 | 16 | 0.9 | 134 | 14.1 | 3.8 |
| SD | 0.079 | 2.0 | 0.13 | 9.3 | 0.63 | 0.26 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 0.45 | 17 | 0.9 | 133 | 14.3 | 3.9 |
| SD | 0.064 | 1.8 | 0.12 | 7.5 | 0.36 | 0.24 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 0.38 | 18 | 1.0 | 134 | 14.4 | 3.8 |
| SD | 0.059 | 4.7 | 0.07 | 6.3 | 0.61 | 0.44 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Table 6 (cont.)

SUMMARY OF CLINICAL CHEMISTRY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: MALE
STUDY NO: 2073023

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | TP | ALB | GLOB | A/G RATIO | CHOL | TG |
|---|---|---|---|---|---|---|
| UNITS: | g/dL | g/dL | g/dL | - | mg/dL | mg/dL |
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | | | | | |
| MEAN | 5.3 | 4.9 | 0.4 | 16.6 | 34 | 117 |
| SD | 0.37 | 0.32 | 0.20 | 14.61 | 9.4 | 86.9 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 5.3 | 5.0 | 0.4 | 14.7 | 25 | 70 |
| SD | 0.28 | 0.22 | 0.09 | 4.37 | 6.3 | 23.4 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 5.4 | 5.0 | 0.4 | 12.4 | 35 | 73 |
| SD | 0.30 | 0.33 | 0.06 | 2.60 | 14.0 | 33.3 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Table 6 (cont.)

SUMMARY OF CLINICAL CHEMISTRY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | NA | K | CL | ALP | ALT | AST | GGT |
|---|---|---|---|---|---|---|---|
| UNITS: | mmol/L | mmol/L | mmol/L | IU/L | IU/L | IU/L | IU/L |
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | | | | | | |
| MEAN | 142 | 5.6 | 109 | 67 | 40 | 31 | 5 |
| SD | 1.7 | 0.97 | 1.8 | 17.4 | 10.3 | 8.9 | 2.0 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| MEAN | 140 | 5.2 | 106 | 86 | 46 | 27 | 6 |
| SD | 1.4 | 0.55 | 2.7 | 46.9 | 15.0 | 6.1 | 1.8 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| MEAN | 140 | 5.0 | 107 | 141 | 38 | 28 | 6 |
| SD | 2.0 | 0.77 | 1.8 | 193.9 | 9.5 | 7.0 | 2.0 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Table 6 (cont.)

SUMMARY OF CLINICAL CHEMISTRY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: FEMALE
STUDY NO: 2073023

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | TBIL | BUN | CRE | GLUC | CALC | PHOS |
|---|---|---|---|---|---|---|
| UNITS: | mg/dL | mg/dL | mg/dL | mg/dL | mg/dL | mg/dL |
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | | | | | |
| MEAN | 0.57 | 19 | 1.2 | 126 | 14.5 | 4.3 |
| SD | 0.074 | 3.7 | 0.10 | 4.5 | 0.55 | 0.15 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 0.53 | 17 | 1.2 | 132 | 14.5 | 4.4 |
| SD | 0.101 | 1.7 | 0.09 | 9.7 | 0.45 | 0.28 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 0.47 | 17 | 1.1 | 135 | 14.4 | 4.2 |
| SD | 0.068 | 2.1 | 0.08 | 7.4 | 0.70 | 0.44 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Table 6 (cont.)

SUMMARY OF CLINICAL CHEMISTRY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003
STUDY NO: 2073023

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | TP | ALB | GLOB | A/G RATIO | CHOL | TG |
|---|---|---|---|---|---|---|
| UNITS: | g/dL | g/dL | g/dL | - | mg/dL | mg/dL |
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | | | | | |
| MEAN | 5.6 | 5.0 | 0.6 | 9.0 | 45 | 49 |
| SD | 0.30 | 0.30 | 0.12 | 2.31 | 10.5 | 22.9 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 5.5 | 4.9 | 0.5 | 10.9 | 52 | 60 |
| SD | 0.42 | 0.35 | 0.20 | 6.25 | 11.0 | 27.3 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 5.5 | 5.0 | 0.5 | 13.6 | 54 | 59 |
| SD | 0.37 | 0.30 | 0.19 | 6.96 | 20.1 | 10.6 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Table 6 (cont.)

SUMMARY OF CLINICAL CHEMISTRY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | NA | K | CL | ALP | ALT | AST | GGT |
|---|---|---|---|---|---|---|---|
| UNITS: | mmol/L | mmol/L | mmol/L | IU/L | IU/L | IU/L | IU/L |
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | | | | | | |
| MEAN | 140 | 4.5 | 107 | 59 | 44 | 24 | 4 |
| SD | 2.1 | 1.11 | 3.0 | 26.0 | 13.8 | 3.8 | 1.9 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| MEAN | 142 | 4.9 | 108 | 61 | 41 | 27 | 5 |
| SD | 3.2 | 1.00 | 1.7 | 14.9 | 8.7 | 7.0 | 1.3 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| MEAN | 142 | 5.1 | 107 | 61 | 33 | 27 | 6 |
| SD | 4.2 | 1.11 | 2.1 | 20.9 | 11.4 | 4.6 | 1.9 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Table 6 (cont.)

SUMMARY OF CLINICAL CHEMISTRY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: MALE
STUDY NO: 2073023

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | TBIL | BUN | CRE | GLUC | CALC | PHOS |
|---|---|---|---|---|---|---|
| UNITS: | mg/dL | mg/dL | mg/dL | mg/dL | mg/dL | mg/dL |
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | | | | | |
| MEAN | 0.50 | 19 | 1.1 | 125 | 13.9 | 4.8 |
| SD | 0.085 | 4.6 | 0.23 | 9.7 | 0.72 | 0.96 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 0.55 | 19 | 1.2 | 124 | 14.5 | 5.0 |
| SD | 0.104 | 1.9 | 0.16 | 8.9 | 0.89 | 0.90 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 0.53 | 19 | 1.2 | 134 | 14.5 | 5.2 |
| SD | 0.055 | 3.7 | 0.18 | 22.8 | 0.69 | 0.93 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Table 6 (cont.)

SUMMARY OF CLINICAL CHEMISTRY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | TP | ALB | GLOB | A/G RATIO | CHOL | TG |
|---|---|---|---|---|---|---|
| UNITS: | g/dL | g/dL | g/dL | - | mg/dL | mg/dL |
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | | | | | |
| MEAN | 5.4 | 5.0 | 0.4 | 16.8 | 33 | 68 |
| SD | 0.35 | 0.35 | 0.20 | 15.69 | 10.4 | 30.3 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 5.7 | 5.2 | 0.5 | 11.2 | 27 | 53 |
| SD | 0.44 | 0.40 | 0.07 | 1.66 | 6.6 | 25.4 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 5.6 | 5.1 | 0.5 | 11.6 | 35 | 44 |
| SD | 0.50 | 0.39 | 0.16 | 3.13 | 9.8 | 14.2 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Table 6 (cont.)

SUMMARY OF CLINICAL CHEMISTRY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003
STUDY NO: 2073023

SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | NA | K | CL | ALP | ALT | AST | GGT |
|---|---|---|---|---|---|---|---|
| UNITS: | mmol/L | mmol/L | mmol/L | IU/L | IU/L | IU/L | IU/L |
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | | | | | | |
| MEAN | 141 | 4.6 | 106 | 63 | 40 | 33 | 4 |
| SD | 2.7 | 0.57 | 3.5 | 11.2 | 10.3 | 9.4 | 2.1 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| MEAN | 142 | 4.6 | 107 | 113 | 50 | 32 | 6 |
| SD | 2.6 | 0.73 | 2.1 | 130.0 | 20.1 | 11.2 | 1.5 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| MEAN | 139 | 4.3 | 106 | 141 | 44 | 40 | 5 |
| SD | 2.8 | 0.32 | 1.8 | 189.8 | 15.4 | 33.1 | 2.7 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Table 6 (cont.)

SUMMARY OF CLINICAL CHEMISTRY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | TBIL | BUN | CRE | GLUC | CALC | PHOS |
|---|---|---|---|---|---|---|
| UNITS: | mg/dL | mg/dL | mg/dL | mg/dL | mg/dL | mg/dL |
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | | | | | |
| MEAN | 0.59 | 21 | 1.5 | 132 | 13.9 | 5.1 |
| SD | 0.094 | 4.9 | 0.23 | 17.2 | 0.42 | 0.61 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 0.57 | 22 | 1.4 | 123 | 14.3 | 5.4 |
| SD | 0.080 | 4.2 | 0.30 | 13.6 | 0.54 | 1.11 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 0.56 | 21 | 1.3 | 121 | 14.0 | 5.0 |
| SD | 0.072 | 3.5 | 0.21 | 10.4 | 0.58 | 0.66 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Table 6 (cont.)

SUMMARY OF CLINICAL CHEMISTRY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: FEMALE
STUDY NO: 2073023

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | TP | ALB | GLOB | A/G RATIO | CHOL | TG |
|---|---|---|---|---|---|---|
| UNITS: | g/dL | g/dL | g/dL | - | mg/dL | mg/dL |
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | | | | | |
| MEAN | 5.5 | 5.0 | 0.6 | 9.4 | 42 | 42 |
| SD | 0.28 | 0.33 | 0.11 | 2.44 | 11.7 | 20.2 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 5.5 | 4.9 | 0.5 | 10.0 | 47 | 48 |
| SD | 0.37 | 0.35 | 0.16 | 3.10 | 9.7 | 22.8 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 5.3 | 4.9 | 0.4 | 18.5 | 48 | 49 |
| SD | 0.26 | 0.12 | 0.21 | 13.86 | 15.5 | 23.4 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Table 6 (cont.)
(Recovery)

SUMMARY OF CLINICAL CHEMISTRY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | NA | K | CL | ALP | ALT | AST | GGT |
|---|---|---|---|---|---|---|---|
| UNITS: | mmol/L | mmol/L | mmol/L | IU/L | IU/L | IU/L | IU/L |
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | | | | | | |
| MEAN | 138 | 4.3 | 107 | 63 | 55 | 27 | 4 |
| SD | 1.2 | 0.29 | 2.1 | 36.9 | 5.5 | 4.6 | 4.2 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| MEAN | 139 | 4.9 | 111* | 47 | 41 | 25 | 3 |
| SD | 2.1 | 1.40 | 0.0 | 11.6 | 13.3 | 5.6 | 1.2 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| MEAN | 140 | 5.7 | 108 | 41 | 24 | 33 | 8 |
| SD | 0.6 | 0.81 | 1.5 | 12.7 | 17.2 | 11.5 | 3.5 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

*-Significant Difference from Control P < .05

Table 6 (cont.)
(Recovery)

SUMMARY OF CLINICAL CHEMISTRY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: MALE
STUDY NO: 2073023

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | TBIL | BUN | CRE | GLUC | CALC | PHOS |
|---|---|---|---|---|---|---|
| UNITS: | mg/dL | mg/dL | mg/dL | mg/dL | mg/dL | mg/dL |
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | | | | | |
| MEAN | 0.52 | 20 | 1.2 | 121 | 14.0 | 5.3 |
| SD | 0.036 | 1.7 | 0.15 | 4.2 | 0.40 | 0.10 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 0.53 | 20 | 1.4 | 120 | 14.1 | 5.4 |
| SD | 0.136 | 1.2 | 0.36 | 4.2 | 0.56 | 0.12 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 0.53 | 20 | 1.4 | 120 | 14.4 | 5.8** |
| SD | 0.092 | 7.6 | 0.15 | 12.1 | 0.51 | 0.20 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |

**-Significant Difference from Control P < .01

Table 6 (cont.)
(Recovery)

SUMMARY OF CLINICAL CHEMISTRY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: MALE
STUDY NO: 2073023

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | TP | ALB | GLOB | A/G RATIO | CHOL | TG |
|---|---|---|---|---|---|---|
| UNITS: | g/dL | g/dL | g/dL | - | mg/dL | mg/dL |
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | | | | | |
| MEAN | 5.3 | 5.1 | 0.2 | 22.6 | 33 | 28 |
| SD | 0.10 | 0.15 | 0.06 | 5.46 | 8.3 | 7.0 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 5.3 | 5.1 | 0.3 | 26.7 | 26 | 26 |
| SD | 0.25 | 0.21 | 0.15 | 20.39 | 6.9 | 5.3 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 5.3 | 4.9 | 0.5 | 11.4 | 32 | 40 |
| SD | 0.25 | 0.23 | 0.15 | 4.61 | 12.0 | 10.8 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |

Table 6 (cont.)
(Recovery)

SUMMARY OF CLINICAL CHEMISTRY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | NA | K | CL | ALP | ALT | AST | GGT |
|---|---|---|---|---|---|---|---|
| UNITS: | mmol/L | mmol/L | mmol/L | IU/L | IU/L | IU/L | IU/L |
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | | | | | | |
| MEAN | 138 | 4.7 | 108 | 53 | 44 | 41 | 4 |
| SD | 2.0 | 0.44 | 1.0 | 5.7 | 19.5 | 21.2 | 2.0 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| MEAN | 140 | 5.0 | 109 | 180 | 45 | 31 | 7 |
| SD | 2.6 | 1.21 | 1.2 | 204.4 | 19.7 | 4.0 | 2.0 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| MEAN | 139 | 4.7 | 109 | 54 | 38 | 25 | 6 |
| SD | 1.0 | 0.10 | 2.6 | 15.9 | 5.9 | 0.6 | 2.5 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

Table 6 (cont.)
(Recovery)

SUMMARY OF CLINICAL CHEMISTRY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | TBIL | BUN | CRE | GLUC | CALC | PHOS |
|---|---|---|---|---|---|---|
| UNITS: | mg/dL | mg/dL | mg/dL | mg/dL | mg/dL | mg/dL |
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | | | | | |
| MEAN | 0.52 | 25 | 1.6 | 113 | 13.6 | 5.6 |
| SD | 0.064 | 1.7 | 0.12 | 4.0 | 0.29 | 0.31 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 0.54 | 26 | 1.6 | 123 | 14.0 | 5.3 |
| SD | 0.082 | 2.5 | 0.21 | 11.8 | 1.01 | 1.22 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 0.43 | 23 | 1.5 | 116 | 13.9 | 6.3 |
| SD | 0.057 | 2.5 | 0.12 | 7.8 | 0.62 | 1.51 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |

Table 6 (cont.)
(Recovery)

SUMMARY OF CLINICAL CHEMISTRY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | TP | ALB | GLOB | A/G RATIO | CHOL | TG |
|---|---|---|---|---|---|---|
| UNITS: | g/dL | g/dL | g/dL | - | mg/dL | mg/dL |
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | | | | | |
| MEAN | 5.3 | 4.9 | 0.3 | 15.2 | 45 | 27 |
| SD | 0.35 | 0.40 | 0.06 | 3.44 | 2.5 | 3.5 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 5.4 | 4.9 | 0.4 | 12.3 | 43 | 43 |
| SD | 0.32 | 0.25 | 0.15 | 3.80 | 13.4 | 22.9 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 5.2 | 4.8 | 0.4 | 16.0 | 57 | 31 |
| SD | 0.29 | 0.10 | 0.21 | 7.90 | 18.4 | 8.5 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |

Table 6 (cont.)

SUMMARY OF CLINICAL CHEMISTRY DATA
TEST: Total Bile Acid

STUDY ID: 2073-002-003
STUDY NO: 2073023
ABBR: TBA

SEX: MALE

UNITS: umol/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| PERIOD(s): | Day 15 | Day 29 |
|---|---|---|
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | |
| MEAN | 11.6 | 10.6 |
| SD | 9.71 | 2.50 |
| N | 8 | 3 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | |
| MEAN | 12.1 | 13.1 |
| SD | 7.15 | 5.11 |
| N | 8 | 3 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM | | |
| MEAN | 15.0 | 10.3 |
| SD | 7.66 | 7.01 |
| N | 8 | 3 |

Table 6 (cont.)

SUMMARY OF CLINICAL CHEMISTRY DATA
TEST: Total Bile Acid

STUDY ID: 2073-002-003
STUDY NO: 2073023
ABBR: TBA
SEX: FEMALE
UNITS: umol/L

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| | PERIOD(s): Day 15 | Day 29 |
|---|---|---|
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | |
| MEAN | 18.1 | 12.3 |
| SD | 8.22 | 4.26 |
| N | 8 | 3 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | |
| MEAN | 25.7 | 22.0 |
| SD | 6.79 | 14.99 |
| N | 8 | 3 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | |
| MEAN | 26.3 | 16.3 |
| SD | 10.51 | 8.40 |
| N | 8 | 3 |

Table 7

Summary Absolute Organ Weights – Males

| Group (CuATSM/ $H_2$ATSM Dose) | | Organ Weight (g) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Adrenals | Brain | Heart | Kidneys | Liver | Spleen | Testes | Thymus | Thyroid Glands[a] |
| Group 1 (0.00 mg/kg/day) | Mean | 0.514 | 9.92 | 9.66 | 16.87 | 88.99 | 1.15 | 6.02 | 4.51 | 0.258 |
| | SD | 0.1729 | 0.457 | 1.400 | 2.708 | 26.068 | 0.232 | 0.868 | 0.684 | 0.1327 |
| | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group 2 (0.030 mg/kg/day) | Mean | 0.540 | 9.73 | 9.55 | 18.02 | 75.98 | 1.17 | 5.41 | 4.41 | 0.254 |
| | SD | 0.2550 | 0.231 | 0.804 | 1.547 | 12.489 | 0.181 | 0.869 | 1.573 | 0.0399 |
| | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group 3 (0.060 mg/kg/day) | Mean | 0.507 | 9.48 | 10.25 | 16.61 | 73.29 | 1.08 | 5.01 | 4.87 | 0.281 |
| | SD | 0.0833 | 0.578 | 2.372 | 1.811 | 8.349 | 0.222 | 0.650 | 1.800 | 0.0915 |
| | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

[a]Including parathyroid

Table 7 (cont.)

Summary Absolute Organ Weights – Females

| Group (CuATSM/ $H_2$ATSM Dose) | | Organ Weight (g) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Adrenals | Brain | Heart | Kidneys | Liver | Ovaries | Spleen | Thymus | Thyroid Glands[a] |
| Group 1 (0.00 mg/kg/day) | Mean | 0.431 | 10.00 | 10.70 | 14.75 | 69.78 | 0.612 | 2.01 | 3.55 | 0.238 |
| | SD | 0.1440 | 0.304 | 1.134 | 1.998 | 10.214 | 0.0941 | 0.468 | 1.044 | 0.0810 |
| | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group 2 (0.030 mg/kg/day) | Mean | 0.400 | 9.70 | 8.64 | 14.34 | 61.00 | 0.503 | 1.27 * | 4.13 | 0.268 |
| | SD | 0.0773 | 0.365 | 1.285 | 0.942 | 6.504 | 0.2755 | 0.286 | 1.371 | 0.0860 |
| | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group 3 (0.060 mg/kg/day) | Mean | 0.370 | 9.74 | 9.19 | 15.37 | 66.10 | 0.455 | 1.30 * | 4.91 | 0.249 |
| | SD | 0.1035 | 0.566 | 1.819 | 1.226 | 4.055 | 0.1589 | 0.219 | 1.064 | 0.0749 |
| | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

[a]Including parathyroid
*Significant difference from Control, $p \leq 0.05$

Table 7 (cont.)

Summary Absolute Organ Weights – Males, Recovery

| Group (CuATSM/ $H_2$ATSM Dose) | | Organ Weight (g) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Adrenals | Brain | Heart | Kidneys | Liver | Spleen | Testes | Thymus | Thyroid Glands[a] |
| Group 1 (0.00 mg/kg/day) | Mean | 0.557 | 9.74 | 9.74 | 17.07 | 71.12 | 1.02 | 5.86 | 4.42 | 0.315 |
| | SD | 0.0716 | 0.761 | 0.245 | 1.089 | 10.943 | 0.364 | 0.434 | 0.999 | 0.0721 |
| | N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group 2 (0.030 mg/kg/day) | Mean | 0.393 | 9.42 | 8.04 | 16.01 | 68.04 | 1.23 | 5.56 | 4.38 | 0.329 |
| | SD | 0.1452 | 0.899 | 1.181 | 2.542 | 9.914 | 0.113 | 1.329 | 0.340 | 0.0613 |
| | N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group 3 (0.060 mg/kg/day) | Mean | 0.480 | 9.92 | 9.83 | 18.64 | 68.93 | 1.06 | 5.96 | 5.31 | 0.389 |
| | SD | 0.0798 | 1.011 | 1.582 | 1.579 | 3.948 | 0.115 | 0.242 | 0.872 | 0.1263 |
| | N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

[a]Including parathyroid

Table 7 (cont.)

Summary Absolute Organ Weights – Females, Recovery

| Group (CuATSM/ $H_2$ATSM Dose) | Organ Weight (g) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Adrenals | Brain | Heart | Kidneys | Liver | Ovaries | Spleen | Thymus | Thyroid Glands[a] |
| Group 1 (0.00 mg/kg/day) | 0.305 | 9.63 | 9.36 | 14.29 | 63.79 | 0.610 | 1.74 | 4.75 | 0.290 |
| | 0.0767 | 0.557 | 0.311 | 1.334 | 6.216 | 0.1541 | 0.263 | 0.475 | 0.0805 |
| | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group 2 (0.030 mg/kg/day) | 0.418 | 9.34 | 12.53 * | 16.64 | 75.70 | 0.548 | 1.59 | 5.57 | 0.364 |
| | 0.0451 | 1.076 | 1.713 | 2.332 | 13.141 | 0.1196 | 0.543 | 1.894 | 0.0641 |
| | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group 3 (0.060 mg/kg/day) | 0.317 | 10.27 | 10.20 | 15.03 | 69.30 | 0.593 | 1.90 | 4.43 | 0.248 |
| | 0.0291 | 0.223 | 1.027 | 0.415 | 9.965 | 0.2272 | 0.499 | 0.655 | 0.1055 |
| | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

[a]Including parathyroid
*Significant difference from Control, $p \leq 0.05$

Table 8

Summary Organ-to-Body Weight Ratios – Males

| Group (CuATSM/ $H_2$ATSM Dose) | | Organ-to-Body Weight Ratio (%)[a] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | FBW[b] | Adrenals | Brain | Heart | Kidneys | Liver | Spleen | Testes | Thymus | Thyroid Glands[c] |
| Group 1 (0.00 mg/kg/day) | Mean | 3.48 | 0.015 | 0.29 | 0.28 | 0.48 | 2.53 | 0.03 | 0.17 | 0.13 | 0.007 |
| | SD | 0.232 | 0.0039 | 0.010 | 0.046 | 0.054 | 0.634 | 0.007 | 0.022 | 0.016 | 0.0032 |
| | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group 2 (0.030 mg/kg/day) | Mean | 3.47 | 0.015 | 0.28 | 0.28 | 0.52 | 2.19 | 0.03 | 0.16 | 0.13 | 0.007 |
| | SD | 0.148 | 0.0071 | 0.010 | 0.014 | 0.033 | 0.308 | 0.006 | 0.026 | 0.043 | 0.0011 |
| | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group 3 (0.060 mg/kg/day) | Mean | 3.34 | 0.015 | 0.28 | 0.31 | 0.50 | 2.20 | 0.03 | 0.15 | 0.15 | 0.008 |
| | SD | 0.173 | 0.0026 | 0.022 | 0.064 | 0.030 | 0.247 | 0.007 | 0.023 | 0.054 | 0.0025 |
| | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

[a]Organ-to-Body Weight Ratio = [Absolute Organ Weight (g) ÷ Fasted Body Weight (g)] x 100
[b]FBW = fasted body weight (kg)
[c]Including parathyroid

Table 8 (cont.)

Summary Organ-to-Body Weight Ratios – Females

| Group (CuATSM/ $H_2$ATSM Dose) | | Organ-to-Body Weight Ratio (%)[a] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | FBW[b] | Adrenals | Brain | Heart | Kidneys | Liver | Ovaries | Spleen | Thymus | Thyroid Glands[c] |
| Group 1 (0.00 mg/kg/day) | Mean | 3.32 | 0.013 | 0.30 | 0.32 | 0.44 | 2.10 | 0.018 | 0.06 | 0.11 | 0.007 |
| | SD | 0.118 | 0.0042 | 0.010 | 0.029 | 0.047 | 0.259 | 0.0028 | 0.014 | 0.031 | 0.0025 |
| | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group 2 (0.030 mg/kg/day) | Mean | 3.25 | 0.012 | 0.30 | 0.27 | 0.44 | 1.88 | 0.015 | 0.04 * | 0.13 | 0.008 |
| | SD | 0.181 | 0.0017 | 0.025 | 0.036 | 0.014 | 0.181 | 0.0083 | 0.008 | 0.039 | 0.0026 |
| | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Group 3 (0.060 mg/kg/day) | Mean | 3.33 | 0.011 | 0.29 | 0.28 | 0.46 | 1.99 | 0.014 | 0.04 * | 0.15 | 0.007 |
| | SD | 0.106 | 0.0029 | 0.024 | 0.061 | 0.043 | 0.164 | 0.0046 | 0.006 | 0.032 | 0.0022 |
| | N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

[a]Organ-to-Body Weight Ratio = [Absolute Organ Weight (g) ÷ Fasted Body Weight (g)] x 100
[b]FBW = fasted body weight (kg)
[c]Including parathyroid
*Significant difference from Control, $p \leq 0.05$

Table 8 (cont.)

Summary Organ-to-Body Weight Ratios – Males, Recovery

| Group (CuATSM/ $H_2$ATSM Dose) | | Organ-to-Body Weight Ratio (%)[a] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | FBW[b] | Adrenals | Brain | Heart | Kidneys | Liver | Spleen | Testes | Thymus | Thyroid Glands[c] |
| Group 1 (0.00 mg/kg/day) | Mean | 3.50 | 0.016 | 0.28 | 0.28 | 0.49 | 2.03 | 0.03 | 0.17 | 0.13 | 0.009 |
| | SD | 0.304 | 0.0028 | 0.046 | 0.023 | 0.014 | 0.194 | 0.014 | 0.002 | 0.023 | 0.0030 |
| | N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group 2 (0.030 mg/kg/day) | Mean | 3.43 | 0.012 | 0.27 | 0.23 | 0.47 | 1.98 | 0.04 | 0.16 | 0.13 | 0.010 |
| | SD | 0.320 | 0.0047 | 0.005 | 0.013 | 0.049 | 0.121 | 0.002 | 0.023 | 0.021 | 0.0009 |
| | N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group 3 (0.060 mg/kg/day) | Mean | 3.51 | 0.014 | 0.28 | 0.28 | 0.53 | 1.96 | 0.03 | 0.17 | 0.15 | 0.011 |
| | SD | 0.245 | 0.0016 | 0.049 | 0.063 | 0.021 | 0.025 | 0.003 | 0.015 | 0.036 | 0.0028 |
| | N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

[a]Organ-to-Body Weight Ratio = [Absolute Organ Weight (g) ÷ Fasted Body Weight (g)] x 100
[b]FBW = fasted body weight (kg)
[c]Including parathyroid

Table 8 (cont.)

Summary Organ-to-Body Weight Ratios – Females, Recovery

| Group (CuATSM/ $H_2$ATSM Dose) | | Organ-to-Body Weight Ratio (%)[a] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | FBW[b] | Adrenals | Brain | Heart | Kidneys | Liver | Ovaries | Spleen | Thymus | Thyroid Glands[c] |
| Group 1 (0.00 mg/kg/day) | Mean | 3.39 | 0.009 | 0.29 | 0.28 | 0.42 | 1.88 | 0.018 | 0.05 | 0.14 | 0.009 |
| | SD | 0.163 | 0.0024 | 0.028 | 0.022 | 0.024 | 0.106 | 0.0038 | 0.007 | 0.008 | 0.0028 |
| | N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group 2 (0.030 mg/kg/day) | Mean | 3.68 | 0.011 | 0.25 | 0.34 | 0.45 | 2.06 | 0.015 | 0.04 | 0.15 | 0.010 |
| | SD | 0.075 | 0.0012 | 0.024 | 0.052 | 0.056 | 0.341 | 0.0030 | 0.014 | 0.055 | 0.0019 |
| | N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group 3 (0.060 mg/kg/day) | Mean | 3.47 | 0.009 | 0.30 | 0.29 | 0.43 | 1.99 | 0.017 | 0.05 | 0.13 | 0.007 |
| | SD | 0.185 | 0.0004 | 0.016 | 0.036 | 0.012 | 0.218 | 0.0059 | 0.012 | 0.014 | 0.0027 |
| | N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

[a]Organ-to-Body Weight Ratio = [Absolute Organ Weight (g) ÷ Fasted Body Weight (g)] x 100
[b]FBW = fasted body weight (kg)
[c]Including parathyroid

Table 4 (cont.)
(Recovery)

**SUMMARY OF WEIGHT GAINS** (Kilograms)

STUDY: 2073-002-003 SEX: FEMALE

| PERIOD | DOSE: (mg/kg) / GROUP: | 0 1-F | 0.030 2-F | 0.060 3-F |
|---|---|---|---|---|
| DAY 15 | MEAN | 0.05 | 0.10 | 0.02 |
| | S.D. | 0.040 | 0.040 | 0.017 |
| | N | 3 | 3 | 3 |
| DAY 22 | MEAN | 0.00 | 0.08 | 0.13 |
| | S.D. | 0.036 | 0.117 | 0.035 |
| | N | 3 | 3 | 3 |
| DAY 28 | MEAN | 0.04 | 0.06 | 0.06 |
| | S.D. | 0.006 | 0.046 | 0.010 |
| | N | 3 | 3 | 3 |
| TOTAL GAIN # | MEAN | 0.10 | 0.25 | 0.21 |
| | S.D. | 0.065 | 0.140 | 0.031 |
| | N | 3 | 3 | 3 |

# Days 1 through 28

Table 5

SUMMARY OF HEMATOLOGY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | WBC | RBC | HGB | HCT | MCV | MCH | MCHC | PLT |
|---|---|---|---|---|---|---|---|---|
| UNITS: | x10e3/uL | x10e6/uL | g/dL | % | fL | pg | g/dL | x10e3/uL |
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| MEAN | 9.35 | 6.09 | 13.1 | 39.0 | 64.1 | 21.6 | 33.7 | 369 |
| SD | 1.874 | 0.244 | 0.61 | 1.44 | 2.11 | 0.50 | 1.12 | 72.1 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 10.51 | 6.14 | 12.7 | 38.8 | 63.4 | 20.8 | 32.8 | 354 |
| SD | 1.668 | 0.692 | 0.93 | 2.85 | 2.52 | 1.04 | 0.81 | 47.2 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 9.03 | 6.14 | 13.2 | 39.5 | 64.4 | 21.6 | 33.5 | 343 |
| SD | 1.376 | 0.372 | 0.59 | 1.61 | 2.41 | 0.77 | 1.00 | 45.2 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Table 5 (cont.)

SUMMARY OF HEMATOLOGY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | %RETIC | #RETIC | %NEUT | %LYMPH | %MONO | %EOS | %BASO | %LUC |
|---|---|---|---|---|---|---|---|---|
| UNITS: | % | x10e9/L | % | % | % | % | % | % |
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| MEAN | 2.0 | 122.8 | 14.7 | 77.8 | 1.0 | 1.7 | 4.6 | 0.2 |
| SD | 0.32 | 19.79 | 5.06 | 6.07 | 0.45 | 0.39 | 1.54 | 0.10 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 2.0 | 120.5 | 16.6 | 76.7 | 1.0 | 1.4 | 4.1 | 0.2 |
| SD | 0.52 | 23.57 | 3.53 | 4.10 | 0.19 | 0.39 | 1.00 | 0.12 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 2.1 | 130.9 | 17.8 | 73.6 | 1.4 | 1.9 | 5.0 | 0.3 |
| SD | 0.73 | 40.06 | 3.55 | 4.93 | 0.67 | 0.68 | 1.97 | 0.20 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Table 5 (cont.)

SUMMARY OF HEMATOLOGY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | #NEUT | #LYMPH | #MONO | #EOS | #BASO | #LUC |
|---|---|---|---|---|---|---|
| UNITS: | x10e3/uL | x10e3/uL | x10e3/uL | x10e3/uL | x10e3/uL | x10e3/uL |
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | |
| MEAN | 1.37 | 7.29 | 0.09 | 0.16 | 0.42 | 0.02 |
| SD | 0.584 | 1.535 | 0.049 | 0.037 | 0.171 | 0.011 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 1.75 | 8.06 | 0.10 | 0.15 | 0.44 | 0.02 |
| SD | 0.466 | 1.313 | 0.013 | 0.042 | 0.142 | 0.010 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM' | | | | | | |
| MEAN | 1.61 | 6.65 | 0.13 | 0.17 | 0.44 | 0.02 |
| SD | 0.443 | 1.104 | 0.078 | 0.050 | 0.155 | 0.017 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Table 5 (cont.)

SUMMARY OF HEMATOLOGY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | WBC | RBC | HGB | HCT | MCV | MCH | MCHC | PLT |
|---|---|---|---|---|---|---|---|---|
| UNITS: | x10e3/uL | x10e6/uL | g/dL | % | fL | pg | g/dL | x10e3/uL |
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| MEAN | 8.78 | 6.12 | 13.1 | 39.8 | 65.2 | 21.5 | 33.0 | 401 |
| SD | 1.340 | 0.398 | 0.69 | 2.55 | 2.77 | 0.75 | 1.11 | 134.1 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 9.24 | 6.09 | 12.8 | 38.9 | 64.0 | 21.1 | 33.0 | 323 |
| SD | 1.740 | 0.607 | 0.81 | 3.16 | 2.71 | 1.02 | 0.85 | 78.2 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 8.85 | 6.18 | 12.9 | 39.4 | 63.9 | 20.9 | 32.8 | 309 |
| SD | 1.090 | 0.393 | 0.73 | 1.96 | 3.46 | 1.01 | 0.79 | 155.6 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Table 5 (cont.)

SUMMARY OF HEMATOLOGY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | %RETIC | #RETIC | %NEUT | %LYMPH | %MONO | %EOS | %BASO | %LUC |
|---|---|---|---|---|---|---|---|---|
| UNITS: | % | x10e9/L | % | % | % | % | % | % |
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| MEAN | 2.2 | 133.2 | 21.1 | 69.4 | 1.3 | 2.2 | 5.8 | 0.2 |
| SD | 1.39 | 74.55 | 2.78 | 3.77 | 0.70 | 0.82 | 1.58 | 0.16 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 1.8 | 106.8 | 17.9 | 74.0* | 1.1 | 2.3 | 4.6 | 0.2 |
| SD | 0.52 | 31.65 | 3.03 | 3.63 | 0.40 | 0.74 | 1.33 | 0.13 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 1.9 | 117.2 | 16.8* | 75.2** | 1.1 | 2.1 | 4.6 | 0.2 |
| SD | 0.39 | 26.67 | 4.07 | 3.90 | 0.40 | 0.55 | 1.30 | 0.24 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

*-Significant Difference from Control P < .05 **-Significant Difference from Control P < .01

Table 5 (cont.)

SUMMARY OF HEMATOLOGY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | #NEUT | #LYMPH | #MONO | #EOS | #BASO | #LUC |
|---|---|---|---|---|---|---|
| UNITS: | x10e3/uL | x10e3/uL | x10e3/uL | x10e3/uL | x10e3/uL | x10e3/uL |
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | |
| MEAN | 1.83 | 6.11 | 0.11 | 0.20 | 0.52 | 0.02 |
| SD | 0.164 | 1.109 | 0.058 | 0.081 | 0.172 | 0.013 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 1.64 | 6.85 | 0.10 | 0.21 | 0.43 | 0.02 |
| SD | 0.305 | 1.353 | 0.052 | 0.086 | 0.174 | 0.011 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 1.51 | 6.64 | 0.10 | 0.18 | 0.40 | 0.02 |
| SD | 0.451 | 0.805 | 0.042 | 0.049 | 0.114 | 0.021 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Table 5 (cont.)

SUMMARY OF HEMATOLOGY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | WBC | RBC | HGB | HCT | MCV | MCH | MCHC | PLT |
|---|---|---|---|---|---|---|---|---|
| UNITS: | x10e3/uL | x10e6/uL | g/dL | % | fL | pg | g/dL | x10e3/uL |
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| MEAN | 8.15 | 6.04 | 13.1 | 39.1 | 64.8 | 21.6 | 33.3 | 330 |
| SD | 1.808 | 0.258 | 0.44 | 1.22 | 1.70 | 0.53 | 0.69 | 57.9 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 8.87 | 6.44 | 13.5 | 41.4 | 64.4 | 21.1 | 32.7 | 337 |
| SD | 2.702 | 0.678 | 0.98 | 3.28 | 2.34 | 0.90 | 0.63 | 58.8 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 7.26 | 6.28 | 13.7 | 41.4 | 66.0 | 21.8 | 33.1 | 350 |
| SD | 2.413 | 0.417 | 0.63 | 3.97 | 3.19 | 0.99 | 1.88 | 110.2 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Table 5 (cont.)

SUMMARY OF HEMATOLOGY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | %RETIC | #RETIC | %NEUT | %LYMPH | %MONO | %EOS | %BASO | %LUC |
|---|---|---|---|---|---|---|---|---|
| UNITS: | % | x10e9/L | % | % | % | % | % | % |
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| MEAN | 3.0 | 178.4 | 16.8 | 73.7 | 1.3 | 2.9 | 5.2 | 0.3 |
| SD | 0.56 | 35.08 | 5.57 | 6.67 | 0.50 | 0.81 | 1.87 | 0.22 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 2.6 | 166.1 | 19.9 | 71.4 | 1.7 | 2.1 | 4.5 | 0.4 |
| SD | 0.37 | 28.70 | 6.04 | 6.24 | 0.88 | 0.45 | 1.70 | 0.25 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 2.9 | 181.2 | 18.5 | 72.0 | 1.7 | 2.1 | 5.1 | 0.5 |
| SD | 0.69 | 45.07 | 6.54 | 8.38 | 0.96 | 0.82 | 1.58 | 0.49 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Table 5 (cont.)

SUMMARY OF HEMATOLOGY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | #NEUT | #LYMPH | #MONO | #EOS | #BASO | #LUC |
|---|---|---|---|---|---|---|
| UNITS: | x10e3/uL | x10e3/uL | x10e3/uL | x10e3/uL | x10e3/uL | x10e3/uL |
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | |
| MEAN | 1.29 | 6.08 | 0.11 | 0.23 | 0.41 | 0.02 |
| SD | 0.210 | 1.695 | 0.048 | 0.090 | 0.160 | 0.017 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 1.70 | 6.42 | 0.15 | 0.18 | 0.39 | 0.04 |
| SD | 0.556 | 2.472 | 0.065 | 0.054 | 0.126 | 0.024 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 1.30 | 5.27 | 0.14 | 0.15 | 0.37 | 0.04 |
| SD | 0.454 | 1.915 | 0.114 | 0.061 | 0.146 | 0.045 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Table 5 (cont.)

SUMMARY OF HEMATOLOGY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | WBC | RBC | HGB | HCT | MCV | MCH | MCHC | PLT |
|---|---|---|---|---|---|---|---|---|
| UNITS: | x10e3/uL | x10e6/uL | g/dL | % | fL | pg | g/dL | x10e3/uL |
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| MEAN | 8.14 | 6.20 | 13.3 | 40.5 | 65.2 | 21.5 | 33.0 | 347 |
| SD | 1.877 | 0.335 | 0.83 | 2.85 | 2.85 | 0.52 | 1.02 | 134.5 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 8.56 | 6.21 | 13.1 | 40.0 | 64.6 | 21.1 | 32.7 | 332 |
| SD | 2.395 | 0.469 | 0.74 | 1.85 | 3.05 | 0.91 | 0.55 | 135.8 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 8.55 | 6.17 | 12.9 | 39.3 | 63.8 | 21.0 | 32.9 | 308 |
| SD | 1.413 | 0.467 | 0.72 | 2.21 | 3.35 | 1.02 | 0.53 | 86.9 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Table 5 (cont.)

SUMMARY OF HEMATOLOGY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | %RETIC | #RETIC | %NEUT | %LYMPH | %MONO | %EOS | %BASO | %LUC |
|---|---|---|---|---|---|---|---|---|
| UNITS: | % | x10e9/L | % | % | % | % | % | % |
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| MEAN | 2.1 | 133.6 | 20.4 | 69.0 | 1.7 | 2.6 | 6.1 | 0.3 |
| SD | 0.62 | 41.73 | 4.93 | 5.16 | 0.85 | 1.03 | 0.94 | 0.22 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 2.3 | 144.1 | 16.8 | 73.6 | 1.9 | 2.7 | 4.9 | 0.2 |
| SD | 0.50 | 27.15 | 2.73 | 4.85 | 0.91 | 1.39 | 1.48 | 0.13 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 2.5 | 154.4 | 16.3 | 73.6 | 2.2 | 2.7 | 4.9 | 0.3 |
| SD | 0.73 | 49.73 | 4.57 | 6.37 | 1.38 | 1.32 | 1.81 | 0.24 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Table 5 (cont.)

SUMMARY OF HEMATOLOGY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | #NEUT | #LYMPH | #MONO | #EOS | #BASO | #LUC |
|---|---|---|---|---|---|---|
| UNITS: | x10e3/uL | x10e3/uL | x10e3/uL | x10e3/uL | x10e3/uL | x10e3/uL |
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | |
| MEAN | 1.60 | 5.69 | 0.13 | 0.21 | 0.49 | 0.02 |
| SD | 0.187 | 1.641 | 0.063 | 0.104 | 0.109 | 0.020 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 1.41 | 6.36 | 0.15 | 0.22 | 0.40 | 0.02 |
| SD | 0.371 | 2.013 | 0.073 | 0.087 | 0.116 | 0.007 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 1.38 | 6.33 | 0.18 | 0.23 | 0.42 | 0.03 |
| SD | 0.387 | 1.267 | 0.087 | 0.119 | 0.150 | 0.026 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Table 5 (cont.)
(Recovery)

SUMMARY OF HEMATOLOGY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | WBC | RBC | HGB | HCT | MCV | MCH | MCHC | PLT |
|---|---|---|---|---|---|---|---|---|
| UNITS: | x10e3/uL | x10e6/uL | g/dL | % | fL | pg | g/dL | x10e3/uL |
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| MEAN | 8.72 | 6.39 | 13.8 | 41.0 | 64.2 | 21.7 | 33.8 | 292 |
| SD | 0.912 | 0.231 | 0.50 | 1.78 | 2.16 | 0.25 | 0.76 | 67.4 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 10.22 | 6.37 | 13.3 | 40.3 | 63.6 | 21.2 | 33.2 | 328 |
| SD | 3.076 | 1.101 | 1.18 | 4.72 | 3.90 | 1.72 | 0.87 | 77.5 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 7.22 | 6.51 | 13.9 | 41.9 | 64.4 | 21.4 | 33.2 | 310 |
| SD | 1.639 | 0.414 | 0.82 | 2.72 | 0.40 | 0.51 | 0.61 | 41.9 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

Table 5 (cont.)
(Recovery)

SUMMARY OF HEMATOLOGY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | %RETIC | #RETIC | %NEUT | %LYMPH | %MONO | %EOS | %BASO | %LUC |
|---|---|---|---|---|---|---|---|---|
| UNITS: | % | x10e9/L | % | % | % | % | % | % |
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| MEAN | 2.3 | 146.6 | 13.2 | 78.6 | 0.9 | 2.2 | 4.9 | 0.2 |
| SD | 0.10 | 12.70 | 2.12 | 1.84 | 0.15 | 0.25 | 1.05 | 0.10 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 2.3 | 148.0 | 15.8 | 77.9 | 0.9 | 1.3* | 3.9 | 0.1 |
| SD | 0.23 | 19.93 | 4.35 | 3.67 | 0.40 | 0.38 | 1.10 | 0.06 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 2.3 | 147.0 | 26.3 | 65.8 | 1.4 | 1.5 | 4.7 | 0.4 |
| SD | 0.21 | 5.37 | 12.87 | 16.23 | 0.81 | 0.25 | 2.05 | 0.36 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

*-Significant Difference from Control P < .05

Table 5 (cont.)
(Recovery)

SUMMARY OF HEMATOLOGY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: MALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | #NEUT | #LYMPH | #MONO | #EOS | #BASO | #LUC |
|---|---|---|---|---|---|---|
| UNITS: | x10e3/uL | x10e3/uL | x10e3/uL | x10e3/uL | x10e3/uL | x10e3/uL |
| Group: 1-M : 0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | |
| MEAN | 1.16 | 6.85 | 0.07 | 0.19 | 0.42 | 0.02 |
| SD | 0.279 | 0.734 | 0.015 | 0.010 | 0.050 | 0.010 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 2-M : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 1.55 | 8.03 | 0.09 | 0.13* | 0.41 | 0.02 |
| SD | 0.336 | 2.698 | 0.035 | 0.015 | 0.180 | 0.006 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 3-M : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| MEAN | 2.04 | 4.57 | 0.11 | 0.11* | 0.36 | 0.04 |
| SD | 1.457 | 0.214 | 0.090 | 0.042 | 0.229 | 0.038 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |

*-Significant Difference from Control P < .05

Table 5 (cont.)
(Recovery)

SUMMARY OF HEMATOLOGY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: FEMALE

ANALYSIS OF VARIANCE FOLLOWED BY DUNNETT'S PROCEDURE

| TEST(s): | WBC | RBC | HGB | HCT | MCV | MCH | MCHC | PLT |
|---|---|---|---|---|---|---|---|---|
| UNITS: | x10e3/uL | x10e6/uL | g/dL | % | fL | pg | g/dL | x10e3/uL |
| Group: 1-F : 0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| MEAN | 8.60 | 6.68 | 14.3 | 42.0 | 62.8 | 21.4 | 34.0 | 342 |
| SD | 1.051 | 0.273 | 0.90 | 2.11 | 0.76 | 0.46 | 0.56 | 232.4 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 2-F : 0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 6.08 | 6.01 | 12.8* | 38.6 | 64.2 | 21.2 | 33.2 | 388 |
| SD | 1.091 | 0.289 | 0.15 | 0.74 | 4.43 | 1.19 | 0.57 | 156.9 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Group: 3-F : 0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| MEAN | 7.23 | 6.29 | 13.4 | 40.6 | 64.6 | 21.4 | 33.1 | 407 |
| SD | 0.819 | 0.331 | 0.40 | 1.14 | 3.38 | 0.95 | 0.30 | 307.6 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

*-Significant Difference from Control P < .05

# VII. APPENDICES

Appendix A. Protocol and Protocol Amendment

# 14-DAY TOXICITY STUDY OF CuATSM / $H_2$ATSM (NSC-D729307) IN RABBITS

| | |
|---|---|
| **SPONSOR:** | Toxicology and Pharmacology Branch<br>Developmental Therapeutics Program<br>Division of Cancer Treatment and Diagnosis<br>National Cancer Institute (NCI)<br>National Institutes of Health<br>Bethesda, Maryland 20892 |
| **PROJECT OFFICER:** | Elizabeth R. Glaze, Ph.D. |
| **CONTRACT NUMBER:** | N01-CM-42202 |
| **CONTRACTOR:** | IIT Research Institute (IITRI)<br>Life Sciences Group<br>10 West 35th Street<br>Chicago, IL 60616 |
| **IITRI PROJECT NUMBER:** | 2073-002-003 |
| **PRINCIPAL INVESTIGATOR:** | David L. McCormick, Ph.D., D.A.B.T. |
| **STUDY DIRECTOR:** | William D. Johnson, Ph.D., D.A.B.T. |
| **PROPOSED IN-LIFE PHASE:** | |
| **Start:** | May 14, 2004 (Day 1) |
| **Finish:** | June 11, 2004 (Day 29) |

## I. OBJECTIVE

The objective of this study is to determine target organ toxicity of CuATSM/$H_2$ATSM (NSC-D729307) and its reversibility when given intravenously to rabbits twice daily (BID) for 14 consecutive days.

## II. MATERIALS AND METHODS

### A. Test and Control Articles

#### 1. Names of Test Article:

Copper-diacetyl-bis(N4-methylthiosemicarbazone) / diacetyl-bis(N4-methylthiosemicarbazone) (CuATSM / $H_2$ATSM; NSC-D729307)

#### 2. Name of Control Articles:

Dimethyl sulfoxide (DMSO)
Ethanol (100%)
Saline (0.9% sodium chloride for injection USP)

#### 3. Characterization and Documentation of Methods of Synthesis, Fabrication or Derivation:

##### a. Test Article:

Compound identity, strength, quality, stability and purity as well as documentation of methods of synthesis, fabrication or derivation are the responsibility of the NCI. Sufficient quantity of test articles shall be reserved for archiving from each lot and shipment used.

##### b. Control Articles:

Characterization of DMSO, ethanol and saline may be attained by recording all pertinent information provided on the container labels or by retaining the container labels themselves (or copies thereof) as raw data.

#### 4. Stability and Storage:

The test article will be stored at controlled room temperature (approximately 20 to 25°C). The DMSO, 100% ethanol and saline will also be stored at controlled room temperature (approximately 20 to 25°C). The control articles are stable unopened through the date of expiration as provided by the manufacturer/supplier.

5. **Formulation Preparation and Storage:**

The test article will be dissolved in DMSO to produce a stock solution (approximately 10 mg/ml). The stock solution will be further diluted with DMSO (if necessary), and then with 100% ethanol and saline to produce a dosing solution with final concentrations of test article, DMSO, ethanol and saline of 0.015 or 0.030 mg/mL, 0.3% (v/v), 7% (v/v) and 92.7% (v/v), respectively. The test article stock solution and each test article dosing formulation will be prepared fresh daily. The vehicle control formulation [0.3% (v/v) DMSO/7% (v/v) ethanol/92.7% (v/v) saline] will also be prepared daily. When not in use, the test article and vehicle control dosing formulations will be stored in the dark at controlled room temperature (approximately 20 to 25°C).

6. **Dose Concentration and Homogeneity Analyses:**

Dose concentration and homogeneity analyses will be performed by an analytical laboratory designated by the Sponsor. An adequate quantity of each test article and vehicle control dosing formulation used for dosing on Study Days 1, 8 and 14 will be obtained for dose concentration analyses and stored frozen. Similarly, an adequate quantity of each test article dosing formulation used on Study Day 1 (consisting of dose concentration analysis of a top, middle and bottom portion) will be obtained for homogeneity analysis and stored frozen. Samples will be shipped (on dry ice) in an insulated container to the Sponsor-designated laboratory for analysis. The reporting of results will be included in IITRI's Final Report.

B. Test System

1. **Species, Sex, Strain, Supplier and Test System Justification:**

Twenty-six (26) male and 26 female (females nulliparous and non-pregnant) New Zealand White (NZW) rabbits will be obtained from Covance Research Products, Inc. (Kalamazoo, MI) for use in this study. This is an accepted species to support studies of compounds used or intended for use in humans.

2. **Initial Age and Weight:**

At the time of receipt, the rabbits will be approximately 6 months of age and will weigh approximately 3 to 3.5 kg.

3. **Care and Housing:**

General procedures for animal care and housing will be in accordance with the *Guide for the Care and Use of Laboratory Animals*, National Research Council, 1996 and the U.S. Department of Agriculture through the Animal Welfare Act (Public Law 99-198). Rabbits will be individually housed in stainless steel cages suspended over excrement pans. Cage liners will be placed in the pan below the stainless steel mesh floor of each animal cage to contain liquid and solid wastes.

Animal room temperature and relative humidity will be recorded manually each day. A 12-hour light/dark cycle (maintained with an automatic timer) will be used. Animal rooms will be held within a temperature range of approximately 18 to 26°C, and a humidity range of approximately 30 to 70%.

4. **Diet and Water Supply:**

Certified Hi-Fiber Rabbit Diet #5325 (PMI Nutrition International, Brentwood, MO) will be provided *ad libitum* to all rabbits, except for overnight fasts prior to scheduled necropsy. City of Chicago public drinking water from an automatic watering system will be provided *ad libitum* to all rabbits throughout the study. No contaminants will be present in the feed or water which could interfere and affect the results of the study. Analytical data from the lots of diet to be used in the study and water analysis records are retained on file at IITRI.

5. **Quarantine:**

All rabbits will be quarantined for a minimum of 7 days prior to dosing. During the quarantine period, each rabbit will receive a detailed physical examination to ensure its suitability as a test animal. No prophylactic or therapeutic treatment will be administered during the quarantine period. Only healthy animals will be placed on study.

6. **Animal Identification:**

All study rabbits will be individually identified by a unique number written on the inner ear with a nontoxic permanent marking pen. Each rabbit cage will be identified by Project Number, Group, Animal Number and Sex.

## C. Experimental Design

### 1. Randomization:

In order to obtain groups that are comparable by weight, all rabbits will be randomly assigned to their respective treatment groups using a computer-based body weight stratification procedure. The individual body weights required for randomization are to be determined during the quarantine period.

### 2. Group Assignments:

After randomization, 48 rabbits (8/sex/dose group) will be assigned to two test article dose groups and a vehicle control group (VCTL) as follows.

| Group | (CuATSM/$H_2$ATSM ) Dose (mg/kg/dose) | (CuATSM/$H_2$ATSM ) Dose (mg/kg/day) | # of Rabbits at Study Start (M + F) | # of Rabbits Sacrificed | |
|---|---|---|---|---|---|
| | | | | Day 15 (M + F) | Day 29 (M + F) |
| I (VCTL) | 0.00 | 0.00 | 8 + 8 | 5 + 5 | 3 + 3 |
| II | 0.015 | 0.030 | 8 + 8 | 5 + 5 | 3 + 3 |
| III | 0.030 | 0.060 | 8 + 8 | 5 + 5 | 3 + 3 |

Study animals will be dosed twice daily for 14 consecutive days. Thirty study rabbits (5/sex/group) will be sacrificed on study day 15 (terminal necropsy) and the remaining study rabbits will then be observed for 15 days thereafter and will be sacrificed on study day 29 (recovery necropsy).

### 3. Route of Administration and Reason for Choice:

The test compounds will be given intravenously because this is the intended route of administration of these compounds in humans.

### 4. Dosing Procedure:

Starting on study day 1, each study rabbit within each test article dose group will receive drug intravenously twice a day for 14 days; rabbits in the vehicle control group will receive an equivalent volume of vehicle twice a day for 14 days. The amount of drug administered to each rabbit will be based on its most recent individual body weight. Daily doses will be separated by a minimum of four hours. All calculations for amount of drug given to each rabbit will be checked by a second individual who will initial and date the verification.

In order to reduce the possibility of masking drug effects, a uniform volume for administration (1.0 mL/kg body weight/dose) will be selected and maintained constant for all rabbits. This can be done by varying the volume within the appropriate concentration to accommodate individual body weights.

5. **Measurements:**

a. **Moribundity/Mortality Observations:**

During the quarantine period, all animals will be observed once daily for mortality or evidence of moribundity. Throughout the treatment period, all animals will be observed twice daily for mortality or evidence of moribundity. Any abnormal clinical signs will be recorded. Mortality/moribundity checks will be separated by a minimum of four hours.

b. **Clinical Signs:**

All study rabbits will be observed daily during the dosing period, at approximately 1-2 hours after dosing, and daily thereafter until study day 29 or more often as clinical signs warrant.

Rabbit identification numbers, dose volumes, drug formulations, vehicle, clinical effects, day(s) of death, individual body weights as specified below and other pertinent information will be recorded.

c. **Body Weight:**

Animals will be weighed at receipt (random sample) and once during quarantine (at randomization). All surviving study rabbits will be individually weighed on Study Days 1, 5, 8, 12, 15 and 22. For all surviving study animals scheduled for terminal or recovery necropsy, a final (non-fasted) body weight will be obtained on Study Days 14 or 28, respectively, and a final (fasted) body weight will be obtained on Study Days 15 or 29, respectively. When applicable, the rabbits should be weighed at approximately the same time each day.

d. **Clinical Pathology:**

Blood will be drawn from each surviving study rabbit for clinical pathology determinations on study days 8, 15 and 29. Blood will not be taken from the treatment site. A blood sample will be obtained prior to the necropsy of each study rabbit sacrificed in a moribund condition.

Hematology:

Erythrocyte count (RBC)
Hemoglobin (HGB)
Hematocrit (HCT)
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Platelet count (PLT)
Reticulocyte count (RETIC; absolute and relative)
Total leukocyte count (WBC)
Differential leukocyte count (absolute and relative)

Clinical Chemistry:

Blood urea nitrogen (BUN)
Serum aspartate aminotransferase (AST)
Serum alanine aminotransferase (ALT)
Alkaline phosphatase (ALP)
Serum glucose (GLU)
Creatinine (CREA)
Total bile acids (TBA; on Days 15 and 29 only)
Gamma glutamyl transferase (GGT)
Total bilirubin (TBIL)
Total protein (TP)
Albumin (ALB)
Globulin (GLOB; by calculation)
Albumin/Globulin (A/G) ratio
Cholesterol (CHOL)
Triglycerides (TG)
Inorganic Phosphorus (PO4)
Sodium (NA)
Potassium (K)
Chloride (CL)
Calcium (CA)

e. **Postmortem Procedure:**

Five male and five female study rabbits from each dose group will be sacrificed on study day 15 (terminal necropsy); surviving study rabbits will be sacrificed on study day 29 (recovery necropsy).

Moribund study rabbits should be terminated out of sequence with complete histopathology and clinical pathology performed as for scheduled necropsies. The authorization to sacrifice moribund study rabbits will be made by the Study Director or other qualified individual after examination of the rabbits.

Study rabbits found dead will have a complete necropsy, unless severely autolyzed.

All study rabbits will have final (fasted) body weights taken and will be bled for clinical pathology determinations prior to termination. A complete necropsy and all antemortem observations will be recorded for each study rabbit and commented on or confirmed at necropsy. Study rabbits which are clinically normal will also be so indicated. A pathologist will be available to examine any unusual findings.

Prior to fixing, tissues from major organs on the list below marked with an asterisk (*) will be weighed (paired organs will be weighed together) at terminal or recovery necropsy; the thyroid and parathyroid glands will be weighed together.

The tissues listed below will be examined, sampled and fixed in 10% neutral buffered formalin. The testes and epididymides will be fixed in Bouin's fixative. The eyes will be fixed in Davidson's solution. The rabbit identification number will be retained with tissues taken during necropsy.

* Adrenal glands (2)
  Aorta
  Bone with articular surface (femur)
  Bone marrow (femur)
* Brain (sections of medulla/pons, cerebellum and cerebral cortex)
  Cecum
  Colon
  Duodenum
  Epididymides
  Esophagus
  Eyes (2)
  Gall Bladder
* Gonads - Testes/ovaries (2)
  Gross lesions
* Heart
  Ileum
  Jejunum
* Kidneys (2)
* Liver
  Lungs (infuse with formalin)
  Lymph nodes (mandibular and mesenteric)
  Mammary gland (when present in regular abdominal skin section)
  Pancreas
* Parathyroid gland

Pituitary gland
Salivary glands (mandibular and parotid)
Sciatic nerve
Skeletal muscle
Skin (1. ventral abdomen; 2. injection site)
Spinal Cord (cervical, mid-thoracic and lumbar)
* Spleen
Stomach (cardiac, fundic, pyloric)
* Thymus
* Thyroid glands
Trachea
Urinary bladder
Uterine horn (2)

f. **Microscopic Pathology:**

Sections of the tissues from the high dose and control animals sacrificed on study day 15 and animals found dead or sacrificed moribund will be embedded, put into blocks, cut approximately 5 microns thick, stained with hematoxylin and eosin, and examined microscopically by a pathologist. Microscopic examination of target tissues in the low dose group will be done at additional expense. Microscopic examination of target tissues in recovery animals will be performed only in the dose groups which demonstrated the lesions seen on study day 15, in addition to corresponding recovery control animals.

Records of gross findings for a specimen from postmortem observations shall be available to the pathologist when examining that specimen histopathologically.

All lesions will be categorized either as drug-related or non-drug-related. Each lesion should be listed and coded by the most specific topographic and morphologic diagnoses, severity and distribution using the Pathology Terminology Guidelines of the Toxicology Data Management System (TDMS) for the National Toxicology Program (July, 1992).

D. <u>Statistical Analysis</u>

Statistical analysis of continuous data will be performed using analysis of variance, with post-hoc comparisons made using Dunnett's test. A minimum significance level of $p \leq 0.05$ will be used for all comparisons.

## III. QUALITY ASSURANCE

### A. Type of Study

This is a nonclinical laboratory study and will require compliance with the FDA Good Laboratory Practice Regulations. Data from this study will be included as part of a final report to be submitted to the FDA.

### B. Standard Operating Procedures

All operations pertaining to this study, unless specifically defined in this protocol, will be performed according to the standard operating procedures of the laboratory and any deviations will be documented.

### C. Protocol Amendments

All changes in or revisions of an approved protocol and the reasons therefore will be documented, signed, and dated by the Principal Investigator, Study Director and the NCI Project Officer. Amendments will be maintained with the protocol. Verbal approval for changes in the protocol may be granted by the NCI Project Officer, but a written amendment will follow.

### D. Records

Data will be audited by the IITRI Quality Assurance Unit. Study data will be archived in the IITRI archives for a period of one year from the date of completion of the study. At that time, the Sponsor will be contacted to determine the final disposition of the archival materials. IITRI's Quality Assurance Unit will maintain a complete record of the disposition of all archival materials.

## IV. REPORTING AND DISCUSSION OF DATA

### A. Progress Reports

Non-GLP status reports summarizing the progress of the study will be provided at monthly intervals. These reports will detail the status of the study on the reporting date, any problems encountered and proposed means of resolution.

### B. Final Report

The data and results of this study will be submitted as a separate draft report, due 60 working days after the last necropsy in this study. The final report will be due 15 working days after return of the draft report for revision.

This report will accurately and completely describe the study design, procedures and findings, present an analysis and summary of the data followed by the conclusions derived from the analyses. The report will also include: (a) a cover page which will include the title, contract number, authors, laboratory address, dates of initiation and completion, and sponsor; (b) an abstract to be placed at the beginning of the final report; (c) a comprehensive summary to be placed after the abstract; (d) a table of contents; (e) the signature of the Study Director and any others deemed necessary; (f) a statement prepared and signed by the Quality Assurance Unit; and (g) a statement of where the raw data records, reports and samples are stored. In addition to the appropriate number of paper copies of each report, an Electronic Copy should also be submitted. The data should be copied to a CD-ROM disk preferably as a text-based Acrobat pdf file.

## V. PROTOCOL APPROVALS

Study Director: William D. Johnson 5-13-04 (Date)

Principal Investigator: 5/13/04 (Date)

NCI Project Officer: 5/17/04 (Date)

# 14-DAY TOXICITY STUDY OF CuATSM / $H_2$ATSM (NSC-D729307) IN RABBITS

## PROTOCOL AMENDMENT #1

## I. NATURE OF REVISION

The analytical results for dose concentration, stability and homogeneity will be included in IITRI's Final Report; however, the methods used, data and the reporting of results will not be performed according to Good Laboratory Practice Regulations.

The formulation samples were shipped for analysis on June 1, 2004 to:

Dr. Ruiwen Zhang
Associate Professor
Department of Pharmacology and Toxicology
University of Alabama at Birmingham
1670 University Blvd., VH 124A
Birmingham, AL 35294-0019.

**REASON FOR CHANGE:** This change is at the request of the Sponsor.

## II. PROTOCOL AMENDMENT APPROVALS

Study Director: William D. Johnson — William D. Johnson, Ph.D., D.A.B.T. — 9-23-04 (Date)

Principal Investigator: — David L. McCormick, Ph.D., D.A.B.T. — 9/23/04 (Date)

NCI Project Officer: — Elizabeth R. Glaze, Ph.D. — 10/12/04 (Date)

# 14-DAY TOXICITY STUDY OF CuATSM / $H_2$ATSM (NSC-D729307) IN RABBITS

## PROTOCOL DEVIATION #1

**II.B.3. Care and Housing:** During the quarantine and treatment phases of the study the animal room was maintained between 16-23°C and 35-80% relative humidity (RH), rather than 18-26°C and 30-70% RH as per the protocol.

This deviation had no effect on the integrity of the study, as the excursions from the protocol specified ranges were infrequent and transient.

**APPROVAL:**

Study Director: William D. Johnson 10-25-04

William D. Johnson, Ph.D., D.A.B.T. Date

Appendix B. Individual Animal Data

Appendix B, Table 1

## INDIVIDUAL CLINICAL SIGNS

STUDY: 2073-002-003 GROUP: 1-M SEX: MALE
DAY 1-DAY 29 DOSE: 0 (mg/kg)

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | ONSET | DURATION | FREQUENCY |
|---|---|---|---|---|---|---|
| 1 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 2 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 3 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 4 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 5 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 6 | Recovery Sacrifice | | | DAY 29 | DAY 29 | 1 |
| | Normal | | | DAY 1 | DAY 29 | 29 |
| 7 | Recovery Sacrifice | | | DAY 29 | DAY 29 | 1 |
| | Normal | | | DAY 1 | DAY 29 | 29 |
| 8 | Recovery Sacrifice | | | DAY 29 | DAY 29 | 1 |
| | Normal | | | DAY 1 | DAY 29 | 29 |

Appendix B, Table 1 (cont.)

## INDIVIDUAL CLINICAL SIGNS

STUDY: 2073-002-003 GROUP: 2-M SEX: MALE
DAY 1-DAY 29 DOSE: 0.030(mg/kg)

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | ONSET | DURATION | FREQUENCY |
|---|---|---|---|---|---|---|
| 17 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 18 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 19 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 20 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 21 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 22 | Recovery Sacrifice | | | DAY 29 | DAY 29 | 1 |
| | Normal | | | DAY 1 | DAY 29 | 29 |
| 23 | Recovery Sacrifice | | | DAY 29 | DAY 29 | 1 |
| | Normal | | | DAY 1 | DAY 29 | 29 |
| 24 | Recovery Sacrifice | | | DAY 29 | DAY 29 | 1 |
| | Normal | | | DAY 1 | DAY 29 | 29 |

INDIVIDUAL CLINICAL SIGNS

STUDY: 2073-002-003 GROUP: 3-M SEX: MALE
DAY 1-DAY 29 DOSE: 0.060 (mg/kg)

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | ONSET | DURATION | FREQUENCY |
|---|---|---|---|---|---|---|
| 33 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 34 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 35 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 36 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 37 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 38 | Recovery Sacrifice | | | DAY 29 | DAY 29 | 1 |
| | Normal | | | DAY 1 | DAY 29 | 29 |
| 39 | Recovery Sacrifice | | | DAY 29 | DAY 29 | 1 |
| | Normal | | | DAY 1 | DAY 29 | 29 |
| 40 | Recovery Sacrifice | | | DAY 29 | DAY 29 | 1 |
| | Normal | | | DAY 1 | DAY 29 | 29 |

Appendix B, Table 1 (cont.)

INDIVIDUAL CLINICAL SIGNS

STUDY: 2073-002-003 GROUP: 1-F SEX: FEMALE
DAY 1-DAY 29 DOSE: 0 (mg/kg)

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | ONSET | DURATION | FREQUENCY |
|---|---|---|---|---|---|---|
| 9 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 10 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 11 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 12 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 13 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 14 | Recovery Sacrifice | | | DAY 29 | DAY 29 | 1 |
| | Normal | | | DAY 1 | DAY 29 | 29 |
| 15 | Recovery Sacrifice | | | DAY 29 | DAY 29 | 1 |
| | Normal | | | DAY 1 | DAY 29 | 29 |
| 16 | Recovery Sacrifice | | | DAY 29 | DAY 29 | 1 |
| | Normal | | | DAY 1 | DAY 29 | 29 |

Appendix B, Table 1 (cont.)

## INDIVIDUAL CLINICAL SIGNS

STUDY: 2073-002-003 GROUP: 2-F SEX: FEMALE
DAY 1-DAY 29 DOSE: 0.030(mg/kg)

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | ONSET | DURATION | FREQUENCY |
|---|---|---|---|---|---|---|
| 25 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 26 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 27 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 28 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 29 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 30 | Recovery Sacrifice | | | DAY 29 | DAY 29 | 1 |
| | Normal | | | DAY 1 | DAY 29 | 29 |
| 31 | Recovery Sacrifice | | | DAY 29 | DAY 29 | 1 |
| | Normal | | | DAY 1 | DAY 29 | 29 |
| 32 | Recovery Sacrifice | | | DAY 29 | DAY 29 | 1 |
| | Normal | | | DAY 1 | DAY 29 | 29 |

Appendix B, Table 1 (cont.)

INDIVIDUAL CLINICAL SIGNS

STUDY: 2073-002-003 GROUP: 3-F SEX: FEMALE
DAY 1-DAY 29 DOSE: 0.060(mg/kg)

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | ONSET | DURATION | FREQUENCY |
|---|---|---|---|---|---|---|
| 41 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 42 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 43 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 44 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 45 | Terminal Sacrifice | | | DAY 15 | DAY 15 | 1 |
| | Normal | | | DAY 1 | DAY 15 | 15 |
| 46 | Recovery Sacrifice | | | DAY 29 | DAY 29 | 1 |
| | Normal | | | DAY 1 | DAY 29 | 29 |
| 47 | Recovery Sacrifice | | | DAY 29 | DAY 29 | 1 |
| | Normal | | | DAY 1 | DAY 29 | 29 |
| 48 | Recovery Sacrifice | | | DAY 29 | DAY 29 | 1 |
| | Normal | | | DAY 1 | DAY 29 | 29 |

Appendix B, Table 2

**INDIVIDUAL BODY WEIGHTS** (Kilograms)

STUDY: 2073-002-003 GROUP: 1-M SEX: MALE
DOSE: 0 (mg/kg)

| ANIMAL # | DAY 1 | DAY 5 | DAY 8 | DAY 12 | DAY 14 |
|---|---|---|---|---|---|
| 1 | 3.63 | 3.72 | 3.75 | 3.86 | 3.90 |
| 2 | 3.53 | 3.56 | 3.57 | 3.66 | 3.70 |
| 3 | 3.39 | 3.42 | 3.24 | 3.40 | 3.41 |
| 4 | 3.26 | 3.29 | 3.30 | 3.39 | 3.42 |
| 5 | 3.23 | 3.27 | 3.30 | 3.35 | 3.39 |
| 6 | 3.27 | 3.44 | 3.49 | 3.58 | -- |
| 7 | 3.34 | 3.44 | 3.46 | 3.52 | -- |
| 8 | 3.08 | 3.07 | 3.04 | 3.10 | -- |
| MEAN | 3.34 | 3.40 | 3.39 | 3.48 | 3.56 |
| S.D. | 0.175 | 0.196 | 0.220 | 0.228 | 0.227 |
| N | 8 | 8 | 8 | 8 | 5 |

--: Data Unavailable

Appendix B, Table 2 (cont.)

**INDIVIDUAL BODY WEIGHTS** (Kilograms)

STUDY: 2073-002-003 GROUP: 2-M SEX: MALE
DOSE: 0.030 (mg/kg)

| ANIMAL # | DAY 1 | DAY 5 | DAY 8 | DAY 12 | DAY 14 |
|---|---|---|---|---|---|
| 17 | 3.31 | 3.41 | 3.39 | 3.47 | 3.50 |
| 18 | 3.17 | 3.18 | 3.25 | 3.27 | 3.29 |
| 19 | 3.35 | 3.44 | 3.47 | 3.56 | 3.65 |
| 20 | 3.45 | 3.53 | 3.54 | 3.64 | 3.69 |
| 21 | 3.41 | 3.47 | 3.52 | 3.60 | 3.64 |
| 22 | 3.38 | 3.25 | 3.33 | 3.33 | -- |
| 23 | 3.57 | 3.64 | 3.65 | 3.70 | -- |
| 24 | 3.07 | 3.07 | 3.05 | 3.08 | -- |
| MEAN | 3.34 | 3.37 | 3.40 | 3.46 | 3.55 |
| S.D. | 0.158 | 0.191 | 0.190 | 0.213 | 0.164 |
| N | 8 | 8 | 8 | 8 | 5 |

--: Data Unavailable

Appendix B, Table 2 (cont.)

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 2073-002-003 GROUP: 3-M SEX: MALE
DOSE: 0.060 (mg/kg)

| ANIMAL # | DAY 1 | DAY 5 | DAY 8 | DAY 12 | DAY 14 |
|---|---|---|---|---|---|
| 33 | 3.50 | 3.41 | 3.45 | 3.50 | 3.52 |
| 34 | 3.16 | 3.12 | 3.11 | 3.15 | 3.14 |
| 35 | 3.45 | 3.48 | 3.50 | 3.60 | 3.63 |
| 36 | 3.24 | 3.28 | 3.34 | 3.37 | 3.43 |
| 37 | 3.26 | 3.29 | 3.31 | 3.37 | 3.38 |
| 38 | 3.50 | 3.50 | 3.54 | 3.64 | -- |
| 39 | 3.39 | 3.42 | 3.48 | 3.57 | -- |
| 40 | 3.21 | 3.26 | 3.32 | 3.36 | -- |
| MEAN | 3.34 | 3.35 | 3.38 | 3.45 | 3.42 |
| S.D. | 0.137 | 0.129 | 0.140 | 0.163 | 0.183 |
| N | 8 | 8 | 8 | 8 | 5 |

--: Data Unavailable

Appendix B, Table 2 (cont.)

**INDIVIDUAL BODY WEIGHTS** (Kilograms)

STUDY: 2073-002-003 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg/kg)

| ANIMAL # | DAY 1 | DAY 5 | DAY 8 | DAY 12 | DAY 14 |
|---|---|---|---|---|---|
| 9 | 3.41 | 3.47 | 3.42 | 3.40 | 3.46 |
| 10 | 3.30 | 3.44 | 3.40 | 3.53 | 3.59 |
| 11 | 3.10 | 3.19 | 3.15 | 3.15 | 3.17 |
| 12 | 3.23 | 3.32 | 3.35 | 3.40 | 3.45 |
| 13 | 3.57 | 3.39 | 3.42 | 3.47 | 3.48 |
| 14 | 3.15 | 3.27 | 3.21 | 3.27 | -- |
| 15 | 3.26 | 3.28 | 3.32 | 3.41 | -- |
| 16 | 3.38 | 3.44 | 3.46 | 3.45 | -- |
| MEAN | 3.30 | 3.35 | 3.34 | 3.39 | 3.43 |
| S.D. | 0.151 | 0.100 | 0.110 | 0.121 | 0.156 |
| N | 8 | 8 | 8 | 8 | 5 |

--: Data Unavailable

**INDIVIDUAL BODY WEIGHTS** (Kilograms)

STUDY: 2073-002-003 GROUP: 2-F SEX: FEMALE
DOSE: 0.030 (mg/kg)

| ANIMAL # | DAY 1 | DAY 5 | DAY 8 | DAY 12 | DAY 14 |
|---|---|---|---|---|---|
| 25 | 3.33 | 3.32 | 3.31 | 3.34 | 3.34 |
| 26 | 3.09 | 3.08 | 3.09 | 3.12 | 3.15 |
| 27 | 3.13 | 3.19 | 3.23 | 3.25 | 3.28 |
| 28 | 3.45 | 3.45 | 3.44 | 3.44 | 3.45 |
| 29 | 3.31 | 3.43 | 3.46 | 3.55 | 3.54 |
| 30 | 3.52 | 3.56 | 3.64 | 3.43 | -- |
| 31 | 3.28 | 3.38 | 3.42 | 3.45 | -- |
| 32 | 3.22 | 3.34 | 3.34 | 3.42 | -- |
| MEAN | 3.29 | 3.34 | 3.37 | 3.38 | 3.35 |
| S.D. | 0.147 | 0.151 | 0.165 | 0.135 | 0.151 |
| N | 8 | 8 | 8 | 8 | 5 |

--: Data Unavailable

Appendix B, Table 2 (cont.)

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 2073-002-003 GROUP: 3-F SEX: FEMALE
DOSE: 0.060 (mg/kg)

| ANIMAL # | DAY 1 | DAY 5 | DAY 8 | DAY 12 | DAY 14 |
|---|---|---|---|---|---|
| 41 | 3.22 | 3.35 | 3.29 | 3.40 | 3.44 |
| 42 | 3.49 | 3.47 | 3.34 | 3.48 | 3.53 |
| 43 | 3.13 | 3.16 | 3.19 | 3.22 | 3.22 |
| 44 | 3.27 | 3.36 | 3.39 | 3.47 | 3.50 |
| 45 | 3.29 | 3.33 | 3.31 | 3.39 | 3.37 |
| 46 | 3.10 | 3.08 | 3.12 | 3.18 | -- |
| 47 | 3.42 | 3.28 | 3.32 | 3.45 | -- |
| 48 | 3.50 | 3.50 | 3.39 | 3.50 | -- |
| MEAN | 3.30 | 3.32 | 3.29 | 3.39 | 3.41 |
| S.D. | 0.154 | 0.143 | 0.095 | 0.121 | 0.124 |
| N | 8 | 8 | 8 | 8 | 5 |

--: Data Unavailable

Appendix B, Table 2 (cont.)
(Recovery)

**INDIVIDUAL BODY WEIGHTS** (Kilograms)

STUDY: 2073-002-003 GROUP: 1-M SEX: MALE
DOSE: 0 (mg/kg)

| ANIMAL # | DAY 15 | DAY 22 | DAY 28 |
|---|---|---|---|
| 6 | 3.71 | 3.67 | 3.70 |
| 7 | 3.59 | 3.67 | 3.72 |
| 8 | 3.12 | 3.15 | 3.22 |
| MEAN | 3.47 | 3.50 | 3.55 |
| S.D. | 0.312 | 0.300 | 0.283 |
| N | 3 | 3 | 3 |

Appendix B, Table 2 (cont.)
(Recovery)

**INDIVIDUAL BODY WEIGHTS** (Kilograms)

STUDY: 2073-002-003 GROUP: 2-M SEX: MALE
DOSE: 0.030 (mg/kg)

| ANIMAL # | DAY 15 | DAY 22 | DAY 28 |
|---|---|---|---|
| 22 | 3.44 | 3.38 | 3.43 |
| 23 | 3.75 | 3.81 | 3.87 |
| 24 | 3.09 | 3.14 | 3.20 |
| MEAN | 3.43 | 3.44 | 3.50 |
| S.D. | 0.330 | 0.339 | 0.340 |
| N | 3 | 3 | 3 |

Appendix B, Table 2 (cont.)
(Recovery)

**INDIVIDUAL BODY WEIGHTS** (Kilograms)

STUDY: 2073-002-003 GROUP: 3-M SEX: MALE
DOSE: 0.060 (mg/kg)

| ANIMAL # | DAY 15 | DAY 22 | DAY 28 |
|---|---|---|---|
| 38 | 3.75 | 3.78 | 3.87 |
| 39 | 3.65 | 3.65 | 3.68 |
| 40 | 3.41 | 3.37 | 3.39 |
| MEAN | 3.60 | 3.60 | 3.65 |
| S.D. | 0.175 | 0.210 | 0.242 |
| N | 3 | 3 | 3 |

Appendix B, Table 2 (cont.)
(Recovery)

**INDIVIDUAL BODY WEIGHTS** (Kilograms)

STUDY: 2073-002-003 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg/kg)

| ANIMAL # | DAY 15 | DAY 22 | DAY 28 |
|---|---|---|---|
| 14 | 3.30 | 3.26 | 3.30 |
| 15 | 3.44 | 3.47 | 3.51 |
| 16 | 3.55 | 3.56 | 3.61 |
| MEAN | 3.43 | 3.43 | 3.47 |
| S.D. | 0.125 | 0.154 | 0.158 |
| N | 3 | 3 | 3 |

Appendix B, Table 2 (cont.)
(Recovery)

**INDIVIDUAL BODY WEIGHTS** (Kilograms)

STUDY: 2073-002-003 GROUP: 2-F SEX: FEMALE
DOSE: 0.030 (mg/kg)

| ANIMAL # | DAY 15 | DAY 22 | DAY 28 |
|---|---|---|---|
| 30 | 3.54 | 3.71 | 3.81 |
| 31 | 3.59 | 3.54 | 3.55 |
| 32 | 3.48 | 3.61 | 3.68 |
| MEAN | 3.54 | 3.62 | 3.68 |
| S.D. | 0.055 | 0.085 | 0.130 |
| N | 3 | 3 | 3 |

Appendix B, Table 2 (cont.)
(Recovery)

INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 2073-002-003 GROUP: 3-F SEX: FEMALE
DOSE: 0.060 (mg/kg)

| ANIMAL # | DAY 15 | DAY 22 | DAY 28 |
|---|---|---|---|
| 46 | 3.22 | 3.31 | 3.36 |
| 47 | 3.46 | 3.62 | 3.69 |
| 48 | 3.51 | 3.64 | 3.70 |
| MEAN | 3.40 | 3.52 | 3.58 |
| S.D. | 0.155 | 0.185 | 0.193 |
| N | 3 | 3 | 3 |

## 14-DAY TOXICITY STUDY OF CuATSM/$H_2$ATSM (NSC-D729307) IN RABBITS

Appendix B, Table 3

**INDIVIDUAL WEIGHT GAIN** (Kilograms)

STUDY: 2073-002-003 GROUP: 1-M SEX: MALE
DOSE: 0 (mg/kg)

| ANIMAL # | DAY 5 | DAY 8 | DAY 12 | DAY 14 | TOTAL GAIN |
|---|---|---|---|---|---|
| 1 | 0.09 | 0.03 | 0.11 | 0.04 | 0.27 |
| 2 | 0.03 | 0.01 | 0.09 | 0.04 | 0.17 |
| 3 | 0.03 | -0.18 | 0.16 | 0.01 | 0.02 |
| 4 | 0.03 | 0.01 | 0.09 | 0.03 | 0.16 |
| 5 | 0.04 | 0.03 | 0.05 | 0.04 | 0.16 |
| 6 | 0.17 | 0.05 | 0.09 | -- | -- |
| 7 | 0.10 | 0.02 | 0.06 | -- | -- |
| 8 | -0.01 | -0.03 | 0.06 | -- | -- |
| MEAN | 0.06 | -0.01 | 0.09 | 0.03 | 0.16 |
| S.D. | 0.057 | 0.073 | 0.035 | 0.013 | 0.089 |
| N | 8 | 8 | 8 | 5 | 5 |

--: Data Unavailable

Appendix B, Table 3 (cont.)

**INDIVIDUAL WEIGHT GAIN** (Kilograms)

STUDY: 2073-002-003 GROUP: 2-M SEX: MALE
DOSE: 0.030 (mg/kg)

| ANIMAL # | DAY 5 | DAY 8 | DAY 12 | DAY 14 | TOTAL GAIN |
|---|---|---|---|---|---|
| 17 | 0.10 | -0.02 | 0.08 | 0.03 | 0.19 |
| 18 | 0.01 | 0.07 | 0.02 | 0.02 | 0.12 |
| 19 | 0.09 | 0.03 | 0.09 | 0.09 | 0.30 |
| 20 | 0.08 | 0.01 | 0.10 | 0.05 | 0.24 |
| 21 | 0.06 | 0.05 | 0.08 | 0.04 | 0.23 |
| 22 | -0.13 | 0.08 | 0.00 | -- | -- |
| 23 | 0.07 | 0.01 | 0.05 | -- | -- |
| 24 | 0.00 | -0.02 | 0.03 | -- | -- |
| MEAN | 0.04 | 0.03 | 0.06 | 0.05 | 0.22 |
| S.D. | 0.076 | 0.038 | 0.037 | 0.027 | 0.067 |
| N | 8 | 8 | 8 | 5 | 5 |

--: Data Unavailable

Appendix B, Table 3 (cont.)

**INDIVIDUAL WEIGHT GAIN** (Kilograms)

STUDY: 2073-002-003 GROUP: 3-M SEX: MALE
DOSE: 0.060 (mg/kg)

| ANIMAL # | DAY 5 | DAY 8 | DAY 12 | DAY 14 | TOTAL GAIN |
|---|---|---|---|---|---|
| 33 | -0.09 | 0.04 | 0.05 | 0.02 | 0.02 |
| 34 | -0.04 | -0.01 | 0.04 | -0.01 | -0.02 |
| 35 | 0.03 | 0.02 | 0.10 | 0.03 | 0.18 |
| 36 | 0.04 | 0.06 | 0.03 | 0.06 | 0.19 |
| 37 | 0.03 | 0.02 | 0.06 | 0.01 | 0.12 |
| 38 | 0.00 | 0.04 | 0.10 | -- | -- |
| 39 | 0.03 | 0.06 | 0.09 | -- | -- |
| 40 | 0.05 | 0.06 | 0.04 | -- | -- |
| MEAN | 0.01 | 0.04 | 0.06 | 0.02 | 0.10 |
| S.D. | 0.048 | 0.025 | 0.029 | 0.026 | 0.094 |
| N | 8 | 8 | 8 | 5 | 5 |

--: Data Unavailable

Appendix B, Table 3 (cont.)

**INDIVIDUAL WEIGHT GAIN** (Kilograms)

STUDY: 2073-002-003 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg/kg)

| ANIMAL # | DAY 5 | DAY 8 | DAY 12 | DAY 14 | TOTAL GAIN |
|---|---|---|---|---|---|
| 9 | 0.06 | -0.05 | -0.02 | 0.06 | 0.05 |
| 10 | 0.14 | -0.04 | 0.13 | 0.06 | 0.29 |
| 11 | 0.09 | -0.04 | 0.00 | 0.02 | 0.07 |
| 12 | 0.09 | 0.03 | 0.05 | 0.05 | 0.22 |
| 13 | -0.18 | 0.03 | 0.05 | 0.01 | -0.09 |
| 14 | 0.12 | -0.06 | 0.06 | -- | -- |
| 15 | 0.02 | 0.04 | 0.09 | -- | -- |
| 16 | 0.06 | 0.02 | -0.01 | -- | -- |
| MEAN | 0.05 | -0.01 | 0.04 | 0.04 | 0.11 |
| S.D. | 0.100 | 0.042 | 0.052 | 0.023 | 0.150 |
| N | 8 | 8 | 8 | 5 | 5 |

--: Data Unavailable

Appendix B, Table 3 (cont.)

**INDIVIDUAL WEIGHT GAIN** (Kilograms)

STUDY: 2073-002-003 GROUP: 2-F SEX: FEMALE
DOSE: 0.030 (mg/kg)

| ANIMAL # | DAY 5 | DAY 8 | DAY 12 | DAY 14 | TOTAL GAIN |
|---|---|---|---|---|---|
| 25 | -0.01 | -0.01 | 0.03 | 0.00 | 0.01 |
| 26 | -0.01 | 0.01 | 0.03 | 0.03 | 0.06 |
| 27 | 0.06 | 0.04 | 0.02 | 0.03 | 0.15 |
| 28 | 0.00 | -0.01 | 0.00 | 0.01 | 0.00 |
| 29 | 0.12 | 0.03 | 0.09 | -0.01 | 0.23 |
| 30 | 0.04 | 0.08 | -0.21 | -- | -- |
| 31 | 0.10 | 0.04 | 0.03 | -- | -- |
| 32 | 0.12 | 0.00 | 0.08 | -- | -- |
| MEAN | 0.05 | 0.02 | 0.01 | 0.01 | 0.09 |
| S.D. | 0.056 | 0.031 | 0.093 | 0.018 | 0.098 |
| N | 8 | 8 | 8 | 5 | 5 |

--: Data Unavailable

Appendix B, Table 3 (cont.)

**INDIVIDUAL WEIGHT GAIN** (Kilograms)

STUDY: 2073-002-003 GROUP: 3-F SEX: FEMALE
DOSE: 0.060 (mg/kg)

| ANIMAL # | DAY 5 | DAY 8 | DAY 12 | DAY 14 | TOTAL GAIN |
|---|---|---|---|---|---|
| 41 | 0.13 | -0.06 | 0.11 | 0.04 | 0.22 |
| 42 | -0.02 | -0.13 | 0.14 | 0.05 | 0.04 |
| 43 | 0.03 | 0.03 | 0.03 | 0.00 | 0.09 |
| 44 | 0.09 | 0.03 | 0.08 | 0.03 | 0.23 |
| 45 | 0.04 | -0.02 | 0.08 | -0.02 | 0.08 |
| 46 | -0.02 | 0.04 | 0.06 | -- | -- |
| 47 | -0.14 | 0.04 | 0.13 | -- | -- |
| 48 | 0.00 | -0.11 | 0.11 | -- | -- |
| MEAN | 0.01 | -0.02 | 0.09 | 0.02 | 0.13 |
| S.D. | 0.081 | 0.070 | 0.037 | 0.029 | 0.087 |
| N | 8 | 8 | 8 | 5 | 5 |

--: Data Unavailable

Appendix B, Table 3 (cont.)
(Recovery)

**INDIVIDUAL WEIGHT GAIN** (Kilograms)

STUDY: 2073-002-003 GROUP: 1-M SEX: MALE
DOSE: 0 (mg/kg)

| ANIMAL # | DAY 15 | DAY 22 | DAY 28 | TOTAL GAIN # |
|---|---|---|---|---|
| 6 | 0.13 | -0.04 | 0.03 | 0.12 |
| 7 | 0.07 | 0.08 | 0.05 | 0.20 |
| 8 | 0.02 | 0.03 | 0.07 | 0.12 |
| MEAN | 0.07 | 0.02 | 0.05 | 0.15 |
| S.D. | 0.055 | 0.060 | 0.020 | 0.046 |
| N | 3 | 3 | 3 | 3 |

# Days 1 through 28

Appendix B, Table 3 (cont.)
(Recovery)

**INDIVIDUAL WEIGHT GAIN** (Kilograms)

STUDY: 2073-002-003 GROUP: 2-M SEX: MALE
DOSE: 0.030 (mg/kg)

| ANIMAL # | DAY 15 | DAY 22 | DAY 28 | TOTAL GAIN # |
|---|---|---|---|---|
| 22 | 0.11 | -0.06 | 0.05 | 0.10 |
| 23 | 0.05 | 0.06 | 0.06 | 0.17 |
| 24 | 0.01 | 0.05 | 0.06 | 0.12 |
| MEAN | 0.06 | 0.02 | 0.06 | 0.13 |
| S.D. | 0.050 | 0.067 | 0.006 | 0.036 |
| N | 3 | 3 | 3 | 3 |

# Days 1 through 28

Appendix B, Table 3 (cont.)
(Recovery)

**INDIVIDUAL WEIGHT GAIN** (Kilograms)

STUDY: 2073-002-003 GROUP: 3-M SEX: MALE
DOSE: 0.060 (mg/kg)

| ANIMAL # | DAY 15 | DAY 22 | DAY 28 | TOTAL GAIN # |
|---|---|---|---|---|
| 38 | 0.11 | 0.03 | 0.09 | 0.23 |
| 39 | 0.08 | 0.00 | 0.03 | 0.11 |
| 40 | 0.05 | -0.04 | 0.02 | 0.03 |
| MEAN | 0.08 | 0.00 | 0.05 | 0.12 |
| S.D. | 0.030 | 0.035 | 0.038 | 0.101 |
| N | 3 | 3 | 3 | 3 |

# Days 1 through 28

Appendix B, Table 3 (cont.)
(Recovery)

**INDIVIDUAL WEIGHT GAIN** (Kilograms)

STUDY: 2073-002-003 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg/kg)

| ANIMAL # | DAY 15 | DAY 22 | DAY 28 | TOTAL GAIN # |
|---|---|---|---|---|
| 14 | 0.03 | -0.04 | 0.04 | 0.03 |
| 15 | 0.03 | 0.03 | 0.04 | 0.10 |
| 16 | 0.10 | 0.01 | 0.05 | 0.16 |
| MEAN | 0.05 | 0.00 | 0.04 | 0.10 |
| S.D. | 0.040 | 0.036 | 0.006 | 0.065 |
| N | 3 | 3 | 3 | 3 |

# Days 1 through 28

Appendix B, Table 3 (cont.)
(Recovery)

**INDIVIDUAL WEIGHT GAIN** (Kilograms)

STUDY: 2073-002-003 GROUP: 2-F SEX: FEMALE
DOSE: 0.030 (mg/kg)

| ANIMAL # | DAY 15 | DAY 22 | DAY 28 | TOTAL GAIN # |
|---|---|---|---|---|
| 30 | 0.11 | 0.17 | 0.10 | 0.38 |
| 31 | 0.14 | -0.05 | 0.01 | 0.10 |
| 32 | 0.06 | 0.13 | 0.07 | 0.26 |
| MEAN | 0.10 | 0.08 | 0.06 | 0.25 |
| S.D. | 0.040 | 0.117 | 0.046 | 0.140 |
| N | 3 | 3 | 3 | 3 |

# Days 1 through 28

Appendix B, Table 3 (cont.)
(Recovery)

**INDIVIDUAL WEIGHT GAIN** (Kilograms)

STUDY: 2073-002-003 GROUP: 3-F SEX: FEMALE
DOSE: 0.060 (mg/kg)

| ANIMAL # | DAY 15 | DAY 22 | DAY 28 | TOTAL GAIN # |
|---|---|---|---|---|
| 46 | 0.04 | 0.09 | 0.05 | 0.18 |
| 47 | 0.01 | 0.16 | 0.07 | 0.24 |
| 48 | 0.01 | 0.13 | 0.06 | 0.20 |
| MEAN | 0.02 | 0.13 | 0.06 | 0.21 |
| S.D. | 0.017 | 0.035 | 0.010 | 0.031 |
| N | 3 | 3 | 3 | 3 |

# Days 1 through 28

Appendix B, Table 4

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: MALE

| Animal ID | WBC x10e3/uL | RBC x10e6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT x10e3/uL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| 1 | 6.92 | 5.77 | 12.1 | 37.2 | 64.4 | 20.9 | 32.5 | 384 |
| 2 | 9.23 | 6.23 | 13.7 | 41.2 | 66.2 | 21.9 | 33.1 | 435 |
| 3 | 6.58 | 6.26 | 13.9 | 39.0 | 62.3 | 22.2 | 35.7 | 331 |
| 4 | 10.17 | 5.97 | 13.0 | 37.6 | 63.0 | 21.8 | 34.6 | 327 |
| 5 | 8.65 | 5.87 | 12.9 | 39.5 | 67.3 | 22.0 | 32.6 | 390 |
| 6 | 10.67 | 6.18 | 13.3 | 40.3 | 65.1 | 21.5 | 33.0 | 389 |
| 7 | 10.67 | 5.93 | 12.6 | 37.5 | 63.2 | 21.3 | 33.6 | 465 |
| 8 | 11.87 | 6.50 | 13.6 | 39.6 | 60.9 | 20.9 | 34.4 | 233 |
| MEAN | 9.35 | 6.09 | 13.1 | 39.0 | 64.1 | 21.6 | 33.7 | 369 |
| SD | 1.874 | 0.244 | 0.61 | 1.44 | 2.11 | 0.50 | 1.12 | 72.1 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 17 | 10.64 | 6.17 | 13.1 | 39.2 | 63.6 | 21.2 | 33.3 | 332 |
| 18 | 12.03 | 6.22 | 13.0 | 38.8 | 62.4 | 20.9 | 33.6 | 342 |
| 19 | 9.91 | 5.74 | 11.6 | 36.5 | 63.6 | 20.2 | 31.7 | 345 |
| 20 | 9.87 | 6.53 | 13.2 | 40.8 | 62.6 | 20.3 | 32.4 | 447 |
| 21 | 9.34 | 5.50 | 11.6 | 36.2 | 65.9 | 21.1 | 32.0 | 285 |
| 22 | 13.90 | 6.03 | 12.8 | 37.9 | 62.8 | 21.2 | 33.8 | 378 |
| 23 | 8.98 | 5.39 | 12.2 | 36.3 | 67.4 | 22.6 | 33.5 | 370 |
| 24 | 9.43 | 7.57 | 14.4 | 44.6 | 58.9 | 19.0 | 32.3 | 329 |
| MEAN | 10.51 | 6.14 | 12.7 | 38.8 | 63.4 | 20.8 | 32.8 | 354 |
| SD | 1.668 | 0.692 | 0.93 | 2.85 | 2.52 | 1.04 | 0.81 | 47.2 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: MALE

| Animal ID | WBC x10e3/uL | RBC x10e6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT x10e3/uL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 33 | 9.92 | 6.49 | 13.3 | 40.7 | 62.7 | 20.4 | 32.6 | 369 |
| 34 | 9.16 | 6.57 | 14.2 | 40.8 | 62.0 | 21.6 | 34.8 | 335 |
| 35 | 11.74 | 5.68 | 12.2 | 37.8 | 66.6 | 21.5 | 32.2 | 350 |
| 36 | 8.72 | 5.79 | 13.0 | 39.5 | 68.2 | 22.4 | 32.8 | 335 |
| 37 | 7.40 | 6.35 | 13.8 | 41.8 | 65.8 | 21.7 | 33.0 | 420 |
| 38 | 7.78 | 6.07 | 13.1 | 38.0 | 62.7 | 21.5 | 34.3 | 367 |
| 39 | 8.20 | 5.72 | 13.0 | 37.4 | 65.4 | 22.7 | 34.7 | 295 |
| 40 | 9.33 | 6.46 | 13.3 | 39.9 | 61.8 | 20.7 | 33.4 | 275 |
| MEAN | 9.03 | 6.14 | 13.2 | 39.5 | 64.4 | 21.6 | 33.5 | 343 |
| SD | 1.376 | 0.372 | 0.59 | 1.61 | 2.41 | 0.77 | 1.00 | 45.2 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: MALE

| Animal ID | %RETIC % | #RETIC x10e9/L | %NEUT % | %LYMPH % | %MONO % | %EOS % | %BASO % | %LUC % |
|---|---|---|---|---|---|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| 1 | 2.4 | 138.7 | 19.0 | 73.4 | 0.7 | 1.7 | 5.0 | 0.3 |
| 2 | 2.1 | 133.2 | 8.8 | 86.9 | 1.1 | 1.2 | 1.9 | 0.1 |
| 3 | 1.6 | 103.0 | 18.8 | 72.4 | 0.7 | 2.3 | 5.5 | 0.2 |
| 4 | 1.6 | 98.0 | 14.4 | 74.4 | 1.9 | 2.0 | 7.0 | 0.4 |
| 5 | 1.8 | 103.5 | 8.9 | 84.5 | 1.1 | 1.5 | 3.8 | 0.1 |
| 6 | 2.0 | 126.3 | 16.3 | 77.3 | 1.1 | 1.8 | 3.3 | 0.2 |
| 7 | 2.1 | 125.6 | 9.7 | 82.8 | 0.4 | 1.9 | 5.0 | 0.2 |
| 8 | 2.4 | 154.1 | 21.6 | 71.1 | 0.8 | 1.2 | 5.0 | 0.2 |
| MEAN | 2.0 | 122.8 | 14.7 | 77.8 | 1.0 | 1.7 | 4.6 | 0.2 |
| SD | 0.32 | 19.79 | 5.06 | 6.07 | 0.45 | 0.39 | 1.54 | 0.10 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 17 | 2.3 | 142.4 | 21.9 | 69.7 | 0.8 | 1.2 | 6.2 | 0.1 |
| 18 | 1.4 | 90.2 | 15.7 | 77.9 | 0.8 | 1.3 | 4.2 | 0.2 |
| 19 | 1.9 | 107.3 | 20.5 | 72.8 | 1.2 | 2.1 | 2.9 | 0.4 |
| 20 | 1.6 | 102.9 | 12.4 | 81.8 | 1.0 | 0.8 | 3.8 | 0.1 |
| 21 | 2.8 | 154.5 | 17.8 | 75.4 | 0.9 | 1.8 | 4.1 | 0.1 |
| 22 | 1.7 | 100.6 | 16.5 | 76.8 | 0.7 | 1.4 | 4.4 | 0.1 |
| 23 | 2.6 | 141.4 | 16.3 | 77.9 | 1.1 | 1.4 | 3.1 | 0.3 |
| 24 | 1.6 | 124.7 | 11.7 | 81.5 | 1.2 | 1.3 | 4.2 | 0.1 |
| MEAN | 2.0 | 120.5 | 16.6 | 76.7 | 1.0 | 1.4 | 4.1 | 0.2 |
| SD | 0.52 | 23.57 | 3.53 | 4.10 | 0.19 | 0.39 | 1.00 | 0.12 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: MALE

| Animal ID | %RETIC % | #RETIC x10e9/L | %NEUT % | %LYMPH % | %MONO % | %EOS % | %BASO % | %LUC % |
|---|---|---|---|---|---|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 33 | 1.7 | 112.6 | 16.3 | 75.7 | 1.2 | 1.8 | 4.8 | 0.2 |
| 34 | 1.5 | 100.9 | 13.7 | 76.4 | 2.2 | 2.1 | 5.0 | 0.7 |
| 35 | 3.4 | 193.8 | 21.5 | 71.3 | 2.4 | 1.2 | 3.3 | 0.3 |
| 36 | 2.4 | 136.5 | 12.5 | 79.5 | 1.5 | 1.4 | 4.7 | 0.4 |
| 37 | 3.0 | 187.7 | 20.1 | 71.6 | 1.8 | 2.3 | 4.1 | 0.1 |
| 38 | 1.5 | 93.7 | 17.7 | 76.0 | 0.7 | 1.5 | 3.9 | 0.3 |
| 39 | 1.6 | 93.6 | 22.5 | 63.3 | 1.0 | 3.3 | 9.7 | 0.2 |
| 40 | 2.0 | 128.1 | 18.2 | 74.9 | 0.6 | 1.5 | 4.7 | 0.1 |
| MEAN | 2.1 | 130.9 | 17.8 | 73.6 | 1.4 | 1.9 | 5.0 | 0.3 |
| SD | 0.73 | 40.06 | 3.55 | 4.93 | 0.67 | 0.68 | 1.97 | 0.20 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: MALE

| Animal ID | #NEUT x10e3/uL | #LYMPH x10e3/uL | #MONO x10e3/uL | #EOS x10e3/uL | #BASO x10e3/uL | #LUC x10e3/uL |
|---|---|---|---|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | |
| 1 | 1.31 | 5.08 | 0.05 | 0.12 | 0.34 | 0.02 |
| 2 | 0.81 | 8.03 | 0.10 | 0.11 | 0.18 | 0.01 |
| 3 | 1.24 | 4.77 | 0.05 | 0.15 | 0.36 | 0.01 |
| 4 | 1.46 | 7.56 | 0.19 | 0.20 | 0.71 | 0.04 |
| 5 | 0.77 | 7.31 | 0.10 | 0.13 | 0.33 | 0.01 |
| 6 | 1.74 | 8.25 | 0.12 | 0.19 | 0.35 | 0.02 |
| 7 | 1.04 | 8.84 | 0.04 | 0.20 | 0.53 | 0.02 |
| 8 | 2.57 | 8.44 | 0.10 | 0.14 | 0.59 | 0.03 |
| MEAN | 1.37 | 7.29 | 0.09 | 0.16 | 0.42 | 0.02 |
| SD | 0.584 | 1.535 | 0.049 | 0.037 | 0.171 | 0.011 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 17 | 2.33 | 7.42 | 0.09 | 0.13 | 0.66 | 0.02 |
| 18 | 1.88 | 9.38 | 0.09 | 0.16 | 0.50 | 0.02 |
| 19 | 2.03 | 7.21 | 0.12 | 0.21 | 0.29 | 0.04 |
| 20 | 1.22 | 8.08 | 0.10 | 0.08 | 0.38 | 0.01 |
| 21 | 1.66 | 7.04 | 0.08 | 0.17 | 0.38 | 0.01 |
| 22 | 2.29 | 10.68 | 0.10 | 0.19 | 0.62 | 0.02 |
| 23 | 1.46 | 6.99 | 0.09 | 0.12 | 0.28 | 0.02 |
| 24 | 1.10 | 7.68 | 0.11 | 0.13 | 0.40 | 0.01 |
| MEAN | 1.75 | 8.06 | 0.10 | 0.15 | 0.44 | 0.02 |
| SD | 0.466 | 1.313 | 0.013 | 0.042 | 0.142 | 0.010 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: MALE

| Animal ID | #NEUT x10e3/uL | #LYMPH x10e3/uL | #MONO x10e3/uL | #EOS x10e3/uL | #BASO x10e3/uL | #LUC x10e3/uL |
|---|---|---|---|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 33 | 1.61 | 7.52 | 0.12 | 0.18 | 0.47 | 0.02 |
| 34 | 1.26 | 6.99 | 0.20 | 0.19 | 0.46 | 0.06 |
| 35 | 2.53 | 8.37 | 0.28 | 0.14 | 0.38 | 0.03 |
| 36 | 1.09 | 6.94 | 0.13 | 0.12 | 0.41 | 0.03 |
| 37 | 1.49 | 5.30 | 0.13 | 0.17 | 0.30 | 0.01 |
| 38 | 1.37 | 5.91 | 0.05 | 0.12 | 0.30 | 0.02 |
| 39 | 1.85 | 5.19 | 0.08 | 0.27 | 0.79 | 0.01 |
| 40 | 1.69 | 6.99 | 0.05 | 0.14 | 0.44 | 0.01 |
| MEAN | 1.61 | 6.65 | 0.13 | 0.17 | 0.44 | 0.02 |
| SD | 0.443 | 1.104 | 0.078 | 0.050 | 0.155 | 0.017 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: FEMALE

| Animal ID | WBC x10e3/uL | RBC x10e6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT x10e3/uL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| 9 | 6.54 | 5.92 | 13.2 | 39.2 | 66.3 | 22.4 | 33.8 | 400 |
| 10 | 7.71 | 5.58 | 12.4 | 37.6 | 67.4 | 22.3 | 33.0 | 407 |
| 11 | 9.40 | 6.56 | 13.8 | 42.6 | 64.9 | 21.1 | 32.5 | 522 |
| 12 | 8.17 | 5.63 | 12.1 | 35.9 | 63.9 | 21.4 | 33.5 | 380 |
| 13 | 9.29 | 6.21 | 13.5 | 43.7 | 70.3 | 21.7 | 30.9 | 469 |
| 14 | 10.89 | 6.45 | 14.1 | 40.5 | 62.8 | 21.8 | 34.7 | 201 |
| 15 | 8.55 | 6.59 | 13.2 | 40.5 | 61.6 | 20.1 | 32.6 | 231 |
| 16 | 9.72 | 6.04 | 12.7 | 38.7 | 64.1 | 21.0 | 32.8 | 594 |
| MEAN | 8.78 | 6.12 | 13.1 | 39.8 | 65.2 | 21.5 | 33.0 | 401 |
| SD | 1.340 | 0.398 | 0.69 | 2.55 | 2.77 | 0.75 | 1.11 | 134.1 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 25 | 8.84 | 5.25 | 11.4 | 33.9 | 64.6 | 21.7 | 33.5 | 379 |
| 26 | 7.30 | 6.59 | 13.2 | 39.0 | 59.2 | 20.1 | 33.9 | 270 |
| 27 | 8.16 | 7.21 | 14.2 | 45.2 | 62.7 | 19.7 | 31.4 | 406 |
| 28 | 9.57 | 6.22 | 13.1 | 40.4 | 65.0 | 21.1 | 32.5 | 336 |
| 29 | 11.97 | 5.79 | 12.4 | 38.1 | 65.8 | 21.5 | 32.6 | 281 |
| 30 | 10.99 | 5.79 | 12.4 | 37.6 | 64.9 | 21.3 | 32.9 | 428 |
| 31 | 7.05 | 6.19 | 12.8 | 38.2 | 61.7 | 20.7 | 33.6 | 282 |
| 32 | 10.06 | 5.69 | 13.1 | 38.7 | 68.0 | 23.0 | 33.8 | 199 |
| MEAN | 9.24 | 6.09 | 12.8 | 38.9 | 64.0 | 21.1 | 33.0 | 323 |
| SD | 1.740 | 0.607 | 0.81 | 3.16 | 2.71 | 1.02 | 0.85 | 78.2 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: FEMALE

| Animal ID | WBC x10e3/uL | RBC x10e6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT x10e3/uL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 41 | 7.74 | 5.48 | 11.4 | 35.7 | 65.2 | 20.9 | 32.0 | 289 |
| 42 | 7.01 | 6.00 | 13.3 | 42.1 | 70.2 | 22.2 | 31.6 | 498 |
| 43 | 9.12 | 6.27 | 12.4 | 37.7 | 60.2 | 19.8 | 32.9 | 332 |
| 44 | 8.62 | 6.19 | 13.0 | 39.3 | 63.5 | 21.1 | 33.2 | 28 |
| 45 | 10.24 | 6.49 | 12.7 | 39.8 | 61.4 | 19.6 | 31.9 | 298 |
| 46 | 10.05 | 5.88 | 13.1 | 39.5 | 67.1 | 22.4 | 33.3 | 315 |
| 47 | 9.28 | 6.34 | 13.3 | 39.7 | 62.6 | 21.0 | 33.5 | 513 |
| 48 | 8.70 | 6.76 | 13.8 | 41.1 | 60.7 | 20.4 | 33.6 | 199 |
| MEAN | 8.85 | 6.18 | 12.9 | 39.4 | 63.9 | 20.9 | 32.8 | 309 |
| SD | 1.090 | 0.393 | 0.73 | 1.96 | 3.46 | 1.01 | 0.79 | 155.6 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: FEMALE

| Animal ID | %RETIC % | #RETIC x10e9/L | %NEUT % | %LYMPH % | %MONO % | %EOS % | %BASO % | %LUC % |
|---|---|---|---|---|---|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| 9 | 1.7 | 99.5 | 25.2 | 69.6 | 0.5 | 1.6 | 3.0 | 0.2 |
| 10 | 5.6 | 311.8 | 25.2 | 61.9 | 2.8 | 3.1 | 6.4 | 0.6 |
| 11 | 1.4 | 88.8 | 18.6 | 70.3 | 1.1 | 1.7 | 8.0 | 0.3 |
| 12 | 1.6 | 87.2 | 19.2 | 72.1 | 0.7 | 1.8 | 6.0 | 0.1 |
| 13 | 1.5 | 95.5 | 19.5 | 73.6 | 1.5 | 1.0 | 4.2 | 0.2 |
| 14 | 2.0 | 127.8 | 18.8 | 71.6 | 1.1 | 2.8 | 5.7 | 0.1 |
| 15 | 2.1 | 138.9 | 22.2 | 65.9 | 1.3 | 3.3 | 7.1 | 0.2 |
| 16 | 1.9 | 116.0 | 19.9 | 70.1 | 1.0 | 2.5 | 6.3 | 0.2 |
| MEAN | 2.2 | 133.2 | 21.1 | 69.4 | 1.3 | 2.2 | 5.8 | 0.2 |
| SD | 1.39 | 74.55 | 2.78 | 3.77 | 0.70 | 0.82 | 1.58 | 0.16 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 25 | 1.8 | 95.1 | 22.0 | 68.0 | 1.7 | 2.0 | 6.0 | 0.3 |
| 26 | 1.0 | 64.4 | 15.6 | 80.0 | 0.6 | 1.2 | 2.6 | 0.0 |
| 27 | 2.1 | 147.9 | 16.4 | 75.9 | 0.9 | 2.4 | 4.3 | 0.2 |
| 28 | 1.5 | 95.6 | 15.8 | 74.2 | 1.1 | 3.5 | 5.4 | 0.1 |
| 29 | 1.7 | 96.5 | 15.8 | 76.0 | 1.7 | 1.7 | 4.7 | 0.2 |
| 30 | 2.8 | 161.1 | 15.3 | 74.3 | 0.9 | 3.1 | 6.4 | 0.1 |
| 31 | 1.5 | 95.0 | 22.4 | 70.5 | 0.9 | 2.4 | 3.4 | 0.4 |
| 32 | 1.7 | 98.5 | 19.9 | 73.3 | 0.9 | 2.0 | 3.6 | 0.3 |
| MEAN | 1.8 | 106.8 | 17.9 | 74.0 | 1.1 | 2.3 | 4.6 | 0.2 |
| SD | 0.52 | 31.65 | 3.03 | 3.63 | 0.40 | 0.74 | 1.33 | 0.13 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: FEMALE

| Animal ID | %RETIC % | #RETIC x10e9/L | %NEUT % | %LYMPH % | %MONO % | %EOS % | %BASO % | %LUC % |
|---|---|---|---|---|---|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 41 | 1.5 | 79.6 | 11.7 | 81.5 | 0.8 | 1.9 | 3.9 | 0.2 |
| 42 | 2.0 | 120.7 | 14.7 | 76.2 | 0.9 | 1.8 | 6.3 | 0.1 |
| 43 | 1.8 | 109.8 | 23.9 | 69.2 | 1.4 | 1.7 | 3.4 | 0.3 |
| 44 | 2.8 | 174.5 | 16.3 | 75.3 | 0.8 | 2.7 | 4.7 | 0.1 |
| 45 | 1.7 | 108.2 | 14.6 | 76.6 | 0.8 | 1.8 | 6.1 | 0.1 |
| 46 | 1.8 | 107.1 | 17.4 | 76.8 | 1.1 | 1.5 | 3.0 | 0.1 |
| 47 | 1.9 | 122.5 | 21.7 | 70.2 | 1.9 | 1.9 | 3.6 | 0.8 |
| 48 | 1.7 | 115.4 | 14.4 | 75.8 | 0.8 | 3.1 | 5.7 | 0.2 |
| MEAN | 1.9 | 117.2 | 16.8 | 75.2 | 1.1 | 2.1 | 4.6 | 0.2 |
| SD | 0.39 | 26.67 | 4.07 | 3.90 | 0.40 | 0.55 | 1.30 | 0.24 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: FEMALE

| Animal ID | #NEUT x10e3/uL | #LYMPH x10e3/uL | #MONO x10e3/uL | #EOS x10e3/uL | #BASO x10e3/uL | #LUC x10e3/uL |
|---|---|---|---|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | |
| 9 | 1.64 | 4.55 | 0.03 | 0.10 | 0.19 | 0.02 |
| 10 | 1.94 | 4.77 | 0.22 | 0.24 | 0.49 | 0.05 |
| 11 | 1.75 | 6.61 | 0.10 | 0.16 | 0.75 | 0.03 |
| 12 | 1.57 | 5.89 | 0.05 | 0.15 | 0.49 | 0.01 |
| 13 | 1.81 | 6.84 | 0.14 | 0.09 | 0.39 | 0.02 |
| 14 | 2.05 | 7.79 | 0.12 | 0.30 | 0.62 | 0.01 |
| 15 | 1.90 | 5.63 | 0.11 | 0.28 | 0.61 | 0.02 |
| 16 | 1.94 | 6.81 | 0.09 | 0.24 | 0.61 | 0.02 |
| MEAN | 1.83 | 6.11 | 0.11 | 0.20 | 0.52 | 0.02 |
| SD | 0.164 | 1.109 | 0.058 | 0.081 | 0.172 | 0.013 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 25 | 1.95 | 6.02 | 0.15 | 0.18 | 0.53 | 0.03 |
| 26 | 1.14 | 5.84 | 0.04 | 0.09 | 0.19 | 0.00 |
| 27 | 1.34 | 6.19 | 0.07 | 0.19 | 0.35 | 0.02 |
| 28 | 1.51 | 7.10 | 0.10 | 0.34 | 0.51 | 0.01 |
| 29 | 1.89 | 9.10 | 0.20 | 0.20 | 0.56 | 0.02 |
| 30 | 1.68 | 8.17 | 0.09 | 0.34 | 0.70 | 0.01 |
| 31 | 1.58 | 4.97 | 0.06 | 0.17 | 0.24 | 0.03 |
| 32 | 2.00 | 7.37 | 0.09 | 0.20 | 0.36 | 0.03 |
| MEAN | 1.64 | 6.85 | 0.10 | 0.21 | 0.43 | 0.02 |
| SD | 0.305 | 1.353 | 0.052 | 0.086 | 0.174 | 0.011 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: FEMALE

| Animal ID | #NEUT x10e3/uL | #LYMPH x10e3/uL | #MONO x10e3/uL | #EOS x10e3/uL | #BASO x10e3/uL | #LUC x10e3/uL |
|---|---|---|---|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 41 | 0.91 | 6.31 | 0.06 | 0.15 | 0.31 | 0.01 |
| 42 | 1.03 | 5.34 | 0.06 | 0.13 | 0.44 | 0.01 |
| 43 | 2.18 | 6.31 | 0.13 | 0.15 | 0.31 | 0.03 |
| 44 | 1.40 | 6.49 | 0.07 | 0.24 | 0.41 | 0.01 |
| 45 | 1.50 | 7.84 | 0.09 | 0.18 | 0.62 | 0.01 |
| 46 | 1.75 | 7.71 | 0.11 | 0.16 | 0.30 | 0.01 |
| 47 | 2.01 | 6.52 | 0.18 | 0.17 | 0.33 | 0.07 |
| 48 | 1.26 | 6.60 | 0.07 | 0.27 | 0.50 | 0.02 |
| MEAN | 1.51 | 6.64 | 0.10 | 0.18 | 0.40 | 0.02 |
| SD | 0.451 | 0.805 | 0.042 | 0.049 | 0.114 | 0.021 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: MALE

| Animal ID | WBC x10e3/uL | RBC x10e6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT x10e3/uL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| 1 | 5.36 | 6.10 | 13.0 | 39.5 | 64.7 | 21.3 | 32.9 | 359 |
| 2 | 8.10 | 5.84 | 13.0 | 38.0 | 65.0 | 22.2 | 34.2 | 336 |
| 3 | 6.01 | 6.44 | 13.8 | 41.0 | 63.7 | 21.5 | 33.7 | 288 |
| 4 | 9.63 | 5.97 | 13.2 | 38.2 | 64.0 | 22.0 | 34.4 | 345 |
| 5 | 7.13 | 5.86 | 13.1 | 39.8 | 68.0 | 22.3 | 32.9 | 279 |
| 6 | 10.23 | 6.01 | 12.9 | 39.6 | 65.9 | 21.4 | 32.5 | 322 |
| 7 | 9.19 | 5.71 | 12.2 | 37.2 | 65.2 | 21.4 | 32.8 | 447 |
| 8 | 9.52 | 6.38 | 13.2 | 39.7 | 62.2 | 20.7 | 33.3 | 265 |
| MEAN | 8.15 | 6.04 | 13.1 | 39.1 | 64.8 | 21.6 | 33.3 | 330 |
| SD | 1.808 | 0.258 | 0.44 | 1.22 | 1.70 | 0.53 | 0.69 | 57.9 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 17 | 6.66 | 6.49 | 13.9 | 41.4 | 63.8 | 21.3 | 33.5 | 366 |
| 18 | 9.85 | 6.41 | 13.4 | 40.6 | 63.3 | 20.8 | 32.9 | 350 |
| 19 | 7.72 | 5.88 | 12.2 | 38.0 | 64.6 | 20.8 | 32.2 | 383 |
| 20 | 6.92 | 6.44 | 13.1 | 40.3 | 62.5 | 20.4 | 32.6 | 365 |
| 21 | 7.24 | 6.33 | 13.7 | 43.0 | 67.9 | 21.6 | 31.8 | 371 |
| 22 | 14.99 | 6.38 | 13.7 | 41.7 | 65.4 | 21.5 | 32.8 | 208 |
| 23 | 8.79 | 5.66 | 12.7 | 37.8 | 66.9 | 22.5 | 33.6 | 358 |
| 24 | 8.76 | 7.95 | 15.5 | 48.2 | 60.7 | 19.5 | 32.2 | 292 |
| MEAN | 8.87 | 6.44 | 13.5 | 41.4 | 64.4 | 21.1 | 32.7 | 337 |
| SD | 2.702 | 0.678 | 0.98 | 3.28 | 2.34 | 0.90 | 0.63 | 58.8 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: MALE

| Animal ID | WBC x10e3/uL | RBC x10e6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT x10e3/uL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 33 | 6.58 | 6.50 | 13.3 | 39.9 | 61.4 | 20.4 | 33.3 | 310 |
| 34 | 8.39 | 6.07 | 13.4 | 38.3 | 63.2 | 22.1 | 34.9 | 321 |
| 35 | 12.33 | 6.02 | 13.1 | 41.5 | 68.9 | 21.7 | 31.5 | 610 |
| 36 | 6.92 | 5.88 | 13.8 | 39.9 | 67.9 | 23.5 | 34.5 | 318 |
| 37 | 4.52 | 6.63 | 14.5 | 43.9 | 66.3 | 21.8 | 32.9 | 325 |
| 38 | 5.26 | 6.08 | 13.0 | 38.8 | 63.8 | 21.4 | 33.5 | 373 |
| 39 | 7.95 | 5.95 | 13.5 | 39.0 | 65.6 | 22.7 | 34.6 | 271 |
| 40 | 6.16 | 7.07 | 14.7 | 50.2 | 71.0 | 20.8 | 29.3 | 269 |
| MEAN | 7.26 | 6.28 | 13.7 | 41.4 | 66.0 | 21.8 | 33.1 | 350 |
| SD | 2.413 | 0.417 | 0.63 | 3.97 | 3.19 | 0.99 | 1.88 | 110.2 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: MALE

| Animal ID | %RETIC % | #RETIC x10e9/L | %NEUT % | %LYMPH % | %MONO % | %EOS % | %BASO % | %LUC % |
|---|---|---|---|---|---|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| 1 | 3.9 | 237.6 | 28.0 | 60.4 | 1.2 | 3.1 | 7.1 | 0.2 |
| 2 | 2.8 | 160.9 | 18.8 | 74.3 | 2.3 | 1.4 | 2.5 | 0.8 |
| 3 | 2.1 | 134.0 | 20.8 | 67.7 | 1.1 | 3.6 | 6.8 | 0.2 |
| 4 | 2.4 | 146.1 | 15.3 | 72.9 | 1.0 | 3.6 | 7.0 | 0.2 |
| 5 | 3.2 | 185.4 | 13.9 | 79.1 | 1.4 | 2.5 | 3.1 | 0.1 |
| 6 | 3.2 | 190.7 | 13.2 | 79.0 | 0.8 | 3.3 | 3.5 | 0.2 |
| 7 | 2.8 | 159.4 | 10.8 | 79.3 | 1.8 | 2.0 | 5.9 | 0.2 |
| 8 | 3.3 | 213.4 | 13.3 | 76.7 | 1.0 | 3.3 | 5.3 | 0.3 |
| MEAN | 3.0 | 178.4 | 16.8 | 73.7 | 1.3 | 2.9 | 5.2 | 0.3 |
| SD | 0.56 | 35.08 | 5.57 | 6.67 | 0.50 | 0.81 | 1.87 | 0.22 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 17 | 2.8 | 183.6 | 22.0 | 65.0 | 1.6 | 2.9 | 8.1 | 0.3 |
| 18 | 2.3 | 148.1 | 29.1 | 63.6 | 1.3 | 1.4 | 4.0 | 0.6 |
| 19 | 3.1 | 184.8 | 19.1 | 74.2 | 1.3 | 2.1 | 2.9 | 0.4 |
| 20 | 2.2 | 142.1 | 22.0 | 67.0 | 3.5 | 2.0 | 5.1 | 0.3 |
| 21 | 3.0 | 189.7 | 22.3 | 71.6 | 1.0 | 1.7 | 3.2 | 0.2 |
| 22 | 2.1 | 134.8 | 12.0 | 81.1 | 1.2 | 1.9 | 3.6 | 0.1 |
| 23 | 2.4 | 136.8 | 22.0 | 70.2 | 1.3 | 2.4 | 3.8 | 0.4 |
| 24 | 2.6 | 208.7 | 10.5 | 78.3 | 2.7 | 2.1 | 5.5 | 0.9 |
| MEAN | 2.6 | 166.1 | 19.9 | 71.4 | 1.7 | 2.1 | 4.5 | 0.4 |
| SD | 0.37 | 28.70 | 6.04 | 6.24 | 0.88 | 0.45 | 1.70 | 0.25 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: MALE

| Animal ID | %RETIC % | #RETIC x10e9/L | %NEUT % | %LYMPH % | %MONO % | %EOS % | %BASO % | %LUC % |
|---|---|---|---|---|---|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 33 | 2.6 | 166.9 | 19.2 | 68.8 | 3.2 | 2.2 | 6.3 | 0.2 |
| 34 | 2.5 | 151.0 | 15.2 | 76.5 | 0.9 | 2.2 | 5.1 | 0.2 |
| 35 | 4.4 | 263.4 | 17.0 | 73.8 | 3.1 | 1.4 | 3.5 | 1.2 |
| 36 | 2.7 | 161.0 | 14.9 | 75.2 | 1.1 | 2.7 | 5.9 | 0.3 |
| 37 | 3.2 | 209.5 | 33.3 | 54.9 | 1.9 | 3.1 | 5.3 | 1.4 |
| 38 | 2.2 | 131.9 | 15.1 | 78.7 | 0.7 | 1.0 | 4.1 | 0.3 |
| 39 | 2.5 | 146.3 | 20.8 | 66.8 | 1.2 | 3.1 | 7.8 | 0.2 |
| 40 | 3.1 | 219.8 | 12.4 | 81.1 | 1.8 | 1.3 | 3.0 | 0.3 |
| MEAN | 2.9 | 181.2 | 18.5 | 72.0 | 1.7 | 2.1 | 5.1 | 0.5 |
| SD | 0.69 | 45.07 | 6.54 | 8.38 | 0.96 | 0.82 | 1.58 | 0.49 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: MALE

| Animal ID | #NEUT x10e3/uL | #LYMPH x10e3/uL | #MONO x10e3/uL | #EOS x10e3/uL | #BASO x10e3/uL | #LUC x10e3/uL |
|---|---|---|---|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | |
| 1 | 1.50 | 3.24 | 0.06 | 0.16 | 0.38 | 0.01 |
| 2 | 1.52 | 6.02 | 0.19 | 0.11 | 0.20 | 0.06 |
| 3 | 1.25 | 4.07 | 0.06 | 0.21 | 0.41 | 0.01 |
| 4 | 1.47 | 7.02 | 0.10 | 0.35 | 0.67 | 0.02 |
| 5 | 0.99 | 5.64 | 0.10 | 0.18 | 0.22 | 0.01 |
| 6 | 1.35 | 8.08 | 0.08 | 0.33 | 0.36 | 0.02 |
| 7 | 1.00 | 7.28 | 0.17 | 0.18 | 0.54 | 0.02 |
| 8 | 1.27 | 7.30 | 0.10 | 0.32 | 0.51 | 0.03 |
| MEAN | 1.29 | 6.08 | 0.11 | 0.23 | 0.41 | 0.02 |
| SD | 0.210 | 1.695 | 0.048 | 0.090 | 0.160 | 0.017 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 17 | 1.47 | 4.33 | 0.11 | 0.19 | 0.54 | 0.02 |
| 18 | 2.86 | 6.26 | 0.13 | 0.14 | 0.39 | 0.06 |
| 19 | 1.48 | 5.73 | 0.10 | 0.16 | 0.23 | 0.03 |
| 20 | 1.52 | 4.64 | 0.24 | 0.14 | 0.35 | 0.02 |
| 21 | 1.62 | 5.18 | 0.07 | 0.12 | 0.23 | 0.01 |
| 22 | 1.80 | 12.16 | 0.18 | 0.29 | 0.54 | 0.02 |
| 23 | 1.94 | 6.17 | 0.11 | 0.21 | 0.33 | 0.04 |
| 24 | 0.92 | 6.86 | 0.24 | 0.18 | 0.49 | 0.08 |
| MEAN | 1.70 | 6.42 | 0.15 | 0.18 | 0.39 | 0.04 |
| SD | 0.556 | 2.472 | 0.065 | 0.054 | 0.126 | 0.024 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: MALE

| Animal ID | #NEUT x10e3/uL | #LYMPH x10e3/uL | #MONO x10e3/uL | #EOS x10e3/uL | #BASO x10e3/uL | #LUC x10e3/uL |
|---|---|---|---|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 33 | 1.27 | 4.53 | 0.21 | 0.15 | 0.42 | 0.01 |
| 34 | 1.27 | 6.42 | 0.07 | 0.18 | 0.43 | 0.01 |
| 35 | 2.10 | 9.10 | 0.39 | 0.17 | 0.44 | 0.14 |
| 36 | 1.03 | 5.20 | 0.08 | 0.19 | 0.40 | 0.02 |
| 37 | 1.51 | 2.48 | 0.09 | 0.14 | 0.24 | 0.06 |
| 38 | 0.79 | 4.14 | 0.04 | 0.06 | 0.22 | 0.01 |
| 39 | 1.66 | 5.31 | 0.09 | 0.25 | 0.62 | 0.02 |
| 40 | 0.76 | 5.00 | 0.11 | 0.08 | 0.18 | 0.02 |
| MEAN | 1.30 | 5.27 | 0.14 | 0.15 | 0.37 | 0.04 |
| SD | 0.454 | 1.915 | 0.114 | 0.061 | 0.146 | 0.045 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: FEMALE

| Animal ID | WBC x10e3/uL | RBC x10e6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT x10e3/uL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| 9 | 5.34 | 5.91 | 12.9 | 40.3 | 68.2 | 21.8 | 31.9 | 393 |
| 10 | 7.04 | 6.58 | 14.3 | 44.8 | 68.1 | 21.7 | 32.0 | 294 |
| 11 | 7.25 | 6.30 | 13.6 | 40.0 | 63.5 | 21.6 | 34.0 | 534 |
| 12 | 7.75 | 5.78 | 12.2 | 36.8 | 63.7 | 21.1 | 33.1 | 364 |
| 13 | 8.24 | 6.21 | 13.7 | 43.2 | 69.5 | 22.1 | 31.8 | 343 |
| 14 | 11.83 | 6.76 | 14.5 | 42.6 | 63.0 | 21.5 | 34.1 | 98 |
| 15 | 8.70 | 6.12 | 12.5 | 38.2 | 62.5 | 20.4 | 32.6 | 266 |
| 16 | 9.00 | 5.97 | 12.9 | 37.8 | 63.3 | 21.6 | 34.1 | 481 |
| MEAN | 8.14 | 6.20 | 13.3 | 40.5 | 65.2 | 21.5 | 33.0 | 347 |
| SD | 1.877 | 0.335 | 0.83 | 2.85 | 2.85 | 0.52 | 1.02 | 134.5 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 25 | 5.76 | 5.87 | 12.5 | 38.7 | 66.0 | 21.3 | 32.3 | 377 |
| 26 | 7.92 | 7.12 | 14.5 | 43.0 | 60.4 | 20.4 | 33.8 | 69 |
| 27 | 4.44 | 6.54 | 13.0 | 40.1 | 61.3 | 19.8 | 32.4 | 421 |
| 28 | 9.72 | 6.34 | 13.4 | 41.2 | 65.0 | 21.1 | 32.5 | 475 |
| 29 | 10.02 | 6.23 | 13.7 | 41.9 | 67.2 | 22.0 | 32.8 | 469 |
| 30 | 10.81 | 5.90 | 12.5 | 37.8 | 64.1 | 21.2 | 33.0 | 324 |
| 31 | 8.71 | 6.10 | 12.4 | 38.5 | 63.0 | 20.2 | 32.1 | 249 |
| 32 | 11.08 | 5.61 | 12.6 | 39.0 | 69.6 | 22.5 | 32.3 | 271 |
| MEAN | 8.56 | 6.21 | 13.1 | 40.0 | 64.6 | 21.1 | 32.7 | 332 |
| SD | 2.395 | 0.469 | 0.74 | 1.85 | 3.05 | 0.91 | 0.55 | 135.8 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: FEMALE

| Animal ID | WBC x10e3/uL | RBC x10e6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT x10e3/uL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 41 | 7.57 | 5.58 | 11.8 | 36.5 | 65.4 | 21.1 | 32.3 | 317 |
| 42 | 5.83 | 6.04 | 13.4 | 40.8 | 67.6 | 22.2 | 32.8 | 295 |
| 43 | 8.44 | 6.26 | 12.4 | 37.0 | 59.2 | 19.9 | 33.5 | 348 |
| 44 | 9.14 | 6.27 | 13.3 | 40.4 | 64.4 | 21.2 | 32.9 | 302 |
| 45 | 8.49 | 6.62 | 12.9 | 39.9 | 60.3 | 19.5 | 32.3 | 294 |
| 46 | 9.42 | 5.62 | 12.6 | 38.6 | 68.7 | 22.4 | 32.6 | 296 |
| 47 | 10.64 | 6.00 | 12.8 | 37.8 | 63.0 | 21.3 | 33.8 | 463 |
| 48 | 8.90 | 6.95 | 14.2 | 43.1 | 62.0 | 20.5 | 33.0 | 145 |
| MEAN | 8.55 | 6.17 | 12.9 | 39.3 | 63.8 | 21.0 | 32.9 | 308 |
| SD | 1.413 | 0.467 | 0.72 | 2.21 | 3.35 | 1.02 | 0.53 | 86.9 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: FEMALE

| Animal ID | %RETIC % | #RETIC x10e9/L | %NEUT % | %LYMPH % | %MONO % | %EOS % | %BASO % | %LUC % |
|---|---|---|---|---|---|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| 9 | 2.0 | 120.9 | 31.3 | 59.1 | 1.1 | 2.9 | 5.4 | 0.2 |
| 10 | 3.2 | 208.9 | 21.0 | 66.1 | 1.8 | 4.3 | 6.5 | 0.3 |
| 11 | 1.9 | 120.2 | 19.6 | 65.9 | 3.6 | 2.6 | 8.0 | 0.3 |
| 12 | 1.5 | 85.7 | 19.4 | 72.1 | 1.0 | 2.1 | 5.3 | 0.2 |
| 13 | 1.9 | 118.3 | 17.5 | 73.9 | 1.7 | 1.0 | 5.7 | 0.2 |
| 14 | 2.0 | 138.3 | 15.4 | 74.5 | 1.2 | 3.5 | 5.2 | 0.2 |
| 15 | 3.0 | 180.5 | 22.1 | 69.0 | 1.1 | 1.7 | 6.0 | 0.1 |
| 16 | 1.6 | 95.8 | 16.8 | 71.5 | 1.7 | 2.7 | 6.6 | 0.8 |
| MEAN | 2.1 | 133.6 | 20.4 | 69.0 | 1.7 | 2.6 | 6.1 | 0.3 |
| SD | 0.62 | 41.73 | 4.93 | 5.16 | 0.85 | 1.03 | 0.94 | 0.22 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 25 | 2.2 | 131.6 | 19.4 | 64.0 | 2.4 | 5.7 | 8.1 | 0.5 |
| 26 | 1.9 | 134.7 | 15.3 | 75.5 | 3.9 | 1.6 | 3.6 | 0.2 |
| 27 | 2.6 | 172.6 | 18.9 | 72.1 | 1.6 | 2.0 | 5.2 | 0.3 |
| 28 | 1.9 | 120.3 | 13.9 | 77.9 | 1.8 | 2.0 | 4.3 | 0.2 |
| 29 | 2.9 | 178.6 | 12.9 | 78.8 | 1.8 | 2.2 | 4.2 | 0.1 |
| 30 | 2.1 | 121.8 | 17.3 | 73.8 | 1.1 | 2.2 | 5.6 | 0.1 |
| 31 | 1.9 | 116.3 | 20.6 | 70.2 | 1.2 | 3.8 | 4.1 | 0.2 |
| 32 | 3.2 | 176.9 | 16.2 | 76.7 | 1.3 | 1.9 | 3.7 | 0.2 |
| MEAN | 2.3 | 144.1 | 16.8 | 73.6 | 1.9 | 2.7 | 4.9 | 0.2 |
| SD | 0.50 | 27.15 | 2.73 | 4.85 | 0.91 | 1.39 | 1.48 | 0.13 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: FEMALE

| Animal ID | %RETIC % | #RETIC x10e9/L | %NEUT % | %LYMPH % | %MONO % | %EOS % | %BASO % | %LUC % |
|---|---|---|---|---|---|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 41 | 1.8 | 102.2 | 10.3 | 84.4 | 0.8 | 1.0 | 3.3 | 0.2 |
| 42 | 2.0 | 118.4 | 23.1 | 64.0 | 4.9 | 1.8 | 5.8 | 0.3 |
| 43 | 2.0 | 128.3 | 15.6 | 74.7 | 1.3 | 4.1 | 4.0 | 0.2 |
| 44 | 3.6 | 226.8 | 23.0 | 67.2 | 1.8 | 3.6 | 4.4 | 0.2 |
| 45 | 1.6 | 103.4 | 12.5 | 71.0 | 3.6 | 4.4 | 8.4 | 0.2 |
| 46 | 2.9 | 165.8 | 16.0 | 77.5 | 1.3 | 1.5 | 3.5 | 0.2 |
| 47 | 2.8 | 169.0 | 14.9 | 76.9 | 2.1 | 1.7 | 3.6 | 0.9 |
| 48 | 3.2 | 220.9 | 14.9 | 73.2 | 1.6 | 3.4 | 6.5 | 0.4 |
| MEAN | 2.5 | 154.4 | 16.3 | 73.6 | 2.2 | 2.7 | 4.9 | 0.3 |
| SD | 0.73 | 49.73 | 4.57 | 6.37 | 1.38 | 1.32 | 1.81 | 0.24 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: FEMALE

| Animal ID | #NEUT x10e3/uL | #LYMPH x10e3/uL | #MONO x10e3/uL | #EOS x10e3/uL | #BASO x10e3/uL | #LUC x10e3/uL |
|---|---|---|---|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | |
| 9 | 1.67 | 3.16 | 0.06 | 0.16 | 0.29 | 0.01 |
| 10 | 1.48 | 4.65 | 0.13 | 0.30 | 0.46 | 0.02 |
| 11 | 1.42 | 4.78 | 0.26 | 0.19 | 0.58 | 0.02 |
| 12 | 1.50 | 5.58 | 0.07 | 0.16 | 0.41 | 0.01 |
| 13 | 1.44 | 6.09 | 0.14 | 0.08 | 0.47 | 0.01 |
| 14 | 1.82 | 8.81 | 0.14 | 0.41 | 0.62 | 0.02 |
| 15 | 1.92 | 6.00 | 0.10 | 0.14 | 0.52 | 0.01 |
| 16 | 1.51 | 6.43 | 0.16 | 0.24 | 0.59 | 0.07 |
| MEAN | 1.60 | 5.69 | 0.13 | 0.21 | 0.49 | 0.02 |
| SD | 0.187 | 1.641 | 0.063 | 0.104 | 0.109 | 0.020 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 25 | 1.12 | 3.68 | 0.14 | 0.33 | 0.47 | 0.03 |
| 26 | 1.21 | 5.98 | 0.31 | 0.12 | 0.28 | 0.02 |
| 27 | 0.84 | 3.20 | 0.07 | 0.09 | 0.23 | 0.01 |
| 28 | 1.35 | 7.57 | 0.17 | 0.19 | 0.42 | 0.02 |
| 29 | 1.30 | 7.89 | 0.18 | 0.22 | 0.42 | 0.01 |
| 30 | 1.86 | 7.97 | 0.11 | 0.24 | 0.61 | 0.01 |
| 31 | 1.79 | 6.11 | 0.10 | 0.33 | 0.36 | 0.01 |
| 32 | 1.80 | 8.50 | 0.14 | 0.21 | 0.41 | 0.02 |
| MEAN | 1.41 | 6.36 | 0.15 | 0.22 | 0.40 | 0.02 |
| SD | 0.371 | 2.013 | 0.073 | 0.087 | 0.116 | 0.007 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: FEMALE

| Animal ID | #NEUT x10e3/uL | #LYMPH x10e3/uL | #MONO x10e3/uL | #EOS x10e3/uL | #BASO x10e3/uL | #LUC x10e3/uL |
|---|---|---|---|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 41 | 0.78 | 6.39 | 0.06 | 0.07 | 0.25 | 0.01 |
| 42 | 1.35 | 3.74 | 0.29 | 0.11 | 0.34 | 0.02 |
| 43 | 1.31 | 6.31 | 0.11 | 0.35 | 0.34 | 0.02 |
| 44 | 2.10 | 6.14 | 0.16 | 0.33 | 0.40 | 0.01 |
| 45 | 1.06 | 6.03 | 0.30 | 0.37 | 0.71 | 0.02 |
| 46 | 1.51 | 7.30 | 0.12 | 0.14 | 0.33 | 0.02 |
| 47 | 1.58 | 8.18 | 0.22 | 0.18 | 0.38 | 0.09 |
| 48 | 1.33 | 6.52 | 0.14 | 0.30 | 0.57 | 0.03 |
| MEAN | 1.38 | 6.33 | 0.18 | 0.23 | 0.42 | 0.03 |
| SD | 0.387 | 1.267 | 0.087 | 0.119 | 0.150 | 0.026 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 4 (cont.)
(Recovery)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: MALE

| Animal ID | WBC x10e3/uL | RBC x10e6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT x10e3/uL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| 1 | a | a | a | a | a | a | a | a |
| 2 | a | a | a | a | a | a | a | a |
| 3 | a | a | a | a | a | a | a | a |
| 4 | a | a | a | a | a | a | a | a |
| 5 | a | a | a | a | a | a | a | a |
| 6 | 9.51 | 6.52 | 14.3 | 43.0 | 66.0 | 21.9 | 33.1 | 363 |
| 7 | 7.72 | 6.12 | 13.3 | 39.7 | 64.8 | 21.7 | 33.6 | 283 |
| 8 | 8.92 | 6.52 | 13.9 | 40.2 | 61.8 | 21.4 | 34.6 | 229 |
| MEAN | 8.72 | 6.39 | 13.8 | 41.0 | 64.2 | 21.7 | 33.8 | 292 |
| SD | 0.912 | 0.231 | 0.50 | 1.78 | 2.16 | 0.25 | 0.76 | 67.4 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 17 | a | a | a | a | a | a | a | a |
| 18 | a | a | a | a | a | a | a | a |
| 19 | a | a | a | a | a | a | a | a |
| 20 | a | a | a | a | a | a | a | a |
| 21 | a | a | a | a | a | a | a | a |
| 22 | 13.46 | 5.86 | 12.6 | 37.2 | 63.5 | 21.5 | 33.8 | 311 |
| 23 | 7.34 | 5.61 | 12.7 | 37.9 | 67.6 | 22.7 | 33.6 | 413 |
| 24 | 9.85 | 7.63 | 14.7 | 45.7 | 59.8 | 19.3 | 32.2 | 261 |
| MEAN | 10.22 | 6.37 | 13.3 | 40.3 | 63.6 | 21.2 | 33.2 | 328 |
| SD | 3.076 | 1.101 | 1.18 | 4.72 | 3.90 | 1.72 | 0.87 | 77.5 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 4 (cont.)
(Recovery)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: MALE

| Animal ID | WBC x10e3/uL | RBC x10e6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT x10e3/uL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 33 | a | a | a | a | a | a | a | a |
| 34 | a | a | a | a | a | a | a | a |
| 35 | a | a | a | a | a | a | a | a |
| 36 | a | a | a | a | a | a | a | a |
| 37 | a | a | a | a | a | a | a | a |
| 38 | 6.02 | 6.03 | 13.0 | 38.8 | 64.2 | 21.5 | 33.5 | 332 |
| 39 | 9.09 | 6.72 | 14.6 | 43.6 | 64.9 | 21.8 | 33.6 | 262 |
| 40 | 6.56 | 6.77 | 14.1 | 43.4 | 64.2 | 20.8 | 32.5 | 337 |
| MEAN | 7.22 | 6.51 | 13.9 | 41.9 | 64.4 | 21.4 | 33.2 | 310 |
| SD | 1.639 | 0.414 | 0.82 | 2.72 | 0.40 | 0.51 | 0.61 | 41.9 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 4 (cont.)
(Recovery)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: MALE

| Animal ID | %RETIC % | #RETIC x10e9/L | %NEUT % | %LYMPH % | %MONO % | %EOS % | %BASO % | %LUC % |
|---|---|---|---|---|---|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| 1 | a | a | a | a | a | a | a | a |
| 2 | a | a | a | a | a | a | a | a |
| 3 | a | a | a | a | a | a | a | a |
| 4 | a | a | a | a | a | a | a | a |
| 5 | a | a | a | a | a | a | a | a |
| 6 | 2.4 | 157.2 | 15.6 | 77.3 | 1.0 | 1.9 | 3.9 | 0.3 |
| 7 | 2.2 | 132.5 | 12.6 | 77.8 | 0.9 | 2.4 | 6.0 | 0.2 |
| 8 | 2.3 | 150.0 | 11.5 | 80.7 | 0.7 | 2.2 | 4.8 | 0.1 |
| MEAN | 2.3 | 146.6 | 13.2 | 78.6 | 0.9 | 2.2 | 4.9 | 0.2 |
| SD | 0.10 | 12.70 | 2.12 | 1.84 | 0.15 | 0.25 | 1.05 | 0.10 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 17 | a | a | a | a | a | a | a | a |
| 18 | a | a | a | a | a | a | a | a |
| 19 | a | a | a | a | a | a | a | a |
| 20 | a | a | a | a | a | a | a | a |
| 21 | a | a | a | a | a | a | a | a |
| 22 | 2.2 | 129.2 | 14.1 | 80.3 | 0.5 | 1.0 | 4.0 | 0.1 |
| 23 | 2.6 | 145.9 | 20.7 | 73.7 | 1.0 | 1.7 | 2.8 | 0.1 |
| 24 | 2.2 | 168.9 | 12.5 | 79.8 | 1.3 | 1.1 | 5.0 | 0.2 |
| MEAN | 2.3 | 148.0 | 15.8 | 77.9 | 0.9 | 1.3 | 3.9 | 0.1 |
| SD | 0.23 | 19.93 | 4.35 | 3.67 | 0.40 | 0.38 | 1.10 | 0.06 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 4 (cont.)
(Recovery)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: MALE

| Animal ID | %RETIC % | #RETIC x10e9/L | %NEUT % | %LYMPH % | %MONO % | %EOS % | %BASO % | %LUC % |
|---|---|---|---|---|---|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 33 | a | a | a | a | a | a | a | a |
| 34 | a | a | a | a | a | a | a | a |
| 35 | a | a | a | a | a | a | a | a |
| 36 | a | a | a | a | a | a | a | a |
| 37 | a | a | a | a | a | a | a | a |
| 38 | 2.5 | 153.1 | 16.0 | 79.1 | 0.9 | 1.3 | 2.6 | 0.1 |
| 39 | 2.2 | 144.9 | 40.7 | 47.7 | 2.3 | 1.8 | 6.7 | 0.8 |
| 40 | 2.1 | 143.0 | 22.1 | 70.5 | 0.9 | 1.5 | 4.7 | 0.3 |
| MEAN | 2.3 | 147.0 | 26.3 | 65.8 | 1.4 | 1.5 | 4.7 | 0.4 |
| SD | 0.21 | 5.37 | 12.87 | 16.23 | 0.81 | 0.25 | 2.05 | 0.36 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 4 (cont.)
(Recovery)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: MALE

| Animal ID | #NEUT x10e3/uL | #LYMPH x10e3/uL | #MONO x10e3/uL | #EOS x10e3/uL | #BASO x10e3/uL | #LUC x10e3/uL |
|---|---|---|---|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | |
| 1 | a | a | a | a | a | a |
| 2 | a | a | a | a | a | a |
| 3 | a | a | a | a | a | a |
| 4 | a | a | a | a | a | a |
| 5 | a | a | a | a | a | a |
| 6 | 1.48 | 7.35 | 0.09 | 0.18 | 0.37 | 0.03 |
| 7 | 0.97 | 6.01 | 0.07 | 0.19 | 0.47 | 0.02 |
| 8 | 1.03 | 7.20 | 0.06 | 0.20 | 0.42 | 0.01 |
| MEAN | 1.16 | 6.85 | 0.07 | 0.19 | 0.42 | 0.02 |
| SD | 0.279 | 0.734 | 0.015 | 0.010 | 0.050 | 0.010 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 17 | a | a | a | a | a | a |
| 18 | a | a | a | a | a | a |
| 19 | a | a | a | a | a | a |
| 20 | a | a | a | a | a | a |
| 21 | a | a | a | a | a | a |
| 22 | 1.90 | 10.80 | 0.07 | 0.14 | 0.53 | 0.02 |
| 23 | 1.52 | 5.41 | 0.07 | 0.13 | 0.20 | 0.01 |
| 24 | 1.23 | 7.87 | 0.13 | 0.11 | 0.49 | 0.02 |
| MEAN | 1.55 | 8.03 | 0.09 | 0.13 | 0.41 | 0.02 |
| SD | 0.336 | 2.698 | 0.035 | 0.015 | 0.180 | 0.006 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 4 (cont.)
(Recovery)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: MALE

| Animal ID | #NEUT x10e3/uL | #LYMPH x10e3/uL | #MONO x10e3/uL | #EOS x10e3/uL | #BASO x10e3/uL | #LUC x10e3/uL |
|---|---|---|---|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 33 | a | a | a | a | a | a |
| 34 | a | a | a | a | a | a |
| 35 | a | a | a | a | a | a |
| 36 | a | a | a | a | a | a |
| 37 | a | a | a | a | a | a |
| 38 | 0.97 | 4.76 | 0.05 | 0.08 | 0.16 | 0.01 |
| 39 | 3.70 | 4.34 | 0.21 | 0.16 | 0.61 | 0.08 |
| 40 | 1.45 | 4.62 | 0.06 | 0.10 | 0.31 | 0.02 |
| MEAN | 2.04 | 4.57 | 0.11 | 0.11 | 0.36 | 0.04 |
| SD | 1.457 | 0.214 | 0.090 | 0.042 | 0.229 | 0.038 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 4 (cont.)
(Recovery)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: FEMALE

| Animal ID | WBC x10e3/uL | RBC x10e6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT x10e3/uL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| 9 | a | a | a | a | a | a | a | a |
| 10 | a | a | a | a | a | a | a | a |
| 11 | a | a | a | a | a | a | a | a |
| 12 | a | a | a | a | a | a | a | a |
| 13 | a | a | a | a | a | a | a | a |
| 14 | 9.63 | 6.99 | 15.3 | 44.3 | 63.3 | 21.9 | 34.5 | 158 |
| 15 | 8.64 | 6.49 | 13.7 | 40.2 | 61.9 | 21.1 | 34.1 | 264 |
| 16 | 7.53 | 6.55 | 13.8 | 41.4 | 63.1 | 21.1 | 33.4 | 603 |
| MEAN | 8.60 | 6.68 | 14.3 | 42.0 | 62.8 | 21.4 | 34.0 | 342 |
| SD | 1.051 | 0.273 | 0.90 | 2.11 | 0.76 | 0.46 | 0.56 | 232.4 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 25 | a | a | a | a | a | a | a | a |
| 26 | a | a | a | a | a | a | a | a |
| 27 | a | a | a | a | a | a | a | a |
| 28 | a | a | a | a | a | a | a | a |
| 29 | a | a | a | a | a | a | a | a |
| 30 | 4.96 | 6.19 | 12.8 | 38.0 | 61.3 | 20.7 | 33.8 | 266 |
| 31 | 7.14 | 6.17 | 12.6 | 38.3 | 62.0 | 20.4 | 33.0 | 333 |
| 32 | 6.13 | 5.68 | 12.9 | 39.4 | 69.3 | 22.6 | 32.7 | 565 |
| MEAN | 6.08 | 6.01 | 12.8 | 38.6 | 64.2 | 21.2 | 33.2 | 388 |
| SD | 1.091 | 0.289 | 0.15 | 0.74 | 4.43 | 1.19 | 0.57 | 156.9 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 4 (cont.)
(Recovery)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: FEMALE

| Animal ID | WBC x10e3/uL | RBC x10e6/uL | HGB g/dL | HCT % | MCV fL | MCH pg | MCHC g/dL | PLT x10e3/uL |
|---|---|---|---|---|---|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 41 | a | a | a | a | a | a | a | a |
| 42 | a | a | a | a | a | a | a | a |
| 43 | a | a | a | a | a | a | a | a |
| 44 | a | a | a | a | a | a | a | a |
| 45 | a | a | a | a | a | a | a | a |
| 46 | 7.13 | 5.97 | 13.4 | 40.9 | 68.5 | 22.5 | 32.8 | 259 |
| 47 | 8.09 | 6.26 | 13.0 | 39.3 | 62.8 | 20.8 | 33.1 | 761 |
| 48 | 6.46 | 6.63 | 13.8 | 41.5 | 62.5 | 20.9 | 33.4 | 202 |
| MEAN | 7.23 | 6.29 | 13.4 | 40.6 | 64.6 | 21.4 | 33.1 | 407 |
| SD | 0.819 | 0.331 | 0.40 | 1.14 | 3.38 | 0.95 | 0.30 | 307.6 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 4 (cont.)
(Recovery)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: FEMALE

| Animal ID | %RETIC % | #RETIC x10e9/L | %NEUT % | %LYMPH % | %MONO % | %EOS % | %BASO % | %LUC % |
|---|---|---|---|---|---|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | | | |
| 9 | a | a | a | a | a | a | a | a |
| 10 | a | a | a | a | a | a | a | a |
| 11 | a | a | a | a | a | a | a | a |
| 12 | a | a | a | a | a | a | a | a |
| 13 | a | a | a | a | a | a | a | a |
| 14 | 1.8 | 126.4 | 16.2 | 75.9 | 1.2 | 1.8 | 4.6 | 0.3 |
| 15 | 1.6 | 102.2 | 19.8 | 68.5 | 2.9 | 1.6 | 7.1 | 0.2 |
| 16 | 1.7 | 109.6 | 19.6 | 73.0 | 1.1 | 1.9 | 4.3 | 0.3 |
| MEAN | 1.7 | 112.7 | 18.5 | 72.5 | 1.7 | 1.8 | 5.3 | 0.3 |
| SD | 0.10 | 12.40 | 2.02 | 3.73 | 1.01 | 0.15 | 1.54 | 0.06 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 25 | a | a | a | a | a | a | a | a |
| 26 | a | a | a | a | a | a | a | a |
| 27 | a | a | a | a | a | a | a | a |
| 28 | a | a | a | a | a | a | a | a |
| 29 | a | a | a | a | a | a | a | a |
| 30 | 1.1 | 68.8 | 14.0 | 75.7 | 0.8 | 2.9 | 6.4 | 0.2 |
| 31 | 1.7 | 105.9 | 17.8 | 75.6 | 1.3 | 1.3 | 3.3 | 0.7 |
| 32 | 2.5 | 143.5 | 28.9 | 64.2 | 1.5 | 1.0 | 4.1 | 0.2 |
| MEAN | 1.8 | 106.1 | 20.2 | 71.8 | 1.2 | 1.7 | 4.6 | 0.4 |
| SD | 0.70 | 37.35 | 7.74 | 6.61 | 0.36 | 1.02 | 1.61 | 0.29 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 4 (cont.)
(Recovery)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: FEMALE

| Animal ID | %RETIC % | #RETIC x10e9/L | %NEUT % | %LYMPH % | %MONO % | %EOS % | %BASO % | %LUC % |
|---|---|---|---|---|---|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | | |
| 41 | a | a | a | a | a | a | a | a |
| 42 | a | a | a | a | a | a | a | a |
| 43 | a | a | a | a | a | a | a | a |
| 44 | a | a | a | a | a | a | a | a |
| 45 | a | a | a | a | a | a | a | a |
| 46 | 1.8 | 105.8 | 17.0 | 74.6 | 1.2 | 1.5 | 5.4 | 0.3 |
| 47 | 2.6 | 164.5 | 22.9 | 68.5 | 2.6 | 2.2 | 3.0 | 0.7 |
| 48 | 2.1 | 140.1 | 13.5 | 77.1 | 1.0 | 1.5 | 6.7 | 0.1 |
| MEAN | 2.2 | 136.8 | 17.8 | 73.4 | 1.6 | 1.7 | 5.0 | 0.4 |
| SD | 0.40 | 29.49 | 4.75 | 4.42 | 0.87 | 0.40 | 1.88 | 0.31 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 4 (cont.)
(Recovery)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: FEMALE

| Animal ID | #NEUT x10e3/uL | #LYMPH x10e3/uL | #MONO x10e3/uL | #EOS x10e3/uL | #BASO x10e3/uL | #LUC x10e3/uL |
|---|---|---|---|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO / 7% ethanol / 92.7% saline) | | | | | | |
| 9 | a | a | a | a | a | a |
| 10 | a | a | a | a | a | a |
| 11 | a | a | a | a | a | a |
| 12 | a | a | a | a | a | a |
| 13 | a | a | a | a | a | a |
| 14 | 1.56 | 7.31 | 0.11 | 0.18 | 0.44 | 0.02 |
| 15 | 1.71 | 5.92 | 0.25 | 0.14 | 0.61 | 0.01 |
| 16 | 1.47 | 5.49 | 0.08 | 0.14 | 0.32 | 0.02 |
| MEAN | 1.58 | 6.24 | 0.15 | 0.15 | 0.46 | 0.02 |
| SD | 0.121 | 0.951 | 0.091 | 0.023 | 0.146 | 0.006 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 25 | a | a | a | a | a | a |
| 26 | a | a | a | a | a | a |
| 27 | a | a | a | a | a | a |
| 28 | a | a | a | a | a | a |
| 29 | a | a | a | a | a | a |
| 30 | 0.69 | 3.76 | 0.04 | 0.14 | 0.32 | 0.01 |
| 31 | 1.27 | 5.40 | 0.09 | 0.09 | 0.24 | 0.05 |
| 32 | 1.77 | 3.94 | 0.09 | 0.06 | 0.25 | 0.01 |
| MEAN | 1.24 | 4.37 | 0.07 | 0.10 | 0.27 | 0.02 |
| SD | 0.540 | 0.899 | 0.029 | 0.040 | 0.044 | 0.023 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 4 (cont.)
(Recovery)

INDIVIDUAL ANIMAL HEMATOLOGY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: FEMALE

| Animal ID | #NEUT x10e3/uL | #LYMPH x10e3/uL | #MONO x10e3/uL | #EOS x10e3/uL | #BASO x10e3/uL | #LUC x10e3/uL |
|---|---|---|---|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 41 | a | a | a | a | a | a |
| 42 | a | a | a | a | a | a |
| 43 | a | a | a | a | a | a |
| 44 | a | a | a | a | a | a |
| 45 | a | a | a | a | a | a |
| 46 | 1.21 | 5.32 | 0.09 | 0.11 | 0.38 | 0.02 |
| 47 | 1.86 | 5.54 | 0.21 | 0.18 | 0.24 | 0.06 |
| 48 | 0.87 | 4.98 | 0.07 | 0.10 | 0.43 | 0.01 |
| MEAN | 1.31 | 5.28 | 0.12 | 0.13 | 0.35 | 0.03 |
| SD | 0.503 | 0.282 | 0.076 | 0.044 | 0.098 | 0.026 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 5

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: MALE

| Animal ID | NA mmol/L | K mmol/L | CL mmol/L | ALP IU/L | ALT IU/L | AST IU/L | GGT IU/L |
|---|---|---|---|---|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | | | | | | |
| 1 | 140 | 4.9 | 108 | 52 | 24 | 19 | 6 |
| 2 | 140 | 4.8 | 108 | 40 | 58 | 23 | 5 |
| 3 | 141 | 4.0 | 108 | 78 | 33 | 19 | 8 |
| 4 | 141 | 4.6 | 107 | 53 | 29 | 21 | 3 |
| 5 | 140 | 6.0 | 107 | 34 | 26 | 19 | 7 |
| 6 | 139 | 4.9 | 109 | 64 | 49 | 19 | 3 |
| 7 | 141 | 4.6 | 105 | 32 | 63 | 26 | 6 |
| 8 | 141 | 4.6 | 106 | 80 | 51 | 19 | 4 |
| MEAN | 140 | 4.8 | 107 | 54 | 42 | 21 | 5 |
| SD | 0.7 | 0.56 | 1.3 | 18.7 | 15.4 | 2.6 | 1.8 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| 17 | 139 | 4.9 | 106 | 51 | 23 | 17 | 3 |
| 18 | 140 | 4.6 | 112 | 51 | 47 | 23 | 9 |
| 19 | 141 | 5.4 | 105 | 61 | 51 | 21 | 8 |
| 20 | 143 | 5.4 | 106 | 53 | 30 | 23 | 7 |
| 21 | 140 | 5.2 | 108 | 60 | 33 | 19 | 6 |
| 22 | 142 | 4.5 | 111 | 57 | 35 | 17 | 6 |
| 23 | 140 | 5.1 | 110 | 59 | 36 | 16 | 4 |
| 24 | 141 | 5.1 | 107 | 38 | 45 | 22 | 3 |
| MEAN | 141 | 5.0 | 108 | 54 | 38 | 20 | 6 |
| SD | 1.3 | 0.34 | 2.6 | 7.5 | 9.4 | 2.9 | 2.3 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: MALE

| Animal ID | NA mmol/L | K mmol/L | CL mmol/L | ALP IU/L | ALT IU/L | AST IU/L | GGT IU/L |
|---|---|---|---|---|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| 33 | 143 | 5.8 | 107 | 50 | 34 | 25 | 6 |
| 34 | 140 | 5.1 | 105 | 73 | 45 | 24 | 9 |
| 35 | 147 | 6.8 | 112 | 53 | 43 | 24 | 7 |
| 36 | 142 | 5.8 | 107 | 37 | 24 | 21 | 6 |
| 37 | 142 | 4.8 | 107 | 94 | 29 | 23 | 5 |
| 38 | 138 | 4.5 | 107 | 54 | 23 | 19 | 4 |
| 39 | 139 | 5.2 | 107 | 52 | 51 | 25 | 9 |
| 40 | 138 | 4.4 | 105 | 37 | 23 | 23 | 5 |
| MEAN | 141 | 5.3 | 107 | 56 | 34 | 23 | 6 |
| SD | 3.0 | 0.80 | 2.2 | 19.0 | 11.1 | 2.1 | 1.8 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: MALE

| Animal ID | TBIL mg/dL | BUN mg/dL | CRE mg/dL | GLUC mg/dL | CALC mg/dL | PHOS mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | | | | | |
| 1 | 0.47 | 16 | 0.7 | 151 | 14.8 | 3.3 |
| 2 | 0.44 | 14 | 0.9 | 128 | 14.3 | 3.7 |
| 3 | 0.39 | 13 | 1.1 | 134 | 13.0 | 3.9 |
| 4 | 0.34 | 19 | 1.0 | 133 | 13.7 | 3.8 |
| 5 | 0.48 | 16 | 0.9 | 139 | 15.0 | 4.2 |
| 6 | 0.32 | 17 | 0.9 | 119 | 13.8 | 3.7 |
| 7 | 0.53 | 18 | 0.9 | 135 | 14.0 | 4.0 |
| 8 | 0.33 | 17 | 1.1 | 129 | 14.0 | 3.9 |
| MEAN | 0.41 | 16 | 0.9 | 134 | 14.1 | 3.8 |
| SD | 0.079 | 2.0 | 0.13 | 9.3 | 0.63 | 0.26 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 17 | 0.38 | 15 | 0.9 | 131 | 14.1 | 4.2 |
| 18 | 0.45 | 19 | 0.8 | 138 | 14.1 | 3.4 |
| 19 | 0.54 | 14 | 0.9 | 129 | 14.6 | 4.0 |
| 20 | 0.39 | 18 | 0.9 | 136 | 15.0 | 4.0 |
| 21 | 0.36 | 16 | 0.9 | 144 | 14.1 | 3.9 |
| 22 | 0.48 | 19 | 0.9 | 124 | 13.9 | 4.0 |
| 23 | 0.51 | 17 | 0.9 | 137 | 14.3 | 3.9 |
| 24 | 0.45 | 16 | 1.2 | 122 | 14.1 | 4.1 |
| MEAN | 0.45 | 17 | 0.9 | 133 | 14.3 | 3.9 |
| SD | 0.064 | 1.8 | 0.12 | 7.5 | 0.36 | 0.24 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: MALE

| Animal ID | TBIL mg/dL | BUN mg/dL | CRE mg/dL | GLUC mg/dL | CALC mg/dL | PHOS mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 33 | 0.33 | 24 | 1.1 | 135 | 15.2 | 4.2 |
| 34 | 0.46 | 15 | 1.0 | 131 | 14.2 | 3.4 |
| 35 | 0.27 | 15 | 0.9 | 141 | 15.0 | 4.2 |
| 36 | 0.40 | 19 | 0.9 | 139 | 15.1 | 3.2 |
| 37 | 0.38 | 13 | 1.0 | 133 | 14.0 | 3.8 |
| 38 | 0.38 | 14 | 0.9 | 125 | 13.9 | 3.4 |
| 39 | 0.43 | 25 | 1.0 | 140 | 14.3 | 4.4 |
| 40 | 0.39 | 15 | 1.0 | 125 | 13.6 | 3.8 |
| MEAN | 0.38 | 18 | 1.0 | 134 | 14.4 | 3.8 |
| SD | 0.059 | 4.7 | 0.07 | 6.3 | 0.61 | 0.44 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: MALE

| Animal ID | TP g/dL | ALB g/dL | GLOB g/dL | A/G RATIO - | CHOL mg/dL | TG mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | | | | | |
| 1 | 5.3 | 5.2 | 0.1 | 52.0 | 22 | 143 |
| 2 | 5.6 | 5.2 | 0.4 | 13.0 | 27 | 147 |
| 3 | 4.7 | 4.4 | 0.3 | 14.7 | 32 | 17 |
| 4 | 5.6 | 4.8 | 0.8 | 6.0 | 34 | 60 |
| 5 | 5.7 | 5.2 | 0.5 | 10.4 | 46 | 290 |
| 6 | 4.8 | 4.5 | 0.3 | 15.0 | 29 | 81 |
| 7 | 5.3 | 4.9 | 0.4 | 12.3 | 29 | 42 |
| 8 | 5.2 | 4.7 | 0.5 | 9.4 | 49 | 152 |
| MEAN | 5.3 | 4.9 | 0.4 | 16.6 | 34 | 117 |
| SD | 0.37 | 0.32 | 0.20 | 14.61 | 9.4 | 86.9 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 17 | 5.3 | 5.0 | 0.3 | 16.7 | 32 | 52 |
| 18 | 5.2 | 4.8 | 0.4 | 12.0 | 31 | 67 |
| 19 | 5.3 | 5.0 | 0.3 | 16.7 | 16 | 54 |
| 20 | 5.9 | 5.4 | 0.5 | 10.8 | 26 | 106 |
| 21 | 5.0 | 4.8 | 0.2 | 24.0 | 21 | 38 |
| 22 | 5.4 | 5.0 | 0.4 | 12.5 | 17 | 73 |
| 23 | 5.1 | 4.7 | 0.4 | 11.8 | 27 | 68 |
| 24 | 5.5 | 5.1 | 0.4 | 12.8 | 30 | 100 |
| MEAN | 5.3 | 5.0 | 0.4 | 14.7 | 25 | 70 |
| SD | 0.28 | 0.22 | 0.09 | 4.37 | 6.3 | 23.4 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: MALE
STUDY NO: 2073023

| Animal ID | TP g/dL | ALB g/dL | GLOB g/dL | A/G RATIO - | CHOL mg/dL | TG mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 33 | 5.2 | 4.8 | 0.4 | 12.0 | 44 | 82 |
| 34 | 5.6 | 5.3 | 0.3 | 17.7 | 62 | 144 |
| 35 | 5.7 | 5.3 | 0.4 | 13.3 | 26 | 74 |
| 36 | 5.7 | 5.3 | 0.4 | 13.3 | 30 | 61 |
| 37 | 5.2 | 4.8 | 0.4 | 12.0 | 27 | 84 |
| 38 | 5.5 | 5.0 | 0.5 | 10.0 | 22 | 56 |
| 39 | 5.1 | 4.6 | 0.5 | 9.2 | 44 | 49 |
| 40 | 4.9 | 4.5 | 0.4 | 11.3 | 23 | 34 |
| MEAN | 5.4 | 5.0 | 0.4 | 12.4 | 35 | 73 |
| SD | 0.30 | 0.33 | 0.06 | 2.60 | 14.0 | 33.3 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: FEMALE

| Animal ID | NA mmol/L | K mmol/L | CL mmol/L | ALP IU/L | ALT IU/L | AST IU/L | GGT IU/L |
|---|---|---|---|---|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | | | | | | |
| 9 | 143 | 6.6 | 111 | 82 | 60 | 33 | 4 |
| 10 | 143 | 6.1 | 111 | 38 | 32 | 23 | 2 |
| 11 | 144 | 7.3 | 108 | 78 | 44 | 40 | 7 |
| 12 | 141 | 5.0 | 106 | 78 | 38 | 21 | 8 |
| 13 | 140 | 5.4 | 108 | 60 | 37 | 44 | 4 |
| 14 | 141 | 5.0 | 108 | 67 | 38 | 37 | 5 |
| 15 | 141 | 4.5 | 109 | 86 | 25 | 25 | 3 |
| 16 | 139 | 4.9 | 107 | 47 | 45 | 23 | 6 |
| MEAN | 142 | 5.6 | 109 | 67 | 40 | 31 | 5 |
| SD | 1.7 | 0.97 | 1.8 | 17.4 | 10.3 | 8.9 | 2.0 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| 25 | 140 | 5.4 | 106 | 59 | 43 | 18 | 4 |
| 26 | 139 | 5.4 | 107 | 96 | 72 | 32 | 6 |
| 27 | 139 | 5.4 | 104 | 56 | 31 | 23 | 4 |
| 28 | 139 | 4.5 | 108 | 63 | 56 | 25 | 7 |
| 29 | 141 | 5.4 | 107 | 69 | 48 | 22 | 4 |
| 30 | 143 | 6.1 | 111 | 82 | 50 | 31 | 9 |
| 31 | 141 | 4.4 | 106 | 63 | 43 | 36 | 5 |
| 32 | 141 | 5.1 | 102 | 197 | 23 | 30 | 7 |
| MEAN | 140 | 5.2 | 106 | 86 | 46 | 27 | 6 |
| SD | 1.4 | 0.55 | 2.7 | 46.9 | 15.0 | 6.1 | 1.8 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003 SEX: FEMALE
STUDY NO: 2073023

| Animal ID | NA mmol/L | K mmol/L | CL mmol/L | ALP IU/L | ALT IU/L | AST IU/L | GGT IU/L |
|---|---|---|---|---|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| 41 | 138 | 4.5 | 105 | 49 | 33 | 23 | 5 |
| 42 | 143 | 5.0 | 107 | 125 | 33 | 42 | 6 |
| 43 | 138 | 4.6 | 109 | 66 | 52 | 33 | 4 |
| 44 | 143 | 6.6 | 108 | 67 | 33 | 25 | 7 |
| 45 | 140 | 4.1 | 107 | 617 | 32 | 22 | 10 |
| 46 | 141 | 5.1 | 110 | 52 | 54 | 32 | 4 |
| 47 | 139 | 5.4 | 107 | 79 | 30 | 27 | 6 |
| 48 | 139 | 4.5 | 105 | 70 | 40 | 22 | 5 |
| MEAN | 140 | 5.0 | 107 | 141 | 38 | 28 | 6 |
| SD | 2.0 | 0.77 | 1.8 | 193.9 | 9.5 | 7.0 | 2.0 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: FEMALE

| Animal ID | TBIL mg/dL | BUN mg/dL | CRE mg/dL | GLUC mg/dL | CALC mg/dL | PHOS mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | | | | | |
| 9 | 0.60 | 21 | 1.3 | 128 | 15.4 | 4.3 |
| 10 | 0.50 | 19 | 1.1 | 129 | 14.4 | 4.4 |
| 11 | 0.63 | 19 | 1.3 | 130 | 14.9 | 4.1 |
| 12 | 0.60 | 16 | 1.2 | 122 | 14.8 | 4.4 |
| 13 | 0.67 | 16 | 1.1 | 121 | 14.4 | 4.6 |
| 14 | 0.48 | 27 | 1.3 | 118 | 14.3 | 4.3 |
| 15 | 0.47 | 16 | 1.1 | 128 | 13.8 | 4.2 |
| 16 | 0.57 | 20 | 1.1 | 128 | 13.8 | 4.3 |
| MEAN | 0.57 | 19 | 1.2 | 126 | 14.5 | 4.3 |
| SD | 0.074 | 3.7 | 0.10 | 4.5 | 0.55 | 0.15 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 25 | 0.42 | 14 | 1.1 | 124 | 14.4 | 4.5 |
| 26 | 0.58 | 18 | 1.2 | 122 | 14.3 | 4.3 |
| 27 | 0.72 | 17 | 1.1 | 132 | 15.4 | 4.7 |
| 28 | 0.51 | 18 | 1.1 | 123 | 14.1 | 4.0 |
| 29 | 0.46 | 16 | 1.2 | 139 | 14.1 | 4.5 |
| 30 | 0.48 | 19 | 1.0 | 132 | 14.6 | 4.9 |
| 31 | 0.44 | 19 | 1.3 | 131 | 14.3 | 4.3 |
| 32 | 0.60 | 17 | 1.2 | 151 | 14.9 | 4.3 |
| MEAN | 0.53 | 17 | 1.2 | 132 | 14.5 | 4.4 |
| SD | 0.101 | 1.7 | 0.09 | 9.7 | 0.45 | 0.28 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: FEMALE

| Animal ID | TBIL mg/dL | BUN mg/dL | CRE mg/dL | GLUC mg/dL | CALC mg/dL | PHOS mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 41 | 0.47 | 17 | 1.0 | 132 | 14.4 | 3.8 |
| 42 | 0.47 | 20 | 1.1 | 142 | 15.2 | 4.6 |
| 43 | 0.46 | 18 | 1.0 | 132 | 14.2 | 4.2 |
| 44 | 0.47 | 17 | 1.1 | 145 | 15.7 | 5.0 |
| 45 | 0.49 | 16 | 1.2 | 139 | 13.8 | 4.0 |
| 46 | 0.55 | 19 | 1.1 | 130 | 13.8 | 4.0 |
| 47 | 0.55 | 17 | 1.2 | 122 | 14.6 | 3.9 |
| 48 | 0.33 | 13 | 1.2 | 137 | 13.8 | 3.7 |
| MEAN | 0.47 | 17 | 1.1 | 135 | 14.4 | 4.2 |
| SD | 0.068 | 2.1 | 0.08 | 7.4 | 0.70 | 0.44 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: FEMALE

| Animal ID | TP g/dL | ALB g/dL | GLOB g/dL | A/G RATIO - | CHOL mg/dL | TG mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | | | | | |
| 9 | 5.8 | 5.3 | 0.5 | 10.6 | 31 | 47 |
| 10 | 5.5 | 4.9 | 0.6 | 8.2 | 36 | 30 |
| 11 | 5.8 | 5.4 | 0.4 | 13.5 | 48 | 69 |
| 12 | 5.3 | 4.7 | 0.6 | 7.8 | 33 | 46 |
| 13 | 6.2 | 5.4 | 0.8 | 6.8 | 53 | 95 |
| 14 | 5.6 | 5.1 | 0.5 | 10.2 | 49 | 25 |
| 15 | 5.4 | 4.7 | 0.7 | 6.7 | 51 | 36 |
| 16 | 5.4 | 4.8 | 0.6 | 8.0 | 60 | 42 |
| MEAN | 5.6 | 5.0 | 0.6 | 9.0 | 45 | 49 |
| SD | 0.30 | 0.30 | 0.12 | 2.31 | 10.5 | 22.9 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 25 | 5.0 | 4.5 | 0.5 | 9.0 | 59 | 123 |
| 26 | 5.3 | 5.1 | 0.2 | 25.5 | 43 | 63 |
| 27 | 6.0 | 5.4 | 0.6 | 9.0 | 53 | 46 |
| 28 | 5.6 | 4.8 | 0.8 | 6.0 | 63 | 39 |
| 29 | 5.0 | 4.6 | 0.4 | 11.5 | 40 | 43 |
| 30 | 5.2 | 4.8 | 0.4 | 12.0 | 70 | 51 |
| 31 | 5.4 | 4.7 | 0.7 | 6.7 | 41 | 48 |
| 32 | 6.1 | 5.4 | 0.7 | 7.7 | 50 | 70 |
| MEAN | 5.5 | 4.9 | 0.5 | 10.9 | 52 | 60 |
| SD | 0.42 | 0.35 | 0.20 | 6.25 | 11.0 | 27.3 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 8

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: FEMALE

| Animal ID | TP g/dL | ALB g/dL | GLOB g/dL | A/G RATIO - | CHOL mg/dL | TG mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 41 | 5.7 | 5.3 | 0.4 | 13.3 | 44 | 57 |
| 42 | 5.6 | 5.1 | 0.5 | 10.2 | 32 | 51 |
| 43 | 5.3 | 5.1 | 0.2 | 25.5 | 40 | 51 |
| 44 | 5.5 | 4.9 | 0.6 | 8.2 | 58 | 84 |
| 45 | 4.8 | 4.6 | 0.2 | 23.0 | 41 | 59 |
| 46 | 5.3 | 4.9 | 0.4 | 12.3 | 50 | 56 |
| 47 | 6.1 | 5.5 | 0.6 | 9.2 | 85 | 56 |
| 48 | 5.4 | 4.7 | 0.7 | 6.7 | 84 | 56 |
| MEAN | 5.5 | 5.0 | 0.5 | 13.6 | 54 | 59 |
| SD | 0.37 | 0.30 | 0.19 | 6.96 | 20.1 | 10.6 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: MALE

| Animal ID | NA mmol/L | K mmol/L | CL mmol/L | ALP IU/L | ALT IU/L | AST IU/L | GGT IU/L |
|---|---|---|---|---|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | | | | | | |
| 1 | 139 | 3.9 | 108 | 69 | 28 | 25 | 2 |
| 2 | 138 | 3.5 | 106 | 39 | 57 | 25 | 3 |
| 3 | 143 | 3.5 | 110 | 97 | 35 | 25 | 5 |
| 4 | 140 | 4.9 | 108 | 48 | 32 | 29 | 5 |
| 5 | 144 | 6.5 | 112 | 36 | 31 | 29 | 3 |
| 6 | 140 | 5.8 | 108 | 64 | 48 | 19 | 0 |
| 7 | 139 | 4.2 | 104 | 28 | 64 | 23 | 6 |
| 8 | 139 | 3.9 | 103 | 93 | 54 | 19 | 4 |
| MEAN | 140 | 4.5 | 107 | 59 | 44 | 24 | 4 |
| SD | 2.1 | 1.11 | 3.0 | 26.0 | 13.8 | 3.8 | 1.9 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| 17 | 139 | 3.5 | 108 | 47 | 25 | 19 | 5 |
| 18 | 138 | 4.0 | 109 | 55 | 46 | 30 | 6 |
| 19 | 142 | 4.4 | 109 | 73 | 50 | 25 | 5 |
| 20 | 148 | 6.5 | 106 | 80 | 41 | 37 | 6 |
| 21 | 143 | 5.5 | 108 | 79 | 44 | 36 | 6 |
| 22 | 145 | 5.9 | 110 | 58 | 35 | 21 | 3 |
| 23 | 141 | 4.7 | 105 | 60 | 34 | 20 | 3 |
| 24 | 143 | 4.8 | 109 | 39 | 50 | 25 | 4 |
| MEAN | 142 | 4.9 | 108 | 61 | 41 | 27 | 5 |
| SD | 3.2 | 1.00 | 1.7 | 14.9 | 8.7 | 7.0 | 1.3 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: MALE
STUDY NO: 2073023

| Animal ID | NA mmol/L | K mmol/L | CL mmol/L | ALP IU/L | ALT IU/L | AST IU/L | GGT IU/L |
|---|---|---|---|---|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| 33 | 140 | 3.8 | 108 | 52 | 36 | 27 | 5 |
| 34 | 139 | 4.4 | 106 | 87 | 38 | 21 | 9 |
| 35 | 148 | 6.1 | 108 | 48 | 46 | 32 | 5 |
| 36 | 144 | 5.5 | 107 | 45 | 29 | 32 | 4 |
| 37 | 145 | 5.7 | 111 | 101 | 34 | 30 | 4 |
| 38 | 138 | 4.4 | 104 | 54 | 18 | 21 | 4 |
| 39 | 136 | 4.2 | 105 | 55 | 46 | 23 | 8 |
| 40 | 145 | 7.0 | 107 | 47 | 16 | 29 | 5 |
| MEAN | 142 | 5.1 | 107 | 61 | 33 | 27 | 6 |
| SD | 4.2 | 1.11 | 2.1 | 20.9 | 11.4 | 4.6 | 1.9 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: MALE
STUDY NO: 2073023

| Animal ID | TBIL mg/dL | BUN mg/dL | CRE mg/dL | GLUC mg/dL | CALC mg/dL | PHOS mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | | | | | |
| 1 | 0.59 | 15 | 0.9 | 125 | 13.2 | 4.3 |
| 2 | 0.45 | 16 | 1.0 | 116 | 13.5 | 4.8 |
| 3 | 0.44 | 17 | 1.5 | 120 | 13.1 | 4.9 |
| 4 | 0.49 | 29 | 1.4 | 114 | 13.5 | 6.2 |
| 5 | 0.50 | 19 | 1.2 | 119 | 14.8 | 6.2 |
| 6 | 0.58 | 16 | 0.9 | 136 | 15.0 | 3.6 |
| 7 | 0.60 | 21 | 1.0 | 141 | 14.2 | 4.3 |
| 8 | 0.36 | 17 | 1.1 | 130 | 14.1 | 4.0 |
| MEAN | 0.50 | 19 | 1.1 | 125 | 13.9 | 4.8 |
| SD | 0.085 | 4.6 | 0.23 | 9.7 | 0.72 | 0.96 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 17 | 0.48 | 18 | 1.1 | 114 | 13.4 | 5.1 |
| 18 | 0.40 | 19 | 1.2 | 123 | 13.2 | 4.7 |
| 19 | 0.61 | 20 | 1.1 | 113 | 14.2 | 5.8 |
| 20 | 0.61 | 20 | 1.2 | 122 | 15.8 | 6.5 |
| 21 | 0.64 | 20 | 1.3 | 131 | 14.8 | 5.6 |
| 22 | 0.61 | 21 | 1.0 | 120 | 15.3 | 4.5 |
| 23 | 0.66 | 15 | 0.9 | 135 | 14.7 | 4.2 |
| 24 | 0.42 | 18 | 1.4 | 136 | 14.8 | 3.8 |
| MEAN | 0.55 | 19 | 1.2 | 124 | 14.5 | 5.0 |
| SD | 0.104 | 1.9 | 0.16 | 8.9 | 0.89 | 0.90 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: MALE
STUDY NO: 2073023

| Animal ID | TBIL mg/dL | BUN mg/dL | CRE mg/dL | GLUC mg/dL | CALC mg/dL | PHOS mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 33 | 0.53 | 22 | 1.2 | 122 | 13.6 | 5.1 |
| 34 | 0.58 | 19 | 1.3 | 125 | 13.8 | 4.9 |
| 35 | 0.59 | 15 | 1.2 | 119 | 15.1 | 6.1 |
| 36 | 0.54 | 21 | 1.2 | 123 | 14.8 | 5.4 |
| 37 | 0.49 | 19 | 1.4 | 135 | 14.6 | 6.3 |
| 38 | 0.42 | 14 | 0.9 | 123 | 14.5 | 3.6 |
| 39 | 0.51 | 24 | 0.9 | 138 | 13.9 | 4.2 |
| 40 | 0.56 | 15 | 1.3 | 188 | 15.6 | 5.8 |
| MEAN | 0.53 | 19 | 1.2 | 134 | 14.5 | 5.2 |
| SD | 0.055 | 3.7 | 0.18 | 22.8 | 0.69 | 0.93 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003
STUDY NO: 2073023

SEX: MALE

| Animal ID | TP g/dL | ALB g/dL | GLOB g/dL | A/G RATIO - | CHOL mg/dL | TG mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | | | | | |
| 1 | 5.6 | 5.5 | 0.1 | 55.0 | 17 | 87 |
| 2 | 5.7 | 5.2 | 0.5 | 10.4 | 25 | 77 |
| 3 | 5.0 | 4.7 | 0.3 | 15.7 | 29 | 16 |
| 4 | 5.8 | 5.0 | 0.8 | 6.3 | 37 | 32 |
| 5 | 5.9 | 5.5 | 0.4 | 13.8 | 47 | 89 |
| 6 | 5.2 | 4.8 | 0.4 | 12.0 | 34 | 99 |
| 7 | 5.2 | 4.7 | 0.5 | 9.4 | 29 | 53 |
| 8 | 5.1 | 4.7 | 0.4 | 11.8 | 47 | 87 |
| MEAN | 5.4 | 5.0 | 0.4 | 16.8 | 33 | 68 |
| SD | 0.35 | 0.35 | 0.20 | 15.69 | 10.4 | 30.3 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 17 | 5.3 | 4.9 | 0.4 | 12.3 | 27 | 30 |
| 18 | 5.4 | 4.9 | 0.5 | 9.8 | 38 | 41 |
| 19 | 5.6 | 5.2 | 0.4 | 13.0 | 18 | 29 |
| 20 | 6.6 | 6.0 | 0.6 | 10.0 | 30 | 49 |
| 21 | 6.0 | 5.6 | 0.4 | 14.0 | 28 | 39 |
| 22 | 5.7 | 5.2 | 0.5 | 10.4 | 18 | 74 |
| 23 | 5.3 | 4.8 | 0.5 | 9.6 | 28 | 104 |
| 24 | 5.8 | 5.3 | 0.5 | 10.6 | 30 | 54 |
| MEAN | 5.7 | 5.2 | 0.5 | 11.2 | 27 | 53 |
| SD | 0.44 | 0.40 | 0.07 | 1.66 | 6.6 | 25.4 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: MALE
STUDY NO: 2073023

| Animal ID | TP g/dL | ALB g/dL | GLOB g/dL | A/G RATIO - | CHOL mg/dL | TG mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 33 | 4.9 | 4.6 | 0.3 | 15.3 | 40 | 36 |
| 34 | 5.5 | 5.1 | 0.4 | 12.8 | 53 | 24 |
| 35 | 6.4 | 5.7 | 0.7 | 8.1 | 30 | 30 |
| 36 | 5.8 | 5.3 | 0.5 | 10.6 | 29 | 38 |
| 37 | 6.0 | 5.5 | 0.5 | 11.0 | 34 | 43 |
| 38 | 5.4 | 5.0 | 0.4 | 12.5 | 21 | 59 |
| 39 | 5.0 | 4.7 | 0.3 | 15.7 | 40 | 61 |
| 40 | 5.5 | 4.8 | 0.7 | 6.9 | 29 | 58 |
| MEAN | 5.6 | 5.1 | 0.5 | 11.6 | 35 | 44 |
| SD | 0.50 | 0.39 | 0.16 | 3.13 | 9.8 | 14.2 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: FEMALE

| Animal ID | NA mmol/L | K mmol/L | CL mmol/L | ALP IU/L | ALT IU/L | AST IU/L | GGT IU/L |
|---|---|---|---|---|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | | | | | | |
| 9 | 145 | 5.1 | 111 | 74 | 58 | 36 | 4 |
| 10 | 143 | 5.5 | 110 | 50 | 37 | 28 | 4 |
| 11 | 138 | 4.1 | 106 | 62 | 39 | 44 | 5 |
| 12 | 137 | 4.2 | 105 | 82 | 39 | 22 | 7 |
| 13 | 143 | 5.1 | 105 | 65 | 32 | 35 | 6 |
| 14 | 141 | 4.2 | 101 | 52 | 38 | 40 | 5 |
| 15 | 140 | 4.0 | 107 | 65 | 25 | 18 | 0 |
| 16 | 142 | 4.7 | 102 | 53 | 51 | 41 | 3 |
| MEAN | 141 | 4.6 | 106 | 63 | 40 | 33 | 4 |
| SD | 2.7 | 0.57 | 3.5 | 11.2 | 10.3 | 9.4 | 2.1 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| 25 | 142 | 4.1 | 109 | 66 | 45 | 21 | 6 |
| 26 | 143 | 4.8 | 105 | 89 | 77 | 53 | 7 |
| 27 | 140 | 4.0 | 106 | 52 | 42 | 33 | 4 |
| 28 | 142 | 4.0 | 106 | 55 | 50 | 35 | 8 |
| 29 | 146 | 6.1 | 108 | 76 | 83 | 43 | 4 |
| 30 | 137 | 4.4 | 106 | 69 | 37 | 23 | 7 |
| 31 | 140 | 5.2 | 109 | 61 | 45 | 24 | 5 |
| 32 | 142 | 4.3 | 103 | 433 | 23 | 26 | 6 |
| MEAN | 142 | 4.6 | 107 | 113 | 50 | 32 | 6 |
| SD | 2.6 | 0.73 | 2.1 | 130.0 | 20.1 | 11.2 | 1.5 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003
STUDY NO: 2073023

SEX: FEMALE

| Animal ID | NA mmol/L | K mmol/L | CL mmol/L | ALP IU/L | ALT IU/L | AST IU/L | GGT IU/L |
|---|---|---|---|---|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| 41 | 139 | 4.0 | 104 | 51 | 34 | 25 | 3 |
| 42 | 142 | 4.0 | 108 | 119 | 38 | 39 | 7 |
| 43 | 133 | 3.8 | 104 | 81 | 49 | 34 | 1 |
| 44 | 141 | 4.6 | 108 | 81 | 45 | 32 | 6 |
| 45 | 141 | 4.6 | 106 | 607 | 37 | 24 | 9 |
| 46 | 139 | 4.4 | 106 | 44 | 44 | 26 | 4 |
| 47 | 138 | 4.6 | 106 | 80 | 27 | 22 | 3 |
| 48 | 138 | 4.4 | 103 | 63 | 78 | 121 | 7 |
| MEAN | 139 | 4.3 | 106 | 141 | 44 | 40 | 5 |
| SD | 2.8 | 0.32 | 1.8 | 189.8 | 15.4 | 33.1 | 2.7 |
| N | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: FEMALE
STUDY NO: 2073023

| Animal ID | TBIL mg/dL | BUN mg/dL | CRE mg/dL | GLUC mg/dL | CALC mg/dL | PHOS mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | | | | | |
| 9 | 0.54 | 27 | 1.8 | 144 | 14.1 | 5.4 |
| 10 | 0.61 | 22 | 1.4 | 115 | 14.4 | 5.2 |
| 11 | 0.70 | 26 | 1.6 | 123 | 13.1 | 4.8 |
| 12 | 0.60 | 25 | 1.6 | 116 | 13.9 | 5.6 |
| 13 | 0.51 | 17 | 1.6 | 128 | 13.9 | 5.9 |
| 14 | 0.70 | 21 | 1.4 | 153 | 14.3 | 5.0 |
| 15 | 0.43 | 14 | 1.1 | 121 | 13.6 | 4.9 |
| 16 | 0.64 | 16 | 1.2 | 159 | 13.6 | 3.9 |
| MEAN | 0.59 | 21 | 1.5 | 132 | 13.9 | 5.1 |
| SD | 0.094 | 4.9 | 0.23 | 17.2 | 0.42 | 0.61 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 25 | 0.53 | 20 | 1.5 | 115 | 14.2 | 5.7 |
| 26 | 0.63 | 23 | 1.7 | 129 | 13.6 | 6.9 |
| 27 | 0.65 | 29 | 1.5 | 103 | 14.6 | 5.6 |
| 28 | 0.46 | 22 | 1.5 | 113 | 13.9 | 5.6 |
| 29 | 0.63 | 24 | 1.7 | 126 | 13.9 | 6.8 |
| 30 | 0.46 | 15 | 1.0 | 126 | 14.2 | 4.2 |
| 31 | 0.59 | 21 | 1.0 | 122 | 15.1 | 4.0 |
| 32 | 0.64 | 18 | 1.1 | 149 | 15.0 | 4.5 |
| MEAN | 0.57 | 22 | 1.4 | 123 | 14.3 | 5.4 |
| SD | 0.080 | 4.2 | 0.30 | 13.6 | 0.54 | 1.11 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: FEMALE
STUDY NO: 2073023

| Animal ID | TBIL mg/dL | BUN mg/dL | CRE mg/dL | GLUC mg/dL | CALC mg/dL | PHOS mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 41 | 0.49 | 22 | 1.2 | 119 | 14.1 | 5.0 |
| 42 | 0.56 | 25 | 1.3 | 109 | 13.8 | 5.2 |
| 43 | 0.53 | 20 | 1.3 | 111 | 13.1 | 5.0 |
| 44 | 0.58 | 25 | 1.5 | 109 | 14.0 | 6.1 |
| 45 | 0.50 | 24 | 1.6 | 121 | 13.6 | 5.7 |
| 46 | 0.64 | 19 | 1.1 | 128 | 14.0 | 4.2 |
| 47 | 0.67 | 16 | 1.0 | 133 | 14.7 | 4.8 |
| 48 | 0.47 | 17 | 1.1 | 134 | 14.9 | 4.2 |
| MEAN | 0.56 | 21 | 1.3 | 121 | 14.0 | 5.0 |
| SD | 0.072 | 3.5 | 0.21 | 10.4 | 0.58 | 0.66 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: FEMALE
STUDY NO: 2073023

| Animal ID | TP g/dL | ALB g/dL | GLOB g/dL | A/G RATIO - | CHOL mg/dL | TG mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | | | | | |
| 9 | 5.7 | 5.1 | 0.6 | 8.5 | 29 | 22 |
| 10 | 5.7 | 5.3 | 0.4 | 13.3 | 39 | 32 |
| 11 | 5.2 | 4.7 | 0.5 | 9.4 | 40 | 35 |
| 12 | 5.4 | 4.8 | 0.6 | 8.0 | 29 | 19 |
| 13 | 5.8 | 5.2 | 0.6 | 8.7 | 37 | 39 |
| 14 | 5.5 | 5.1 | 0.4 | 12.8 | 49 | 80 |
| 15 | 5.0 | 4.3 | 0.7 | 6.1 | 44 | 50 |
| 16 | 5.7 | 5.1 | 0.6 | 8.5 | 65 | 58 |
| MEAN | 5.5 | 5.0 | 0.6 | 9.4 | 42 | 42 |
| SD | 0.28 | 0.33 | 0.11 | 2.44 | 11.7 | 20.2 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 25 | 5.4 | 4.7 | 0.7 | 6.7 | 51 | 49 |
| 26 | 5.7 | 5.2 | 0.5 | 10.4 | 40 | 43 |
| 27 | 6.0 | 5.4 | 0.6 | 9.0 | 49 | 22 |
| 28 | 5.5 | 4.7 | 0.8 | 5.9 | 57 | 23 |
| 29 | 5.7 | 5.2 | 0.5 | 10.4 | 45 | 34 |
| 30 | 4.9 | 4.6 | 0.3 | 15.3 | 63 | 60 |
| 31 | 5.0 | 4.5 | 0.5 | 9.0 | 34 | 69 |
| 32 | 5.6 | 5.2 | 0.4 | 13.0 | 39 | 87 |
| MEAN | 5.5 | 4.9 | 0.5 | 10.0 | 47 | 48 |
| SD | 0.37 | 0.35 | 0.16 | 3.10 | 9.7 | 22.8 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 15

STUDY ID: 2073-002-003 SEX: FEMALE
STUDY NO: 2073023

| Animal ID | TP g/dL | ALB g/dL | GLOB g/dL | A/G RATIO - | CHOL mg/dL | TG mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 41 | 5.3 | 5.1 | 0.2 | 25.5 | 37 | 31 |
| 42 | 5.4 | 4.9 | 0.5 | 9.8 | 36 | 27 |
| 43 | 5.2 | 4.9 | 0.3 | 16.3 | 34 | 27 |
| 44 | 5.6 | 5.0 | 0.6 | 8.3 | 59 | 29 |
| 45 | 4.9 | 4.8 | 0.1 | 48.0 | 37 | 47 |
| 46 | 4.9 | 4.7 | 0.2 | 23.5 | 44 | 72 |
| 47 | 5.4 | 4.8 | 0.6 | 8.0 | 61 | 78 |
| 48 | 5.5 | 4.9 | 0.6 | 8.2 | 76 | 77 |
| MEAN | 5.3 | 4.9 | 0.4 | 18.5 | 48 | 49 |
| SD | 0.26 | 0.12 | 0.21 | 13.86 | 15.5 | 23.4 |
| N | 8 | 8 | 8 | 8 | 8 | 8 |

Appendix B, Table 5 (cont.)
(Recovery)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: MALE
STUDY NO: 2073023

| Animal ID | NA mmol/L | K mmol/L | CL mmol/L | ALP IU/L | ALT IU/L | AST IU/L | GGT IU/L |
|---|---|---|---|---|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | | | | | | |
| 1 | a | a | a | a | a | a | a |
| 2 | a | a | a | a | a | a | a |
| 3 | a | a | a | a | a | a | a |
| 4 | a | a | a | a | a | a | a |
| 5 | a | a | a | a | a | a | a |
| 6 | 139 | 4.5 | 109 | 51 | 51 | 30 | 1 |
| 7 | 137 | 4.5 | 106 | 33 | 61 | 30 | 3 |
| 8 | 137 | 4.0 | 105 | 104 | 52 | 22 | 9 |
| MEAN | 138 | 4.3 | 107 | 63 | 55 | 27 | 4 |
| SD | 1.2 | 0.29 | 2.1 | 36.9 | 5.5 | 4.6 | 4.2 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| 17 | a | a | a | a | a | a | a |
| 18 | a | a | a | a | a | a | a |
| 19 | a | a | a | a | a | a | a |
| 20 | a | a | a | a | a | a | a |
| 21 | a | a | a | a | a | a | a |
| 22 | 138 | 3.9 | 111 | 53 | 33 | 20 | 4 |
| 23 | 137 | 4.3 | 111 | 55 | 33 | 24 | 2 |
| 24 | 141 | 6.5 | 111 | 34 | 56 | 31 | 2 |
| MEAN | 139 | 4.9 | 111 | 47 | 41 | 25 | 3 |
| SD | 2.1 | 1.40 | 0.0 | 11.6 | 13.3 | 5.6 | 1.2 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 5 (cont.)
(Recovery)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003
STUDY NO: 2073023

SEX: MALE

| Animal ID | NA mmol/L | K mmol/L | CL mmol/L | ALP IU/L | ALT IU/L | AST IU/L | GGT IU/L |
|---|---|---|---|---|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| 33 | a | a | a | a | a | a | a |
| 34 | a | a | a | a | a | a | a |
| 35 | a | a | a | a | a | a | a |
| 36 | a | a | a | a | a | a | a |
| 37 | a | a | a | a | a | a | a |
| 38 | 140 | 6.4 | 108 | 46 | 21 | 46 | 10 |
| 39 | 140 | 5.8 | 110 | 51 | 43 | 29 | 10 |
| 40 | 139 | 4.8 | 107 | 27 | 9 | 24 | 4 |
| MEAN | 140 | 5.7 | 108 | 41 | 24 | 33 | 8 |
| SD | 0.6 | 0.81 | 1.5 | 12.7 | 17.2 | 11.5 | 3.5 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 5 (cont.)
(Recovery)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: MALE
STUDY NO: 2073023

| Animal ID | TBIL mg/dL | BUN mg/dL | CRE mg/dL | GLUC mg/dL | CALC mg/dL | PHOS mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | | | | | |
| 1 | a | a | a | a | a | a |
| 2 | a | a | a | a | a | a |
| 3 | a | a | a | a | a | a |
| 4 | a | a | a | a | a | a |
| 5 | a | a | a | a | a | a |
| 6 | 0.51 | 19 | 1.1 | 126 | 13.6 | 5.2 |
| 7 | 0.56 | 22 | 1.2 | 120 | 14.0 | 5.3 |
| 8 | 0.49 | 19 | 1.4 | 118 | 14.4 | 5.4 |
| MEAN | 0.52 | 20 | 1.2 | 121 | 14.0 | 5.3 |
| SD | 0.036 | 1.7 | 0.15 | 4.2 | 0.40 | 0.10 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 17 | a | a | a | a | a | a |
| 18 | a | a | a | a | a | a |
| 19 | a | a | a | a | a | a |
| 20 | a | a | a | a | a | a |
| 21 | a | a | a | a | a | a |
| 22 | 0.60 | 19 | 1.1 | 123 | 13.5 | 5.3 |
| 23 | 0.61 | 21 | 1.3 | 115 | 14.2 | 5.5 |
| 24 | 0.37 | 21 | 1.8 | 121 | 14.6 | 5.5 |
| MEAN | 0.53 | 20 | 1.4 | 120 | 14.1 | 5.4 |
| SD | 0.136 | 1.2 | 0.36 | 4.2 | 0.56 | 0.12 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 5 (cont.)
(Recovery)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003
STUDY NO: 2073023

SEX: MALE

| Animal ID | TBIL mg/dL | BUN mg/dL | CRE mg/dL | GLUC mg/dL | CALC mg/dL | PHOS mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 33 | a | a | a | a | a | a |
| 34 | a | a | a | a | a | a |
| 35 | a | a | a | a | a | a |
| 36 | a | a | a | a | a | a |
| 37 | a | a | a | a | a | a |
| 38 | 0.63 | 17 | 1.3 | 131 | 14.5 | 5.8 |
| 39 | 0.51 | 29 | 1.6 | 121 | 14.8 | 6.0 |
| 40 | 0.45 | 15 | 1.4 | 107 | 13.8 | 5.6 |
| MEAN | 0.53 | 20 | 1.4 | 120 | 14.4 | 5.8 |
| SD | 0.092 | 7.6 | 0.15 | 12.1 | 0.51 | 0.20 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 5 (cont.)
(Recovery)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: MALE
STUDY NO: 2073023

| Animal ID | TP g/dL | ALB g/dL | GLOB g/dL | A/G RATIO - | CHOL mg/dL | TG mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | | | | | |
| 1 | a | a | a | a | a | a |
| 2 | a | a | a | a | a | a |
| 3 | a | a | a | a | a | a |
| 4 | a | a | a | a | a | a |
| 5 | a | a | a | a | a | a |
| 6 | 5.3 | 5.1 | 0.2 | 25.5 | 26 | 31 |
| 7 | 5.4 | 5.2 | 0.2 | 26.0 | 30 | 33 |
| 8 | 5.2 | 4.9 | 0.3 | 16.3 | 42 | 20 |
| MEAN | 5.3 | 5.1 | 0.2 | 22.6 | 33 | 28 |
| SD | 0.10 | 0.15 | 0.06 | 5.46 | 8.3 | 7.0 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 17 | a | a | a | a | a | a |
| 18 | a | a | a | a | a | a |
| 19 | a | a | a | a | a | a |
| 20 | a | a | a | a | a | a |
| 21 | a | a | a | a | a | a |
| 22 | 5.3 | 4.9 | 0.4 | 12.3 | 18 | 22 |
| 23 | 5.1 | 5.0 | 0.1 | 50.0 | 30 | 32 |
| 24 | 5.6 | 5.3 | 0.3 | 17.7 | 30 | 24 |
| MEAN | 5.3 | 5.1 | 0.3 | 26.7 | 26 | 26 |
| SD | 0.25 | 0.21 | 0.15 | 20.39 | 6.9 | 5.3 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 5 (cont.)
(Recovery)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: MALE

| Animal ID | TP g/dL | ALB g/dL | GLOB g/dL | A/G RATIO - | CHOL mg/dL | TG mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 33 | a | a | a | a | a | a |
| 34 | a | a | a | a | a | a |
| 35 | a | a | a | a | a | a |
| 36 | a | a | a | a | a | a |
| 37 | a | a | a | a | a | a |
| 38 | 5.3 | 5.0 | 0.3 | 16.7 | 20 | 52 |
| 39 | 5.6 | 5.0 | 0.6 | 8.3 | 44 | 35 |
| 40 | 5.1 | 4.6 | 0.5 | 9.2 | 31 | 32 |
| MEAN | 5.3 | 4.9 | 0.5 | 11.4 | 32 | 40 |
| SD | 0.25 | 0.23 | 0.15 | 4.61 | 12.0 | 10.8 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 5 (cont.)
(Recovery)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: FEMALE

| Animal ID | NA mmol/L | K mmol/L | CL mmol/L | ALP IU/L | ALT IU/L | AST IU/L | GGT IU/L |
|---|---|---|---|---|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | | | | | | |
| 9 | a | a | a | a | a | a | a |
| 10 | a | a | a | a | a | a | a |
| 11 | a | a | a | a | a | a | a |
| 12 | a | a | a | a | a | a | a |
| 13 | a | a | a | a | a | a | a |
| 14 | 140 | 5.2 | 107 | 51 | 44 | 38 | 4 |
| 15 | 136 | 4.4 | 109 | 48 | 24 | 22 | 2 |
| 16 | 138 | 4.5 | 108 | 59 | 63 | 64 | 6 |
| MEAN | 138 | 4.7 | 108 | 53 | 44 | 41 | 4 |
| SD | 2.0 | 0.44 | 1.0 | 5.7 | 19.5 | 21.2 | 2.0 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| 25 | a | a | a | a | a | a | a |
| 26 | a | a | a | a | a | a | a |
| 27 | a | a | a | a | a | a | a |
| 28 | a | a | a | a | a | a | a |
| 29 | a | a | a | a | a | a | a |
| 30 | 143 | 6.4 | 108 | 74 | 60 | 35 | 9 |
| 31 | 138 | 4.1 | 110 | 51 | 53 | 27 | 5 |
| 32 | 139 | 4.6 | 110 | 416 | 23 | 30 | 7 |
| MEAN | 140 | 5.0 | 109 | 180 | 45 | 31 | 7 |
| SD | 2.6 | 1.21 | 1.2 | 204.4 | 19.7 | 4.0 | 2.0 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 5 (cont.)
(Recovery)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: FEMALE

| Animal ID | NA mmol/L | K mmol/L | CL mmol/L | ALP IU/L | ALT IU/L | AST IU/L | GGT IU/L |
|---|---|---|---|---|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | | |
| 41 | a | a | a | a | a | a | a |
| 42 | a | a | a | a | a | a | a |
| 43 | a | a | a | a | a | a | a |
| 44 | a | a | a | a | a | a | a |
| 45 | a | a | a | a | a | a | a |
| 46 | 138 | 4.7 | 111 | 36 | 42 | 26 | 3 |
| 47 | 139 | 4.8 | 106 | 58 | 31 | 25 | 8 |
| 48 | 140 | 4.6 | 110 | 67 | 40 | 25 | 6 |
| MEAN | 139 | 4.7 | 109 | 54 | 38 | 25 | 6 |
| SD | 1.0 | 0.10 | 2.6 | 15.9 | 5.9 | 0.6 | 2.5 |
| N | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 5 (cont.)
(Recovery)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003
STUDY NO: 2073023

SEX: FEMALE

| Animal ID | TBIL mg/dL | BUN mg/dL | CRE mg/dL | GLUC mg/dL | CALC mg/dL | PHOS mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | | | | | |
| 9 | a | a | a | a | a | a |
| 10 | a | a | a | a | a | a |
| 11 | a | a | a | a | a | a |
| 12 | a | a | a | a | a | a |
| 13 | a | a | a | a | a | a |
| 14 | 0.56 | 26 | 1.7 | 117 | 13.8 | 5.5 |
| 15 | 0.45 | 23 | 1.5 | 109 | 13.3 | 5.9 |
| 16 | 0.56 | 26 | 1.5 | 113 | 13.8 | 5.3 |
| MEAN | 0.52 | 25 | 1.6 | 113 | 13.6 | 5.6 |
| SD | 0.064 | 1.7 | 0.12 | 4.0 | 0.29 | 0.31 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 25 | a | a | a | a | a | a |
| 26 | a | a | a | a | a | a |
| 27 | a | a | a | a | a | a |
| 28 | a | a | a | a | a | a |
| 29 | a | a | a | a | a | a |
| 30 | 0.45 | 26 | 1.8 | 133 | 15.2 | 6.7 |
| 31 | 0.61 | 23 | 1.5 | 110 | 13.4 | 4.5 |
| 32 | 0.56 | 28 | 1.4 | 126 | 13.5 | 4.7 |
| MEAN | 0.54 | 26 | 1.6 | 123 | 14.0 | 5.3 |
| SD | 0.082 | 2.5 | 0.21 | 11.8 | 1.01 | 1.22 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 5 (cont.)
(Recovery)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: FEMALE

| Animal ID | TBIL mg/dL | BUN mg/dL | CRE mg/dL | GLUC mg/dL | CALC mg/dL | PHOS mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 41 | a | a | a | a | a | a |
| 42 | a | a | a | a | a | a |
| 43 | a | a | a | a | a | a |
| 44 | a | a | a | a | a | a |
| 45 | a | a | a | a | a | a |
| 46 | 0.49 | 23 | 1.6 | 120 | 13.4 | 6.1 |
| 47 | 0.38 | 26 | 1.6 | 107 | 14.6 | 7.9 |
| 48 | 0.41 | 21 | 1.4 | 121 | 13.7 | 4.9 |
| MEAN | 0.43 | 23 | 1.5 | 116 | 13.9 | 6.3 |
| SD | 0.057 | 2.5 | 0.12 | 7.8 | 0.62 | 1.51 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 5 (cont.)
(Recovery)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003 SEX: FEMALE
STUDY NO: 2073023

| Animal ID | TP g/dL | ALB g/dL | GLOB g/dL | A/G RATIO - | CHOL mg/dL | TG mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | | | | | |
| 9 | a | a | a | a | a | a |
| 10 | a | a | a | a | a | a |
| 11 | a | a | a | a | a | a |
| 12 | a | a | a | a | a | a |
| 13 | a | a | a | a | a | a |
| 14 | 5.6 | 5.3 | 0.3 | 17.7 | 48 | 23 |
| 15 | 4.9 | 4.5 | 0.4 | 11.3 | 45 | 30 |
| 16 | 5.3 | 5.0 | 0.3 | 16.7 | 43 | 27 |
| MEAN | 5.3 | 4.9 | 0.3 | 15.2 | 45 | 27 |
| SD | 0.35 | 0.40 | 0.06 | 3.44 | 2.5 | 3.5 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 25 | a | a | a | a | a | a |
| 26 | a | a | a | a | a | a |
| 27 | a | a | a | a | a | a |
| 28 | a | a | a | a | a | a |
| 29 | a | a | a | a | a | a |
| 30 | 5.5 | 4.9 | 0.6 | 8.2 | 58 | 68 |
| 31 | 5.0 | 4.7 | 0.3 | 15.7 | 37 | 23 |
| 32 | 5.6 | 5.2 | 0.4 | 13.0 | 33 | 38 |
| MEAN | 5.4 | 4.9 | 0.4 | 12.3 | 43 | 43 |
| SD | 0.32 | 0.25 | 0.15 | 3.80 | 13.4 | 22.9 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 5 (cont.)
(Recovery)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
PERIOD: Day 29

STUDY ID: 2073-002-003
STUDY NO: 2073023
SEX: FEMALE

| Animal ID | TP g/dL | ALB g/dL | GLOB g/dL | A/G RATIO - | CHOL mg/dL | TG mg/dL |
|---|---|---|---|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | | | | | |
| 41 | a | a | a | a | a | a |
| 42 | a | a | a | a | a | a |
| 43 | a | a | a | a | a | a |
| 44 | a | a | a | a | a | a |
| 45 | a | a | a | a | a | a |
| 46 | 5.0 | 4.8 | 0.2 | 24.0 | 44 | 21 |
| 47 | 5.5 | 4.9 | 0.6 | 8.2 | 78 | 34 |
| 48 | 5.0 | 4.7 | 0.3 | 15.7 | 49 | 37 |
| MEAN | 5.2 | 4.8 | 0.4 | 16.0 | 57 | 31 |
| SD | 0.29 | 0.10 | 0.21 | 7.90 | 18.4 | 8.5 |
| N | 3 | 3 | 3 | 3 | 3 | 3 |

a - Sacrificed day 15

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
TEST: Total Bile Acid

STUDY ID: 2073-002-003 SEX: MALE
STUDY NO: 2073023
ABBR: TBA UNITS: umol/L

| Animal ID | Day 15 | Day 29 |
|---|---|---|
| GROUP: 1-M:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline) | | |
| 1 | 5.0 | a |
| 2 | 9.2 | a |
| 3 | 4.8 | a |
| 4 | 9.1 | a |
| 5 | 7.8 | a |
| 6 | 9.5 | 8.9 |
| 7 | 12.5 | 9.5 |
| 8 | 34.8 | 13.5 |
| MEAN | 11.6 | 10.6 |
| SD | 9.71 | 2.50 |
| N | 8 | 3 |
| GROUP: 2-M:0.030 mg/kg/day CuATSM / H2ATSM | | |
| 17 | 4.6 | a |
| 18 | 9.2 | a |
| 19 | 4.9 | a |
| 20 | 11.8 | a |
| 21 | 15.3 | a |
| 22 | 7.4 | 18.6 |
| 23 | 18.0 | 12.2 |
| 24 | 25.3 | 8.5 |
| MEAN | 12.1 | 13.1 |
| SD | 7.15 | 5.11 |
| N | 8 | 3 |

a - Sacrificed day 15

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
TEST: Total Bile Acid

STUDY ID: 2073-002-003 SEX: MALE
STUDY NO: 2073023
ABBR: TBA UNITS: umol/L

| Animal ID | Day 15 | Day 29 |
|---|---|---|
| GROUP: 3-M:0.060 mg/kg/day CuATSM / H2ATSM | | |
| 33 | 13.2 | a |
| 34 | 15.3 | a |
| 35 | 4.8 | a |
| 36 | 11.0 | a |
| 37 | 11.2 | a |
| 38 | 13.3 | 17.8 |
| 39 | 21.0 | 9.3 |
| 40 | 30.3 | 3.9 |
| MEAN | 15.0 | 10.3 |
| SD | 7.66 | 7.01 |
| N | 8 | 3 |

a - Sacrificed day 15

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
TEST: Total Bile Acid

STUDY ID: 2073-002-003 SEX: FEMALE
STUDY NO: 2073023
ABBR: TBA UNITS: umol/L

| Animal ID | Day 15 | Day 29 |
|---|---|---|
| GROUP: 1-F:0.000 mg/kg/day (0.3% DMSO/7% ethanol/ 92.7% saline | | |
| 9 | 13.3 | a |
| 10 | 13.0 | a |
| 11 | 21.2 | a |
| 12 | 13.5 | a |
| 13 | 12.9 | a |
| 14 | 15.1 | 9.5 |
| 15 | 37.0 | 10.2 |
| 16 | 18.5 | 17.2 |
| MEAN | 18.1 | 12.3 |
| SD | 8.22 | 4.26 |
| N | 8 | 3 |
| GROUP: 2-F:0.030 mg/kg/day CuATSM / H2ATSM | | |
| 25 | 31.2 | a |
| 26 | 29.7 | a |
| 27 | 18.7 | a |
| 28 | 28.8 | a |
| 29 | 20.1 | a |
| 30 | 35.3 | 33.0 |
| 31 | 25.4 | 28.0 |
| 32 | 16.0 | 4.9 |
| MEAN | 25.7 | 22.0 |
| SD | 6.79 | 14.99 |
| N | 8 | 3 |

a - Sacrificed day 15

Appendix B, Table 5 (cont.)

INDIVIDUAL ANIMAL CLINICAL CHEMISTRY DATA
TEST: Total Bile Acid

STUDY ID: 2073-002-003
STUDY NO: 2073023
ABBR: TBA

SEX: FEMALE

UNITS: umol/L

| Animal ID | Day 15 | Day 29 |
|---|---|---|
| GROUP: 3-F:0.060 mg/kg/day CuATSM / H2ATSM | | |
| 41 | 30.2 | a |
| 42 | 26.4 | a |
| 43 | 26.3 | a |
| 44 | 15.7 | a |
| 45 | 9.9 | a |
| 46 | 23.3 | 13.5 |
| 47 | 42.9 | 25.7 |
| 48 | 35.9 | 9.6 |
| MEAN | 26.3 | 16.3 |
| SD | 10.51 | 8.40 |
| N | 8 | 3 |

a - Sacrificed day 15

## 14-DAY TOXICITY STUDY OF CuATSM/$H_2$ATSM (NSC-D729307) IN RABBITS

Appendix B, Table 6

Individual Animal Absolute Organ Weights – Males

| Group (CuATSM/ $H_2$ATSM Dose) | Animal Number | Organ Weight (g) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Adrenals | Brain | Heart | Kidneys | Liver | Spleen | Testes | Thymus | Thyroid Glands[a] |
| Group 1 (0.00 mg/kg/day) | 1 | 0.819 | 10.44 | 9.06 | 20.47 | 118.15 | 1.29 | 6.05 | 5.32 | 0.491 |
| | 2 | 0.394 | 10.12 | 10.03 | 18.59 | 106.44 | 0.89 | 7.51 | 4.81 | 0.193 |
| | 3 | 0.477 | 10.17 | 9.60 | 13.54 | 55.69 | 1.17 | 5.38 | 3.98 | 0.234 |
| | 4 | 0.440 | 9.46 | 11.71 | 15.46 | 95.86 | 1.44 | 5.56 | 3.64 | 0.210 |
| | 5 | 0.441 | 9.42 | 7.89 | 16.28 | 68.81 | 0.94 | 5.61 | 4.81 | 0.163 |
| Group 2 (0.030 mg/kg/day) | 17 | 0.523 | 9.56 | 8.67 | 16.69 | 78.41 | 1.42 | 6.16 | 3.04 | 0.205 |
| | 18 | 0.250 | 9.62 | 8.76 | 16.94 | 54.23 | 1.00 | 4.70 | 3.72 | 0.260 |
| | 19 | 0.551 | 9.73 | 9.93 | 19.43 | 81.59 | 1.27 | 4.68 | 3.25 | 0.223 |
| | 20 | 0.945 | 9.62 | 9.87 | 19.96 | 85.96 | 1.00 | 5.00 | 6.74 | 0.303 |
| | 21 | 0.432 | 10.13 | 10.52 | 17.08 | 79.70 | 1.14 | 6.53 | 5.29 | 0.278 |
| Group 3 (0.060 mg/kg/day) | 33 | 0.502 | 10.23 | 11.96 | 18.08 | 66.09 | 1.14 | 4.34 | 4.73 | 0.434 |
| | 34 | 0.588 | 9.74 | 6.17 | 14.54 | 62.62 | 1.23 | 4.66 | 3.55 | 0.274 |
| | 35 | 0.593 | 8.90 | 10.40 | 18.88 | 79.53 | 1.31 | 4.90 | 4.58 | 0.191 |
| | 36 | 0.449 | 9.62 | 11.83 | 15.98 | 80.94 | 0.77 | 5.07 | 7.94 | 0.240 |
| | 37 | 0.405 | 8.89 | 10.90 | 15.55 | 77.25 | 0.93 | 6.06 | 3.57 | 0.265 |

[a]Including parathyroid

Appendix B, Table 6 (cont.)

Individual Animal Absolute Organ Weights – Females

| Group (CuATSM/ $H_2$ATSM Dose) | Animal Number | Organ Weight (g) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Adrenals | Brain | Heart | Kidneys | Liver | Ovaries | Spleen | Thymus | Thyroid Glands[a] |
| Group 1 (0.00 mg/kg/day) | 9 | 0.429 | 10.34 | 11.39 | 13.49 | 58.34 | 0.751 | 2.36 | 4.06 | 0.129 |
| | 10 | 0.343 | 10.09 | 10.58 | 17.58 | 82.51 | 0.548 | 1.99 | 4.34 | 0.255 |
| | 11 | 0.279 | 9.68 | 9.09 | 12.42 | 61.03 | 0.543 | 2.12 | 3.51 | 0.295 |
| | 12 | 0.443 | 10.22 | 10.34 | 15.70 | 70.33 | 0.669 | 2.35 | 1.76 | 0.327 |
| | 13 | 0.659 | 9.69 | 12.09 | 14.57 | 76.67 | 0.549 | 1.22 | 4.07 | 0.184 |
| Group 2 (0.030 mg/kg/day) | 25 | 0.340 | 9.61 | 9.92 | 13.24 | 54.89 | 0.240 | 0.79 | 2.74 | 0.333 |
| | 26 | 0.316 | 10.28 | 6.52 | 13.85 | 56.59 | 0.297 | 1.28 | 4.35 | 0.275 |
| | 27 | 0.389 | 9.49 | 8.57 | 13.97 | 66.92 | 0.823 | 1.44 | 3.68 | 0.156 |
| | 28 | 0.454 | 9.79 | 9.26 | 15.36 | 57.52 | 0.378 | 1.53 | 6.36 | 0.365 |
| | 29 | 0.501 | 9.33 | 8.92 | 15.30 | 69.08 | 0.775 | 1.29 | 3.53 | 0.210 |
| Group 3 (0.060 mg/kg/day) | 41 | 0.341 | 9.17 | 11.23 | 16.94 | 67.72 | 0.325 | 1.07 | 6.53 | 0.303 |
| | 42 | 0.531 | 9.34 | 9.01 | 14.52 | 60.22 | 0.722 | 1.48 | 5.07 | 0.129 |
| | 43 | 0.256 | 10.24 | 9.99 | 15.75 | 70.32 | 0.470 | 1.15 | 4.33 | 0.223 |
| | 44 | 0.323 | 9.50 | 6.30 | 15.83 | 68.45 | 0.397 | 1.23 | 4.97 | 0.308 |
| | 45 | 0.400 | 10.44 | 9.41 | 13.80 | 63.81 | 0.359 | 1.58 | 3.67 | 0.280 |

[a]Including parathyroid

Appendix B, Table 6 (cont.)

Individual Animal Absolute Organ Weights – Males, Recovery

| Group (CuATSM/ $H_2$ATSM Dose) | Animal Number | Organ Weight (g) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Adrenals | Brain | Heart | Kidneys | Liver | Spleen | Testes | Thymus | Thyroid Glands[a] |
| Group 1 (0.00 mg/kg/day) | 6 | 0.478 | 8.93 | 9.59 | 17.53 | 83.14 | 0.83 | 6.14 | 3.98 | 0.284 |
| | 7 | 0.617 | 9.85 | 10.02 | 17.86 | 68.50 | 0.79 | 6.08 | 5.56 | 0.263 |
| | 8 | 0.577 | 10.44 | 9.60 | 15.83 | 61.73 | 1.44 | 5.36 | 3.71 | 0.397 |
| Group 2 (0.030 mg/kg/day) | 22 | 0.529 | 9.18 | 8.10 | 17.66 | 70.08 | 1.30 | 5.17 | 4.10 | 0.308 |
| | 23 | 0.240 | 10.41 | 9.19 | 17.28 | 76.77 | 1.29 | 7.04 | 4.29 | 0.398 |
| | 24 | 0.409 | 8.66 | 6.83 | 13.08 | 57.26 | 1.10 | 4.47 | 4.76 | 0.281 |
| Group 3 (0.060 mg/kg/day) | 38 | 0.572 | 8.94 | 9.46 | 19.56 | 72.79 | 1.17 | 6.06 | 4.59 | 0.528 |
| | 39 | 0.426 | 9.86 | 8.46 | 19.55 | 69.10 | 0.94 | 5.68 | 5.06 | 0.359 |
| | 40 | 0.443 | 10.96 | 11.56 | 16.82 | 64.90 | 1.06 | 6.13 | 6.28 | 0.281 |

[a]Including parathyroid

Appendix B, Table 6 (cont.)

Individual Animal Absolute Organ Weights – Females, Recovery

| Group (CuATSM/ $H_2$ATSM Dose) | Animal Number | Organ Weight (g) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Adrenals | Brain | Heart | Kidneys | Liver | Ovaries | Spleen | Thymus | Thyroid Glands[a] |
| Group 1 (0.00 mg/kg/day) | 14 | 0.299 | 9.90 | 9.57 | 12.76 | 58.68 | 0.499 | 1.54 | 4.29 | 0.380 |
| | 15 | 0.384 | 10.00 | 9.50 | 15.21 | 61.98 | 0.545 | 2.04 | 4.73 | 0.225 |
| | 16 | 0.231 | 8.99 | 9.00 | 14.90 | 70.71 | 0.786 | 1.65 | 5.24 | 0.265 |
| Group 2 (0.030 mg/kg/day) | 30 | 0.404 | 10.55 | 12.41 | 17.99 | 74.95 | 0.686 | 2.20 | 4.15 | 0.291 |
| | 31 | 0.381 | 8.50 | 14.30 | 13.95 | 62.95 | 0.475 | 1.16 | 7.72 | 0.392 |
| | 32 | 0.468 | 8.96 | 10.88 | 17.99 | 89.20 | 0.483 | 1.41 | 4.84 | 0.410 |
| Group 3 (0.060 mg/kg/day) | 46 | 0.284 | 10.20 | 10.41 | 14.57 | 60.37 | 0.371 | 1.46 | 3.79 | 0.143 |
| | 47 | 0.340 | 10.52 | 11.10 | 15.16 | 80.05 | 0.825 | 2.44 | 5.10 | 0.248 |
| | 48 | 0.326 | 10.09 | 9.08 | 15.37 | 67.48 | 0.582 | 1.79 | 4.41 | 0.354 |

[a]Including parathyroid

## 14-DAY TOXICITY STUDY OF CuATSM/$H_2$ATSM (NSC-D729307) IN RABBITS

Appendix B, Table 7

Individual Animal Organ-to-Body Weight Ratios – Males

| Group (CuATSM/ $H_2$ATSM Dose) | Animal Number | Organ-to-Body Weight Ratio (%)[a] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | FBW[b] | Adrenals | Brain | Heart | Kidneys | Liver | Spleen | Testes | Thymus | Thyroid Glands[c] |
| Group 1 (0.00 mg/kg/day) | 1 | 3.85 | 0.021 | 0.27 | 0.24 | 0.53 | 3.07 | 0.03 | 0.16 | 0.14 | 0.013 |
| | 2 | 3.56 | 0.011 | 0.28 | 0.28 | 0.52 | 2.99 | 0.03 | 0.21 | 0.14 | 0.005 |
| | 3 | 3.41 | 0.014 | 0.30 | 0.28 | 0.40 | 1.63 | 0.03 | 0.16 | 0.12 | 0.007 |
| | 4 | 3.33 | 0.013 | 0.28 | 0.35 | 0.46 | 2.88 | 0.04 | 0.17 | 0.11 | 0.006 |
| | 5 | 3.27 | 0.013 | 0.29 | 0.24 | 0.50 | 2.10 | 0.03 | 0.17 | 0.15 | 0.005 |
| Group 2 (0.030 mg/kg/day) | 17 | 3.34 | 0.016 | 0.29 | 0.26 | 0.50 | 2.35 | 0.04 | 0.18 | 0.09 | 0.006 |
| | 18 | 3.28 | 0.008 | 0.29 | 0.27 | 0.52 | 1.65 | 0.03 | 0.14 | 0.11 | 0.008 |
| | 19 | 3.62 | 0.015 | 0.27 | 0.27 | 0.54 | 2.25 | 0.04 | 0.13 | 0.09 | 0.006 |
| | 20 | 3.53 | 0.027 | 0.27 | 0.28 | 0.57 | 2.44 | 0.03 | 0.14 | 0.19 | 0.009 |
| | 21 | 3.56 | 0.012 | 0.28 | 0.30 | 0.48 | 2.24 | 0.03 | 0.18 | 0.15 | 0.008 |
| Group 3 (0.060 mg/kg/day) | 33 | 3.53 | 0.014 | 0.29 | 0.34 | 0.51 | 1.87 | 0.03 | 0.12 | 0.13 | 0.012 |
| | 34 | 3.12 | 0.019 | 0.31 | 0.20 | 0.47 | 2.01 | 0.04 | 0.15 | 0.11 | 0.009 |
| | 35 | 3.50 | 0.017 | 0.25 | 0.30 | 0.54 | 2.27 | 0.04 | 0.14 | 0.13 | 0.005 |
| | 36 | 3.30 | 0.014 | 0.29 | 0.36 | 0.48 | 2.45 | 0.02 | 0.15 | 0.24 | 0.007 |
| | 37 | 3.25 | 0.012 | 0.27 | 0.34 | 0.48 | 2.38 | 0.03 | 0.19 | 0.11 | 0.008 |

[a]Organ-to-Body Weight Ratio = [Absolute Organ Weight (g) ÷ Fasted Body Weight (g)] x 100
[b]FBW = fasted body weight (kg)
[c]Including parathyroid

Appendix B, Table 7 (cont.)

Individual Animal Organ-to-Body Weight Ratios – Females

| Group (CuATSM/ $H_2$ATSM Dose) | Animal Number | Organ-to-Body Weight Ratio (%)[a] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | FBW[b] | Adrenals | Brain | Heart | Kidneys | Liver | Ovaries | Spleen | Thymus | Thyroid Glands[c] |
| Group 1 (0.00 mg/kg/day) | 9 | 3.33 | 0.013 | 0.31 | 0.34 | 0.41 | 1.75 | 0.023 | 0.07 | 0.12 | 0.004 |
| | 10 | 3.44 | 0.010 | 0.29 | 0.31 | 0.51 | 2.40 | 0.016 | 0.06 | 0.13 | 0.007 |
| | 11 | 3.12 | 0.009 | 0.31 | 0.29 | 0.40 | 1.96 | 0.017 | 0.07 | 0.11 | 0.009 |
| | 12 | 3.35 | 0.013 | 0.31 | 0.31 | 0.47 | 2.10 | 0.020 | 0.07 | 0.05 | 0.010 |
| | 13 | 3.34 | 0.020 | 0.29 | 0.36 | 0.44 | 2.30 | 0.016 | 0.04 | 0.12 | 0.006 |
| Group 2 (0.030 mg/kg/day) | 25 | 3.17 | 0.011 | 0.30 | 0.31 | 0.42 | 1.73 | 0.008 | 0.02 | 0.09 | 0.011 |
| | 26 | 3.05 | 0.010 | 0.34 | 0.21 | 0.45 | 1.86 | 0.010 | 0.04 | 0.14 | 0.009 |
| | 27 | 3.16 | 0.012 | 0.30 | 0.27 | 0.44 | 2.12 | 0.026 | 0.05 | 0.12 | 0.005 |
| | 28 | 3.42 | 0.013 | 0.29 | 0.27 | 0.45 | 1.68 | 0.011 | 0.04 | 0.19 | 0.011 |
| | 29 | 3.47 | 0.014 | 0.27 | 0.26 | 0.44 | 1.99 | 0.022 | 0.04 | 0.10 | 0.006 |
| Group 3 (0.060 mg/kg/day) | 41 | 3.29 | 0.010 | 0.28 | 0.34 | 0.51 | 2.06 | 0.010 | 0.03 | 0.20 | 0.009 |
| | 42 | 3.41 | 0.016 | 0.27 | 0.26 | 0.43 | 1.77 | 0.021 | 0.04 | 0.15 | 0.004 |
| | 43 | 3.18 | 0.008 | 0.32 | 0.31 | 0.50 | 2.21 | 0.015 | 0.04 | 0.14 | 0.007 |
| | 44 | 3.45 | 0.009 | 0.28 | 0.18 | 0.46 | 1.98 | 0.012 | 0.04 | 0.14 | 0.009 |
| | 45 | 3.31 | 0.012 | 0.32 | 0.28 | 0.42 | 1.93 | 0.011 | 0.05 | 0.11 | 0.008 |

[a]Organ-to-Body Weight Ratio = [Absolute Organ Weight (g) ÷ Fasted Body Weight (g)] x 100
[b]FBW = fasted body weight (kg)
[c]Including parathyroid

Appendix B, Table 7 (cont.)

Individual Animal Organ-to-Body Weight Ratios – Males, Recovery

| Group (CuATSM/ $H_2$ATSM Dose) | Animal Number | Organ-to-Body Weight Ratio (%)[a] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | FBW[b] | Adrenals | Brain | Heart | Kidneys | Liver | Spleen | Testes | Thymus | Thyroid Glands[c] |
| Group 1 (0.00 mg/kg/day) | 6 | 3.70 | 0.013 | 0.24 | 0.26 | 0.47 | 2.25 | 0.02 | 0.17 | 0.11 | 0.008 |
| | 7 | 3.65 | 0.017 | 0.27 | 0.27 | 0.49 | 1.88 | 0.02 | 0.17 | 0.15 | 0.007 |
| | 8 | 3.15 | 0.018 | 0.33 | 0.30 | 0.50 | 1.96 | 0.05 | 0.17 | 0.12 | 0.013 |
| Group 2 (0.030 mg/kg/day) | 22 | 3.42 | 0.015 | 0.27 | 0.24 | 0.52 | 2.05 | 0.04 | 0.15 | 0.12 | 0.009 |
| | 23 | 3.76 | 0.006 | 0.28 | 0.24 | 0.46 | 2.04 | 0.03 | 0.19 | 0.11 | 0.011 |
| | 24 | 3.12 | 0.013 | 0.28 | 0.22 | 0.42 | 1.84 | 0.04 | 0.14 | 0.15 | 0.009 |
| Group 3 (0.060 mg/kg/day) | 38 | 3.75 | 0.015 | 0.24 | 0.25 | 0.52 | 1.94 | 0.03 | 0.16 | 0.12 | 0.014 |
| | 39 | 3.52 | 0.012 | 0.28 | 0.24 | 0.56 | 1.96 | 0.03 | 0.16 | 0.14 | 0.010 |
| | 40 | 3.26 | 0.014 | 0.34 | 0.35 | 0.52 | 1.99 | 0.03 | 0.19 | 0.19 | 0.009 |

[a]Organ-to-Body Weight Ratio = [Absolute Organ Weight (g) ÷ Fasted Body Weight (g)] x 100
[b]FBW = fasted body weight (kg)
[c]Including parathyroid

Appendix B, Table 7 (cont.)

Individual Animal Organ-to-Body Weight Ratios – Females, Recovery

| Group (CuATSM/ $H_2$ATSM Dose) | Animal Number | Organ-to-Body Weight Ratio (%)[a] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | FBW[b] | Adrenals | Brain | Heart | Kidneys | Liver | Ovaries | Spleen | Thymus | Thyroid Glands[c] |
| Group 1 (0.00 mg/kg/day) | 14 | 3.21 | 0.009 | 0.31 | 0.30 | 0.40 | 1.83 | 0.016 | 0.05 | 0.13 | 0.012 |
| | 15 | 3.42 | 0.011 | 0.29 | 0.28 | 0.44 | 1.81 | 0.016 | 0.06 | 0.14 | 0.007 |
| | 16 | 3.53 | 0.007 | 0.25 | 0.25 | 0.42 | 2.00 | 0.022 | 0.05 | 0.15 | 0.008 |
| Group 2 (0.030 mg/kg/day) | 30 | 3.75 | 0.011 | 0.28 | 0.33 | 0.48 | 2.00 | 0.018 | 0.06 | 0.11 | 0.008 |
| | 31 | 3.60 | 0.011 | 0.24 | 0.40 | 0.39 | 1.75 | 0.013 | 0.03 | 0.21 | 0.011 |
| | 32 | 3.68 | 0.013 | 0.24 | 0.30 | 0.49 | 2.42 | 0.013 | 0.04 | 0.13 | 0.011 |
| Group 3 (0.060 mg/kg/day) | 46 | 3.26 | 0.009 | 0.31 | 0.32 | 0.45 | 1.85 | 0.011 | 0.04 | 0.12 | 0.004 |
| | 47 | 3.57 | 0.010 | 0.29 | 0.31 | 0.42 | 2.24 | 0.023 | 0.07 | 0.14 | 0.007 |
| | 48 | 3.59 | 0.009 | 0.28 | 0.25 | 0.43 | 1.88 | 0.016 | 0.05 | 0.12 | 0.010 |

[a]Organ-to-Body Weight Ratio = [Absolute Organ Weight (g) ÷ Fasted Body Weight (g)] x 100
[b]FBW = fasted body weight (kg)
[c]Including parathyroid

Appendix C. Dose Formulation Analysis Report

SPECIAL REPORT

"Analysis of dose formulation samples of Cu-ATSM + $H_2$-ATSM (NSC 729307) submitted to UAB"

Accomplished as part of

WORK ASSIGNMENT # 12

on

Contract N01-CM-07111

Preclinical Pharmacological Studies of Antitumor and Anti-HIV Agents

Submitted to: Dr. Joseph M. Covey, Project Officer

Submitted by:

Department of Pharmacology and Toxicology
University of Alabama at Birmingham
Birmingham, AL 35294-0019

Period of performance:

June 2004

**Analysis of dose formulation samples of Cu-ATSM + $H_2$-ATSM (NSC 729307) submitted to UAB**

*Statement of work.* As part of an effort in supporting preliminary toxicology studies with Cu-ATSM + $H_2$-ATSM (NSC 729307), we analyzed dose formulation samples from studies conducted by IITRI, another NCI contractor.

*Analytical Method.* The HPLC system consisted of a Hewlett Packard 1050 ChemStation with a UV detector (Agilent 1050 series). Determination of $H_2$-ATSM and Ni+Cu-ATSM was achieved using a Zorbax SB-18 (5 μm, 150×4.6 mm) analytical column with a LiChroCART 100 RP-18 guard column. The flow rate was 1 mL/min. The column elute was monitored by UV at 345 nm.

Peak areas were determined for quantification of $H_2$-ATSM and Ni+Cu-ATSM. Linear regression and correlation analysis were accomplished to establish the standard peak-area/concentration curves for $H_2$-ATSM and Ni+Cu-ATSM. This method, which was previously developed and validated, is described in more detail in Appendix A. Standard curves for $H_2$-ATSM and Ni+Cu-ATSM in aqueous solution are presented in Figure 1.

*Analysis of samples* .We analyzed dosing formulations sent to us by IITRI. The results are in Tables 1 and 2. For these tables, each number under "Conc. (ng/mL)" is intended to represent the total amount of "ATSM" (Cu-ATSM + Ni-ATSM + $H_2$-ATSM) in the sample. As determined by the derived data, there was no apparent problem with the analytical procedure, for duplicate analyses gave similar values. It also appears that there were no gross errors in dose preparation, for most of the samples supposedly containing 15 or 30 μg/mL contained about those amounts, as determined by measurement of the $H_2$-ATSM peak. It is not clear why quantitation using the Ni+Cu-ATSM curve was lower overall. At both concentrations, there were losses of compound in the stored samples (Day 8 and Day 14 Stability). The 15 μg/mL samples appeared to be more stable than the 30 μg/mL samples. This observation could be due to precipitation of the material, but we noted no precipitate.

**CONTRIBUTING PERSONNEL**

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Donald L. Hill, Ph.D., Co-Principal Investigator
Hui Wang, M.D., Ph.D., Instructor, Laboratory Manager
Mao Li, M.D., Post-Doctoral Fellow

Figure 1. Standard Curves for ATSM and Ni+Cu-ATSM

| Concentration | ATSM | | | Ni+ Cu ATSM | | |
|---|---|---|---|---|---|---|
| (ng/mL) | Peak Area | Peak Area | Average | Peak Area | Peak Area | Average |
| 0.00 | 0.000 | 0.000 | 0.00 | 0.000 | 0.000 | 0.00 |
| 5.00 | 0.086 | 0.069 | 0.08 | 0.028 | 0.014 | 0.02 |
| 10.00 | 0.204 | 0.153 | 0.18 | 0.141 | 0.115 | 0.13 |
| 25.00 | 0.915 | 0.788 | 0.85 | 0.284 | 0.288 | 0.29 |
| 50.00 | 2.003 | 1.974 | 1.99 | 0.518 | 0.595 | 0.56 |
| 100.00 | 4.078 | 4.034 | 4.06 | 0.988 | 1.120 | 1.05 |
| 250.00 | 10.439 | 10.307 | 10.37 | 2.542 | 2.559 | 2.55 |
| 500.00 | 20.553 | 19.864 | 20.21 | 5.074 | 5.162 | 5.12 |
| 1000.00 | 42.972 | 41.545 | 42.26 | 9.669 | 9.661 | 9.67 |

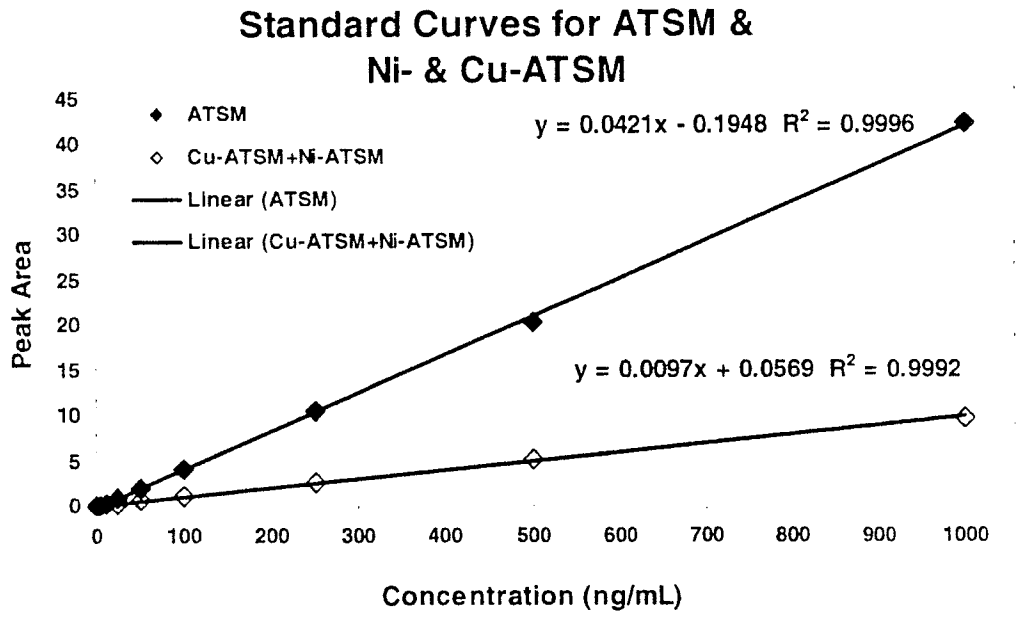

Table 1. Dose Formulation Samples for IITRI Project 2073-002-003

| Group Number | Name on Vial Label | Preparation Date | Conc. (mg/mL) | Sampling Date | Sample # on Vial | ATSM Peak Area | | | ATSM Conc. | Ni+Cu-ATSM Peak Area | | | Ni+Cu-ATSM Conc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 1 | 2 | Mean | (ug/mL) | 1 | 2 | Mean | (ng/mL) |
| 1 | Vehicle (Concentration Sample) | 5/14/2004 | 0 | 5/14/2004 | 2073002002-5/14/04-0-1a | 0.00 | 0.00 | 0.00 | **0.00** | 0.00 | 0.00 | 0.00 | **0.00** |
| 1 | Vehicle (Day8) | 5/21/2004 | 0 | 5/21/2004 | 2073002002-5/21/04-0-1 | 0.00 | 0.00 | 0.00 | **0.00** | 0.00 | 0.00 | 0.00 | **0.00** |
| 1 | Vehicle (Day14) | 5/27/2004 | 0 | 5/27/2004 | 2073002002-5/27/04-0-1 | 0.00 | 0.00 | 0.00 | **0.00** | 0.00 | 0.00 | 0.00 | **0.00** |
| 2 | CuATSM/H2ATSM (Top) | 5/14/2004 | 0.015 | 5/14/2004 | 2073002002-5/14/04-0.015-1a | 564.06 | 572.29 | 568.17 | **13500.43** | 89.06 | 91.40 | 90.23 | **9296.13** |
| 2 | CuATSM/H2ATSM (Middle) | 5/14/2004 | 0.015 | 5/14/2004 | 2073002002-5/14/04-0.015-1b | 590.53 | 593.65 | 592.09 | **14068.61** | 92.87 | 92.94 | 92.91 | **9572.01** |
| 2 | CuATSM/H2ATSM (Bottom) | 5/14/2004 | 0.015 | 5/14/2004 | 2073002002-5/14/04-0.015-1c | 602.04 | 578.71 | 590.37 | **14027.70** | 86.67 | 93.42 | 90.04 | **9276.94** |
| 2 | CuATSM/H2ATSM (Day8) | 5/21/2004 | 0.015 | 5/21/2004 | 2073002002-5/21/04-0.015-1 | 636.51 | 645.79 | 641.15 | **15233.90** | 79.79 | 80.44 | 80.11 | **8253.32** |
| 2 | CuATSM/H2ATSM (Day14) | 5/27/2004 | 0.015 | 5/27/2004 | 2073002002-5/27/04-0.015-1 | 799.85 | 804.93 | 802.39 | **19063.70** | 103.48 | 105.39 | 104.43 | **10760.47** |
| 3 | CuATSM/H2ATSM (Top) | 5/14/2004 | 0.030 | 5/14/2004 | 2073002002-5/14/04-0.030-1a | 724.06 | 713.94 | 719.00 | **17082.99** | 170.22 | 176.14 | 173.18 | **17847.87** |
| 3 | CuATSM/H2ATSM (Middle) | 5/14/2004 | 0.030 | 5/14/2004 | 2073002002-5/14/04-0.030-1b | 1108.90 | 1126.42 | 1117.66 | **26552.44** | 144.20 | 146.46 | 145.33 | **14976.47** |
| 3 | CuATSM/H2ATSM (Bottom) | 5/14/2004 | 0.030 | 5/14/2004 | 2073002002-5/14/04-0.030-1c | 951.02 | 958.38 | 954.70 | **22681.62** | 111.27 | 113.14 | 112.20 | **11561.61** |
| 3 | CuATSM/H2ATSM (Day8) | 5/21/2004 | 0.030 | 5/21/2004 | 2073002002-5/21/04-0.030-1 | 1017.99 | 1020.28 | 1019.13 | **24212.04** | 147.16 | 149.73 | 148.45 | **15297.85** |
| 3 | CuATSM/H2ATSM (Day14) | 5/27/2004 | 0.030 | 5/27/2004 | 2073002002-5/27/04-0.030-1 | 1406.24 | 1406.53 | 1406.39 | **33410.50** | 232.64 | 234.80 | 233.72 | **24088.97** |

Table 2. Dose Formulation Samples for IITRI Project 2073-002-002

| Group Number | Name on Vial Label | Preparation Date | Conc. (mg/mL) | Sampling Date | Sample # on Vial | ATSM Peak Area | | | ATSM Conc. | Ni+Cu-ATSM Peak Area | | | Ni+Cu-ATSM Conc. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 1 | 2 | Mean | (ng/mL) | 1 | 2 | Mean | (ng/mL) |
| 1 | Vehicle (Concentration Sample) | 5/6/2004 | 0 | 5/6/2004 | 2073002002-5/6/04-0-1a | 0.00 | 0.00 | 0.00 | **0.00** | 0.00 | 0.00 | 0.00 | **0.00** |
| 1 | Vehicle (Day 8 Stability) | 5/6/2004 | 0 | 5/13/2004 | 2073002002-5/6/04-0-2a | 0.00 | 0.00 | 0.00 | **0.00** | 0.00 | 0.00 | 0.00 | **0.00** |
| 1 | Vehicle (Day 14 Stability) | 5/6/2004 | 0 | 5/19/2004 | 2073002002-5/6/04-0-3a | 0.00 | 0.00 | 0.00 | **0.00** | 0.00 | 0.00 | 0.00 | **0.00** |
| 1 | Vehicle (Day8) | 5/13/2004 | 0 | 5/13/2004 | 2073002002-5/13/04-0-1a | 0.00 | 0.00 | 0.00 | **0.00** | 0.00 | 0.00 | 0.00 | **0.00** |
| 1 | Vehicle (Day14) | 5/19/2004 | 0 | 5/19/2004 | 2073002002-5/19/04-0-1a | 0.00 | 0.00 | 0.00 | **0.00** | 0.00 | 0.00 | 0.00 | **0.00** |
| 2 | CuATSM/H2ATSM (Top) | 5/6/2004 | 0.015 | 5/6/2004 | 2073002002-5/6/04-0.015-1a | 513.23 | 499.91 | 506.57 | **12037.23** | 85.80 | 93.20 | 89.50 | **9220.58** |
| 2 | CuATSM/H2ATSM (Middle) | 5/6/2004 | 0.015 | 5/6/2004 | 2073002002-5/6/04-0.015-1b | 663.49 | 655.93 | 659.71 | **15674.60** | 100.41 | 98.73 | 99.57 | **10259.15** |
| 2 | CuATSM/H2ATSM (Bottom) | 5/6/2004 | 0.015 | 5/6/2004 | 2073002002-5/6/04-0.015-1c | 586.69 | 582.87 | 584.78 | **13894.95** | 108.23 | 110.12 | 109.17 | **11249.15** |
| 2 | CuATSM/H2ATSM (Day 8 Stability) | 5/6/2004 | 0.015 | 5/13/2004 | 2073002002-5/6/04-0.015-2a | 274.84 | 273.64 | 274.24 | **6518.58** | 66.30 | 66.49 | 66.40 | **6839.01** |
| 2 | CuATSM/H2ATSM (Day 14 Stability) | 5/6/2004 | 0.015 | 5/19/2004 | 2073002002-5/6/04-0.015-3a | 283.57 | 281.44 | 282.50 | **6714.92** | 81.12 | 82.91 | 82.01 | **8449.27** |
| 2 | CuATSM/H2ATSM (Day8) | 5/13/2004 | 0.015 | 5/13/2004 | 2073002002-5/13/04-0.015-1a | 641.98 | 644.76 | 643.37 | **15286.66** | 79.71 | 81.56 | 80.64 | **8307.14** |
| 2 | CuATSM/H2ATSM (Day14) | 5/19/2004 | 0.015 | 5/19/2004 | 2073002002-5/19/04-0.015-1a | 653.09 | 714.65 | 683.87 | **16248.64** | 83.13 | 73.23 | 78.18 | **8054.12** |
| 3 | CuATSM/H2ATSM (Top) | 5/6/2004 | 0.030 | 5/6/2004 | 2073002002-5/6/04-0.030-1a | 1213.44 | 1211.34 | 1212.39 | **28802.43** | 167.65 | 169.27 | 168.46 | **17360.82** |
| 3 | CuATSM/H2ATSM (Middle) | 5/6/2004 | 0.030 | 5/6/2004 | 2073002002-5/6/04-0.030-1b | 1153.25 | 1132.60 | 1142.93 | **27152.54** | 208.22 | 214.97 | 211.60 | **21808.19** |
| 3 | CuATSM/H2ATSM (Bottom) | 5/6/2004 | 0.030 | 5/6/2004 | 2073002002-5/6/04-0.030-1c | 701.98 | 689.62 | 695.80 | **16531.91** | 211.85 | 215.61 | 213.73 | **22027.89** |
| 3 | CuATSM/H2ATSM (Day 8 Stability) | 5/6/2004 | 0.030 | 5/13/2004 | 2073002002-5/6/04-0.030-2a | 197.60 | 194.16 | 195.88 | **4657.31** | 38.23 | 37.37 | 37.80 | **3891.07** |
| 3 | CuATSM/H2ATSM (Day 14 Stability) | 5/6/2004 | 0.030 | 5/19/2004 | 2073002002-5/6/04-0.030-3a | 156.23 | 154.68 | 155.46 | **3697.21** | 49.71 | 51.08 | 50.39 | **5189.12** |
| 3 | CuATSM/H2ATSM (Day8) | 5/13/2004 | 0.030 | 5/13/2004 | 2073002002-5/13/04-0.030-1a | 1621.32 | 1635.42 | 1628.37 | **38683.26** | 176.58 | 179.83 | 178.20 | **18365.77** |
| 3 | CuATSM/H2ATSM (Day14) | 5/19/2004 | 0.030 | 5/19/2004 | 2073002002-5/19/04-0.030-1a | 1154.70 | 1146.17 | 1150.43 | **27330.77** | 223.47 | 226.46 | 224.97 | **23186.50** |

# APPENDIX A

# HPLC Method for Determination of Cu-ATSM + $H_2$-ATSM

## 1. Reagents and Drugs

- Acetonitrile, HPLC grade (Fisher Chemicals A998-4)
- Methanol, HPLC grade (Fisher Chemicals A452-4)
- Cu-ATSM + $H_2$-ATSM (D729307-J/D1)

## 2. Preparation of standard stock solutions

Weigh 2.1 mg of Cu-ATSM + $H_2$-ATSM and dissolve in methanol in a polypropylene tube to make the final concentration of 1.0 mg/mL. Store at –80°C.

## 3. Preparation of mobile phase

The mobile phase is composed of 50:50 acetonitrile:dd$H_2O$ (vol/vol). Prior to application, the mobile phase is filtered and degassed using Millipore glass filter system with nylon membrane (0.2 µm).

## 4. HPLC conditions

The HPLC system consists of a Hewlett Packard 1050 ChemStation with a UV detector (Agilent 1050 series). Determination of Cu-ATSM + $H_2$-ATSM is achieved using a Zorbax SB-18 (5 µm, 150×4.6 mm) analytical column with a LiChroCART 100 RP-18 guard column. The flow rate is 1 mL/min. The column elute is monitored by UV at 345 nm.

## 5. Preparation of standards

- Dilute Cu-ATSM + $H_2$-ATSM stock solution with methanol to prepare the serial standard concentrations of 0, 0.05, 0.10, 0.25, 0.5, 1.0, 2.5, 5.0 and 10.0µg/mL. (Daily freshly prepared standard solutions are required.)
- Mix 10 µL of standard solution with 90 µL of the mobile phase. This will yield standards with final Cu-ATSM + $H_2$-ATSM concentrations of 0, 0.005, 0.010, 0.025, 0.05, 0.1, 0.25, 0.5 and 1.0 µg/mL, respectively.

## 7. Quantification of Cu-ATSM and $H_2$-ATSM

Peak area is determined for quantification of Cu-ATSM and $H_2$-ATSM. Linear regression and correlation analysis is accomplished to establish the standard peak-area/concentration curves for Cu-ATSM + $H_2$-ATSM.

Appendix D. Pathology Report

# FINAL PATHOLOGY REPORT FOR 14-DAY TOXICITY STUDY OF CuATSM/$H_2$ATSM (NSC-D729307) IN RABBITS IITRI PROJECT NUMBER 2073-002-003

PREPARED
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DECEMBER 7, 2004

TABLE OF CONTENTS

SECTION I

PATHOLOGY NARRATIVE

# FINAL PATHOLOGY REPORT

## 14-DAY TOXICITY STUDY OF CuATSM/$H_2$ATSM (NSC-D729307) IN RABBITS

### INTRODUCTION

This pathology report, submitted by Pathology Associates Division of Charles River Laboratories, Inc. to IIT Research Institute (IITRI), represents the histopathology findings for the study designated as "14-Day Toxicity Study of CuATSM/$H_2$ATSM (NSC-D729307) in Rabbits," Project Number 2073-002-003.

The study was conducted to determine target organ toxicity of CuATSM/$H_2$ATSM (NSC-D729307) and its reversibility when given intravenously to rabbits twice daily (BID) for 14 consecutive days.

### EXPERIMENTAL DESIGN AND METHODS

This study was composed of 3 groups. All groups were composed of 8 male and 8 female New Zealand White rabbits. Group 1 animals received the test article vehicle [(dimethyl sulfoxide, ethanol (100%), and saline (0.9% sodium chloride for injection USP)] by intravenous injection twice a day for 14 consecutive days. Two groups (Groups 2 and 3), were given the test article for a total dose of 0.030 or 0.060 mg/kg/day, respectively by intravenous injection twice a day for 14 consecutive days. The experimental design is summarized in Table I (Summary of Experimental Design).

Five animals/sex/group were euthanized and necropsied on study day 15 (terminal sacrifice). The remaining 3 animals/sex/group were euthanized and necropsied on study day 29 (recovery sacrifice). All necropsies were performed according to IITRI Standard Operating Procedures and were conducted by Pathology Associates Division of Charles River Laboratories, Inc. personnel. Tissues required by the protocol (see Table II, Protocol-Required Tissues) were examined and placed in 10% neutral buffered formalin, with the exception of eyes which were placed in Davidson's fixative and testes and epididymides which were placed in Bouin's fixative.

Tissues required for histopathologic evaluation were trimmed, processed, sectioned, and stained with hematoxylin and eosin in accordance with Pathology Associates Division of Charles River Laboratories, Inc. Standard Operating Procedures. All protocol required tissues were processed and evaluated for terminal sacrifice animals in Groups 1 and 3. Some tissues are inherently difficult to obtain in sections because of their small size (e.g. parathyroid gland). Tissues were recorded as "unavailable/unsuitable for complete evaluation" when they were missing in both the original section and in recut and/or retrim attempts to obtain them.

Histopathologic observations were tabulated using the LABCAT® histopathology data management system (version 4.33). Microscopic findings for all groups are summarized in the Project Summary reports (Section II). Where applicable, all tissue changes received a severity grade based upon the following scale: 1 = minimal, 2 = mild, 3 = moderate and 4 = marked. Mean group severity scores (SEV) for each change were determined by dividing the sum of the severity scores by the number of tissues examined in that group. The mean group severity scores are found in the Severity Summary reports (Section III). Microscopic findings in the protocol-required tissues for individual animals are presented in the Tabulated Animal Data reports (Section IV). The correlation of the necropsy findings and histopathology findings are reported in the Correlation of Gross and Microscopic (Micro) Findings reports (Section V). The codes used as entries in these tables are explained in the Reports Code Table.

The portion of this study performed by Pathology Associates Division of Charles River Laboratories, Inc. was conducted in compliance with the U.S. Food and Drug Administration's Good Laboratory Practice (GLP) regulations for nonclinical studies (21 CFR Part 58).

## RESULTS AND DISCUSSION

The Results and Discussion section is divided into three parts: Necropsy Findings, Diagnostic Terms, and Histopathology Findings. The Necropsy Findings portion describes lesions seen at necropsy and trimming. The Diagnostic Terms portion lists and clarifies diagnostic terminology that may be unclear. Terms listed in the Diagnostic Terms portion of this section include, but are not limited to, those that are considered to be test article-related. The Histopathology Findings portion of this section reports the results and provides discussion of the histopathologic evaluation of the tissues.

### Necropsy Findings

Black foci were noted on the ovaries of terminal sacrifice Group 1 female animal numbers 0009, 0010, and 0012 and Group 3 animal number 0045. Microscopically, these all correlated to the presence of normal corpora hemorrhagicae in the ovary. Group 1 female animal number 0012 was noted to have two clear cysts on the oviduct; microscopically these correlated with cysts on the exterior surface of the oviduct. Group 3 animal number 0045 was noted to have multiple red foci on the right thyroid gland; microscopically, there was no corresponding lesion.

Black foci were noted in the ovaries of Group 2 female animal number 0027; microscopic evaluation of this was not required by protocol. Pigmentation in the lung was noted in Group 2 male animal number 0021; microscopic evaluation was not required. A deformity of the lung was noted in Group 2 female animal number 0029; microscopic evaluation was not required by protocol.

These and all other gross lesions observed in this study were interpreted as incidental findings typically present in rabbit toxicology studies. Gross observations are summarized in Tables IIIA

(Terminal Sacrifice) and IIIB (Recovery Sacrifice), Summary of Gross Necropsy Observations and listed in the Correlation of Gross and Microscopic (Micro) Findings report in Section V. Microscopic findings were correlated with gross lesions when possible.

Diagnostic Terms

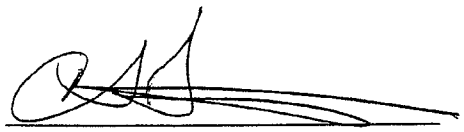
The morphologic diagnoses used in this study were considered to be self-explanatory and were not discussed.

Histopathology Findings

There were no treatment-related pathologic findings in the tissues examined microscopically from Groups 1 and 3 from the terminal sacrifice. All microscopic findings were interpreted as either incidental findings that are commonly present in rabbit toxicology studies or related to trauma associated with repeated intravenous injection in the sections of skin from the injection site. The minimal to mild hemorrhage, edema, inflammation, and fibrin deposition/fibrosis in the injection site skin were, in general, present in the control group as well as the test article-treated group.

CONCLUSIONS

Under conditions of this study, an intravenous injection of CuATSM/$H_2$ATSM (NSC-D729307) twice a day for 14 consecutive days to rabbits at a total dose of 0.060 mg/kg/day resulted in no histologic treatment-related findings. The no observed effect level (NOEL) in this 14 day intravenous study was 0.060 mg/kg/day.



Carol J. Detrisac, DVM, PhD
Diplomate, ACVP

12/7/04
Date

TABLE I
SUMMARY OF EXPERIMENTAL DESIGN

| Group | CuATSM/$H_2$ATSM Dose (mg/kg/dose) | CuATSM/$H_2$ATSM Dose (mg/kg/day) | Number of Rabbits | | | |
|---|---|---|---|---|---|---|
| | | | Day 15 (Terminal Sacrifice) | | Day 29 (Recovery Sacrifice) | |
| | | | Male | Female | Male | Female |
| 1 | 0.00 | 0.00 | 5 | 5 | 3 | 3 |
| 2 | 0.015 | 0.030 | 5 | 5 | 3 | 3 |
| 3 | 0.030 | 0.060 | 5 | 5 | 3 | 3 |

TABLE II
PROTOCOL-REQUIRED TISSUES

Adrenal glands
Aorta
Bone with articular surface (femur)
Bone marrow (femur)
Brain (medulla/pons, cerebellum, and cerebral cortex)
Cecum
Colon
Duodenum
Epididymides
Esophagus
Eyes
Gallbladder
Heart
Ileum
Jejunum
Kidneys
Liver
Lungs
Lymph nodes (mandibular and mesenteric)
Mammary gland (when present in regular abdominal skin section)
Ovaries
Pancreas
Parathyroid glands
Pituitary gland
Salivary gland (mandibular and parotid)
Sciatic nerve
Skeletal muscle
Skin (ventral abdomen and injection site)
Spinal cord (cervical, midthoracic, and lumbar)
Spleen
Stomach (cardiac, fundic, and pyloric)
Testes
Thymus
Thyroid glands
Trachea
Urinary bladder
Uterine horns

TABLE IIIA (TERMINAL SACRIFICE)
SUMMARY OF GROSS NECROPSY OBSERVATIONS [a]

| | Group 1 | | Group 2 | | Group 3 | |
|---|---|---|---|---|---|---|
| | M | F | M | F | M | F |
| Number of animals examined | 5 | 5 | 5 | 5 | 5 | 5 |
| Tissue/Lesion | | | | | | |
| Lung | | | | | | |
| Deformity | -- | -- | -- | 1 | -- | -- |
| Pigmentation | -- | -- | 1 | -- | -- | -- |
| Ovary | | | | | | |
| Focus | -- | 3 | -- | 1 | -- | 1 |
| Oviduct | | | | | | |
| Cyst | -- | 1 | -- | -- | -- | -- |
| Skin | | | | | | |
| Alopecia | -- | -- | 1 | -- | -- | -- |
| Thyroid gland | | | | | | |
| Focus | -- | -- | -- | -- | -- | 1 |
| Pigmentation | -- | -- | 1 | -- | -- | -- |

[a] = Number of animals in which each lesion was observed
-- = No signs observed
Group 1 = 0.00 mg/kg/day CuATSM/$H_2$ATSM
Group 2 = 0.030 mg/kg/day CuATSM/$H_2$ATSM
Group 3 = 0.060 mg/kg/day CuATSM/$H_2$ATSM

TABLE IIIB (RECOVERY SACRIFICE)
SUMMARY OF GROSS NECROPSY OBSERVATIONS [a]

| | Group 1 | | Group 2 | | Group 3 | |
|---|---|---|---|---|---|---|
| | M | F | M | F | M | F |
| Number of animals examined | 3 | 3 | 3 | 3 | 3 | 3 |
| Tissue/Lesion | | | | | | |
| Ovary | | | | | | |
| Cyst | -- | 1 | -- | -- | -- | -- |
| Thymus | | | | | | |
| Pigmentation | -- | -- | -- | -- | 1 | -- |
| Thyroid gland | | | | | | |
| Cyst | -- | -- | 1 | -- | -- | -- |

[a] = Number of animals in which each lesion was observed
-- = No signs observed
Group 1 = 0.00 mg/kg/day CuATSM/$H_2$ATSM
Group 2 = 0.030 mg/kg/day CuATSM/$H_2$ATSM
Group 3 = 0.060 mg/kg/day CuATSM/$H_2$ATSM

PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/$H_2$ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

Reports Code Table

A. Codes applying to organs

| | |
|---|---|
| N | Tissues within normal histological limits |
| A | Autolysis precluding adequate evaluation |
| U | Tissues unavailable/unsuitable for complete evaluation |

B. Codes applying to microscopic diagnoses

| | |
|---|---|
| 1 | minimal |
| 2 | mild |
| 3 | moderate |
| 4 | marked |
| P | Present |
| I | Bilateral |
| L | Unilateral |
| - | No data entered |

SECTION II

PROJECT SUMMARY

PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## PROJECT SUMMARY

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice
DAYS ON TEST: ALL SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

| GROUP: | | 1 (1) | | 3 (2) | |
|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 5 | | 5 | |
| | | # | % | # | % |
| BRAIN,CEREBRAL CORTEX | # EX | 5 | | 5 | |
| Inflammation, chronic, choroid plexus | | 1 | 20.0 | 0 | 0.0 |
| Gliosis | | 1 | 20.0 | 0 | 0.0 |
| BRAIN,CEREBELLUM | # EX | 5 | | 5 | |
| Satellitosis, molecular layer | | 3 | 60.0 | 0 | 0.0 |
| BRAIN,MEDULLA/PONS | # EX | 5 | | 5 | |
| SPINAL CORD,CERVICAL | # EX | 5 | | 5 | |
| PERIPHERAL NERVE,SCIATIC | # EX | 5 | | 5 | |
| SPINAL CORD,MIDTHORACIC | # EX | 5 | | 5 | |
| Axonal spheroid | | 1 | 20.0 | 0 | 0.0 |
| Degeneration, neuroaxonal | | 1 | 20.0 | 0 | 0.0 |
| PITUITARY GLAND | # EX | 5 | | 5 | |
| THYROID GLAND | # EX | 5 | | 5 | |
| Inflammation, chronic | | 0 | 0.0 | 1 | 20.0 |
| PARATHYROID GLAND | # EX | 4 | | 4 | |
| ADRENAL GLAND | # EX | 5 | | 5 | |
| Congestion | | 1 | 20.0 | 0 | 0.0 |
| SPINAL CORD,LUMBAR | # EX | 5 | | 5 | |
| Chromatolysis, neuron | | 0 | 0.0 | 1 | 20.0 |
| KIDNEY | # EX | 5 | | 5 | |
| Mineralization | | 1 | 20.0 | 2 | 40.0 |
| Fibrosis, interstitial | | 0 | 0.0 | 2 | 40.0 |

Incidence Calculated by No. of Tissues Scored (2) - 0.060 mg/kg/day CuATSM/H2ATSM
(1) - 0 mg/kg/day (vehicle control)

LABCAT HP4.33 16-AUG-2004

PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## PROJECT SUMMARY

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice
DAYS ON TEST: ALL SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

| GROUP: | | 1 | | 3 | |
|---|---|---|---|---|---|
| | | (1) | | (2) | |
| NUMBER OF ANIMALS: | | 5 | | 5 | |
| | | # | % | # | % |
| SKELETAL MUSCLE | # EX | 5 | | 5 | |
| SKIN, INJECTION SITE | # EX | 5 | | 5 | |
| Inflammation, heterophilic, dermis | | 1 | 20.0 | 1 | 20.0 |
| Edema, dermis | | 2 | 40.0 | 0 | 0.0 |
| Hemorrhage, acute, dermis | | 2 | 40.0 | 3 | 60.0 |
| Hemosiderophages, dermis | | 2 | 40.0 | 0 | 0.0 |
| Serocellular crust | | 1 | 20.0 | 0 | 0.0 |
| Inflammation, chronic, dermis | | 2 | 40.0 | 1 | 20.0 |
| Fibrin deposition, dermis | | 1 | 20.0 | 0 | 0.0 |
| URINARY BLADDER | # EX | 5 | | 5 | |
| TRACHEA | # EX | 5 | | 5 | |
| Inflammation, chronic, submucosa | | 1 | 20.0 | 0 | 0.0 |
| Inflammation, heterophilic, submucosa | | 3 | 60.0 | 0 | 0.0 |
| ESOPHAGUS | # EX | 5 | | 5 | |
| LUNG | # EX | 5 | | 5 | |
| Inflammation, heterophilic, perivascular | | 5 | 100.0 | 3 | 60.0 |
| Hyperplasia, pneumocyte | | 2 | 40.0 | 1 | 20.0 |
| Intimal heterophils, pulmonary arteries | | 3 | 60.0 | 2 | 40.0 |
| Fibrosis, intimal, pulmonary arteries | | 3 | 60.0 | 0 | 0.0 |
| Histiocytosis, alveolar | | 0 | 0.0 | 1 | 20.0 |
| Ectopic bone | | 1 | 20.0 | 1 | 20.0 |
| Fibrosis, interstitial | | 0 | 0.0 | 1 | 20.0 |
| Hypertrophy, endothelial | | 1 | 20.0 | 0 | 0.0 |
| Granuloma | | 0 | 0.0 | 1 | 20.0 |
| HEART | # EX | 5 | | 5 | |
| Fibrosis, epicardial | | 1 | 20.0 | 0 | 0.0 |

Incidence Calculated by No. of Tissues Scored (2) - 0.060 mg/kg/day CuATSM/H2ATSM
(1) - 0 mg/kg/day (vehicle control)

LABCAT HP4.33 16-AUG-2004

PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## PROJECT SUMMARY

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice
DAYS ON TEST: ALL SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

| GROUP: | | 1 (1) | | 3 (2) | |
|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 5 | | 5 | |
| | | # | % | # | % |
| AORTA | # EX | 5 | | 5 | |
| SKIN, VENTRAL ABDOMEN | # EX | 5 | | 5 | |
| Inflammation, heterophilic | | 1 | 20.0 | 0 | 0.0 |
| SPLEEN | # EX | 5 | | 5 | |
| Hemosiderophage aggregates | | 1 | 20.0 | 0 | 0.0 |
| LIVER | # EX | 5 | | 5 | |
| Inflammation, chronic | | 3 | 60.0 | 3 | 60.0 |
| GALLBLADDER | # EX | 5 | | 5 | |
| SALIVARY GLAND, MANDIBULAR | # EX | 5 | | 5 | |
| SALIVARY GLAND, PAROTID | # EX | 5 | | 5 | |
| Atrophy, acinar | | 0 | 0.0 | 1 | 20.0 |
| LYMPH NODE, MANDIBULAR | # EX | 5 | | 4 | |
| Edema | | 1 | 20.0 | 0 | 0.0 |
| Hyperplasia, paracortical | | 0 | 0.0 | 1 | 25.0 |
| Drainage of erythrocytes | | 2 | 40.0 | 0 | 0.0 |
| Drainage of heterophils | | 1 | 20.0 | 0 | 0.0 |
| STOMACH | # EX | 5 | | 5 | |
| SMALL INTESTINE, DUODENUM | # EX | 5 | | 5 | |
| SMALL INTESTINE, ILEUM | # EX | 5 | | 5 | |
| Lymphangiectasia | | 1 | 20.0 | 0 | 0.0 |
| LARGE INTESTINE, COLON | # EX | 4 | | 5 | |

Incidence Calculated by No. of Tissues Scored
(1) - 0 mg/kg/day (vehicle control)
(2) - 0.060 mg/kg/day CuATSM/H2ATSM

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## PROJECT SUMMARY

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice
DAYS ON TEST: ALL SEX: MALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

| GROUP: | | 1 (1) | | 3 (2) | |
|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 5 | | 5 | |
| | | # | % | # | % |
| SMALL INTESTINE,JEJUNUM | # EX | 5 | | 5 | |
| Lymphangiectasia | | 1 | 20.0 | 0 | 0.0 |
| LARGE INTESTINE,CECUM | # EX | 5 | | 5 | |
| PANCREAS | # EX | 5 | | 5 | |
| Necrosis, adipose with saponification | | 1 | 20.0 | 0 | 0.0 |
| THYMUS | # EX | 5 | | 5 | |
| Hemorrhage, acute | | 1 | 20.0 | 0 | 0.0 |
| LYMPH NODE,MESENTERIC | # EX | 5 | | 5 | |
| Drainage of erythrocytes | | 1 | 20.0 | 0 | 0.0 |
| Hyperplasia, paracortical | | 1 | 20.0 | 0 | 0.0 |
| TESTES | # EX | 5 | | 5 | |
| EPIDIDYMIS | # EX | 5 | | 5 | |
| EYE | # EX | 5 | | 5 | |
| BONE,FEMUR | # EX | 5 | | 5 | |
| BONE MARROW,FEMORAL | # EX | 5 | | 5 | |

Incidence Calculated by No. of Tissues Scored (2) - 0.060 mg/kg/day CuATSM/H2ATSM
(1) - 0 mg/kg/day (vehicle control)

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## PROJECT SUMMARY

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice
DAYS ON TEST: ALL SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

| GROUP: | | 1 (1) | | 3 (2) | |
|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 5 | | 5 | |
| | | # | % | # | % |
| BRAIN,CEREBRAL CORTEX | # EX | 5 | | 5 | |
| BRAIN,CEREBELLUM | # EX | 5 | | 5 | |
| Satellitosis, molecular layer | | 2 | 40.0 | 2 | 40.0 |
| BRAIN,MEDULLA/PONS | # EX | 5 | | 5 | |
| SPINAL CORD,CERVICAL | # EX | 5 | | 5 | |
| Degeneration, neuroaxonal | | 2 | 40.0 | 0 | 0.0 |
| PERIPHERAL NERVE,SCIATIC | # EX | 5 | | 5 | |
| Axonal spheroid | | 1 | 20.0 | 0 | 0.0 |
| SPINAL CORD,MIDTHORACIC | # EX | 5 | | 5 | |
| PITUITARY GLAND | # EX | 5 | | 5 | |
| Cyst, pars intermedia | | 3 | 60.0 | 0 | 0.0 |
| THYROID GLAND | # EX | 5 | | 5 | |
| PARATHYROID GLAND | # EX | 4 | | 3 | |
| ADRENAL GLAND | # EX | 5 | | 5 | |
| SPINAL CORD,LUMBAR | # EX | 5 | | 5 | |
| KIDNEY | # EX | 5 | | 5 | |
| Mineralization | | 2 | 40.0 | 2 | 40.0 |
| Tubular proteinosis | | 0 | 0.0 | 1 | 20.0 |
| SKELETAL MUSCLE | # EX | 5 | | 5 | |
| Inflammation, chronic | | 1 | 20.0 | 0 | 0.0 |

Incidence Calculated by No. of Tissues Scored (2) - 0.060 mg/kg/day CuATSM/H2ATSM
(1) - 0 mg/kg/day (vehicle control)

LABCAT HP4.33 16-AUG-2004

PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## PROJECT SUMMARY

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice
DAYS ON TEST: ALL SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

| GROUP: | | 1 (1) | | 3 (2) | |
|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 5 | | 5 | |
| | | # | % | # | % |
| SKIN,INJECTION SITE | # EX | 5 | | 5 | |
| Inflammation, heterophilic, dermis | | 2 | 40.0 | 0 | 0.0 |
| Edema, dermis | | 1 | 20.0 | 0 | 0.0 |
| Hemorrhage, acute, dermis | | 5 | 100.0 | 2 | 40.0 |
| Fibrosis, dermis | | 1 | 20.0 | 0 | 0.0 |
| URINARY BLADDER | # EX | 5 | | 5 | |
| Inflammation, heterophilic | | 1 | 20.0 | 0 | 0.0 |
| TRACHEA | # EX | 5 | | 5 | |
| Inflammation, chronic, submucosa | | 0 | 0.0 | 1 | 20.0 |
| Inflammation, heterophilic, submucosa | | 1 | 20.0 | 1 | 20.0 |
| ESOPHAGUS | # EX | 5 | | 5 | |
| LUNG | # EX | 5 | | 5 | |
| Inflammation, heterophilic, perivascular | | 5 | 100.0 | 4 | 80.0 |
| Hyperplasia, pneumocyte | | 1 | 20.0 | 2 | 40.0 |
| Intimal heterophils, pulmonary arteries | | 2 | 40.0 | 3 | 60.0 |
| Histiocytosis, alveolar | | 3 | 60.0 | 1 | 20.0 |
| Granuloma | | 1 | 20.0 | 0 | 0.0 |
| Inflammation, alveolar, heterophilic | | 0 | 0.0 | 1 | 20.0 |
| HEART | # EX | 5 | | 5 | |
| AORTA | # EX | 5 | | 5 | |
| SKIN,VENTRAL ABDOMEN | # EX | 5 | | 5 | |
| Inflammation, chronic, dermis | | 2 | 40.0 | 0 | 0.0 |
| MAMMARY GLAND | # EX | 3 | | 3 | |

Incidence Calculated by No. of Tissues Scored (2) - 0.060 mg/kg/day CuATSM/H2ATSM
(1) - 0 mg/kg/day (vehicle control)

LABCAT HP4.33 16-AUG-2004

PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## PROJECT SUMMARY

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice
DAYS ON TEST: ALL SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

| GROUP: | | 1 (1) | | 3 (2) | |
|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 5 | | 5 | |
| | | # | % | # | % |
| SPLEEN | # EX | 5 | | 5 | |
| LIVER | # EX | 5 | | 5 | |
| Inflammation, chronic | | 3 | 60.0 | 4 | 80.0 |
| Fibrosis, portal | | 0 | 0.0 | 1 | 20.0 |
| Hyperplasia, bile ductule | | 0 | 0.0 | 1 | 20.0 |
| GALLBLADDER | # EX | 5 | | 5 | |
| SALIVARY GLAND,MANDIBULAR | # EX | 4 | | 5 | |
| SALIVARY GLAND,PAROTID | # EX | 5 | | 4 | |
| LYMPH NODE,MANDIBULAR | # EX | 5 | | 5 | |
| Edema | | 1 | 20.0 | 0 | 0.0 |
| Drainage of erythrocytes | | 1 | 20.0 | 1 | 20.0 |
| STOMACH | # EX | 5 | | 5 | |
| Inflammation, heterophilic | | 1 | 20.0 | 0 | 0.0 |
| Ectasia, gastric gland | | 1 | 20.0 | 0 | 0.0 |
| SMALL INTESTINE,DUODENUM | # EX | 5 | | 5 | |
| SMALL INTESTINE,ILEUM | # EX | 5 | | 5 | |
| LARGE INTESTINE,COLON | # EX | 4 | | 5 | |
| SMALL INTESTINE,JEJUNUM | # EX | 5 | | 5 | |
| LARGE INTESTINE,CECUM | # EX | 5 | | 5 | |
| PANCREAS | # EX | 5 | | 5 | |

Incidence Calculated by No. of Tissues Scored (2) - 0.060 mg/kg/day CuATSM/H2ATSM
(1) - 0 mg/kg/day (vehicle control)

LABCAT HP4.33 16-AUG-2004

PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## PROJECT SUMMARY

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice
DAYS ON TEST: ALL SEX: FEMALE

INCIDENCE OF NEOPLASTIC and NON-NEOPLASTIC MICROSCOPIC FINDINGS

| GROUP: | | 1 (1) | | 3 (2) | |
|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 5 | | 5 | |
| | | # | % | # | % |
| THYMUS | # EX | 5 | | 5 | |
| Hemorrhage, acute | | 1 | 20.0 | 0 | 0.0 |
| LYMPH NODE,MESENTERIC | # EX | 5 | | 5 | |
| Drainage of erythrocytes | | 2 | 40.0 | 1 | 20.0 |
| OVARY | # EX | 5 | | 5 | |
| Corpora hemorrhagica | | 3 | 60.0 | 1 | 20.0 |
| Mineralization | | 2 | 40.0 | 0 | 0.0 |
| UTERUS,HORN | # EX | 5 | | 5 | |
| EYE | # EX | 5 | | 5 | |
| BONE,FEMUR | # EX | 5 | | 5 | |
| Open physis | | 1 | 20.0 | 0 | 0.0 |
| BONE MARROW,FEMORAL | # EX | 5 | | 5 | |
| OVIDUCT | # EX | 1 | | 0 | |
| Cyst | | 1 | 100.0 | 0 | 0.0 |

Incidence Calculated by No. of Tissues Scored (2) - 0.060 mg/kg/day CuATSM/H2ATSM
(1) - 0 mg/kg/day (vehicle control)

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SECTION III

SEVERITY SUMMARY

PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## SEVERITY SUMMARY

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice
DAYS ON TEST: ALL SEX: MALE

| GROUP: | | 1 (1) | 3 (2) |
|---|---|---|---|
| NUMBER OF ANIMALS: | | 5 | 5 |
| | | # SEV | # SEV |
| BRAIN,CEREBRAL CORTEX | # EX | 5 | 5 |
| Inflammation, chronic, choroid plexus | | 1 0.20 | 0 0.00 |
| Gliosis | | 1 0.20 | 0 0.00 |
| BRAIN,CEREBELLUM | # EX | 5 | 5 |
| Satellitosis, molecular layer | | 3 0.60 | 0 0.00 |
| BRAIN,MEDULLA/PONS | # EX | 5 | 5 |
| SPINAL CORD,CERVICAL | # EX | 5 | 5 |
| PERIPHERAL NERVE,SCIATIC | # EX | 5 | 5 |
| SPINAL CORD,MIDTHORACIC | # EX | 5 | 5 |
| Axonal spheroid | | 1 0.20 | 0 0.00 |
| Degeneration, neuroaxonal | | 1 0.20 | 0 0.00 |
| PITUITARY GLAND | # EX | 5 | 5 |
| THYROID GLAND | # EX | 5 | 5 |
| Inflammation, chronic | | 0 0.00 | 1 0.20 |
| PARATHYROID GLAND | # EX | 4 | 4 |
| ADRENAL GLAND | # EX | 5 | 5 |
| Congestion | | 1 0.40 | 0 0.00 |
| SPINAL CORD,LUMBAR | # EX | 5 | 5 |
| Chromatolysis, neuron | | 0 0.00 | 1 0.20 |
| KIDNEY | # EX | 5 | 5 |
| Mineralization | | 1 0.20 | 2 0.40 |
| Fibrosis, interstitial | | 0 0.00 | 2 0.60 |

Severity Calculated by No. of Tissues Scored (2) - 0.060 mg/kg/day CuATSM/H2ATSM
(1) - 0 mg/kg/day (vehicle control)

LABCAT HP4.33 16-AUG-2004

PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## SEVERITY SUMMARY

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice
DAYS ON TEST: ALL SEX: MALE

| GROUP: | | 1 (1) | 3 (2) |
|---|---|---|---|
| NUMBER OF ANIMALS: | | 5 | 5 |
| | | # SEV | # SEV |
| SKELETAL MUSCLE | # EX | 5 | 5 |
| SKIN, INJECTION SITE | # EX | 5 | 5 |
| Inflammation, heterophilic, dermis | | 1 0.40 | 1 0.20 |
| Edema, dermis | | 2 0.40 | 0 0.00 |
| Hemorrhage, acute, dermis | | 2 0.40 | 3 0.80 |
| Hemosiderophages, dermis | | 2 0.40 | 0 0.00 |
| Serocellular crust | | 1 0.20 | 0 0.00 |
| Inflammation, chronic, dermis | | 2 0.40 | 1 0.20 |
| Fibrin deposition, dermis | | 1 0.20 | 0 0.00 |
| URINARY BLADDER | # EX | 5 | 5 |
| TRACHEA | # EX | 5 | 5 |
| Inflammation, chronic, submucosa | | 1 0.20 | 0 0.00 |
| Inflammation, heterophilic, submucosa | | 3 0.60 | 0 0.00 |
| ESOPHAGUS | # EX | 5 | 5 |
| LUNG | # EX | 5 | 5 |
| Inflammation, heterophilic, perivascular | | 5 1.40 | 3 1.00 |
| Hyperplasia, pneumocyte | | 2 0.40 | 1 0.20 |
| Intimal heterophils, pulmonary arteries | | 3 0.60 | 2 0.40 |
| Fibrosis, intimal, pulmonary arteries | | 3 0.60 | 0 0.00 |
| Histiocytosis, alveolar | | 0 0.00 | 1 0.20 |
| Ectopic bone | | 1 0.20 | 1 0.20 |
| Fibrosis, interstitial | | 0 0.00 | 1 0.20 |
| Hypertrophy, endothelial | | 1 0.20 | 0 0.00 |
| Granuloma | | 0 0.00 | 1 0.40 |
| HEART | # EX | 5 | 5 |
| Fibrosis, epicardial | | 1 0.20 | 0 0.00 |

Severity Calculated by No. of Tissues Scored (2) - 0.060 mg/kg/day CuATSM/H2ATSM
(1) - 0 mg/kg/day (vehicle control)

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## SEVERITY SUMMARY

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice
DAYS ON TEST: ALL SEX: MALE

| GROUP: | | 1 (1) | | 3 (2) | |
|---|---|---|---|---|---|
| NUMBER OF ANIMALS: | | 5 | | 5 | |
| | | # | SEV | # | SEV |
| AORTA | # EX | 5 | | 5 | |
| SKIN,VENTRAL ABDOMEN | # EX | 5 | | 5 | |
| Inflammation, heterophilic | | 1 | 0.20 | 0 | 0.00 |
| SPLEEN | # EX | 5 | | 5 | |
| Hemosiderophage aggregates | | 1 | 0.20 | 0 | 0.00 |
| LIVER | # EX | 5 | | 5 | |
| Inflammation, chronic | | 3 | 0.60 | 3 | 0.60 |
| GALLBLADDER | # EX | 5 | | 5 | |
| SALIVARY GLAND,MANDIBULAR | # EX | 5 | | 5 | |
| SALIVARY GLAND,PAROTID | # EX | 5 | | 5 | |
| Atrophy, acinar | | 0 | 0.00 | 1 | 0.20 |
| LYMPH NODE,MANDIBULAR | # EX | 5 | | 4 | |
| Edema | | 1 | 0.20 | 0 | 0.00 |
| Hyperplasia, paracortical | | 0 | 0.00 | 1 | 0.25 |
| Drainage of erythrocytes | | 2 | 0.40 | 0 | 0.00 |
| Drainage of heterophils | | 1 | 0.20 | 0 | 0.00 |
| STOMACH | # EX | 5 | | 5 | |
| SMALL INTESTINE,DUODENUM | # EX | 5 | | 5 | |
| SMALL INTESTINE,ILEUM | # EX | 5 | | 5 | |
| Lymphangiectasia | | 1 | 0.20 | 0 | 0.00 |
| LARGE INTESTINE,COLON | # EX | 4 | | 5 | |

Severity Calculated by No. of Tissues Scored (2) - 0.060 mg/kg/day CuATSM/H2ATSM
(1) - 0 mg/kg/day (vehicle control)

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## SEVERITY SUMMARY

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice
DAYS ON TEST: ALL SEX: MALE

| GROUP: | | 1 (1) | 3 (2) |
|---|---|---|---|
| NUMBER OF ANIMALS: | | 5 | 5 |
| | | # SEV | # SEV |
| SMALL INTESTINE,JEJUNUM | # EX | 5 | 5 |
| Lymphangiectasia | | 1 0.20 | 0 0.00 |
| LARGE INTESTINE,CECUM | # EX | 5 | 5 |
| PANCREAS | # EX | 5 | 5 |
| Necrosis, adipose with saponification | | 1 0.20 | 0 0.00 |
| THYMUS | # EX | 5 | 5 |
| Hemorrhage, acute | | 1 0.20 | 0 0.00 |
| LYMPH NODE,MESENTERIC | # EX | 5 | 5 |
| Drainage of erythrocytes | | 1 0.20 | 0 0.00 |
| Hyperplasia, paracortical | | 1 0.20 | 0 0.00 |
| TESTES | # EX | 5 | 5 |
| EPIDIDYMIS | # EX | 5 | 5 |
| EYE | # EX | 5 | 5 |
| BONE,FEMUR | # EX | 5 | 5 |
| BONE MARROW,FEMORAL | # EX | 5 | 5 |

Severity Calculated by No. of Tissues Scored
(1) - 0 mg/kg/day (vehicle control)
(2) - 0.060 mg/kg/day CuATSM/H2ATSM

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## SEVERITY SUMMARY

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice
DAYS ON TEST: ALL SEX: FEMALE

| | | GROUP: | 1 (1) | 3 (2) |
|---|---|---|---|---|
| | | NUMBER OF ANIMALS: | 5 | 5 |
| | | | # SEV | # SEV |
| BRAIN,CEREBRAL CORTEX | # EX | | 5 | 5 |
| BRAIN,CEREBELLUM | # EX | | 5 | 5 |
| Satellitosis, molecular layer | | | 2 0.40 | 2 0.40 |
| BRAIN,MEDULLA/PONS | # EX | | 5 | 5 |
| SPINAL CORD,CERVICAL | # EX | | 5 | 5 |
| Degeneration, neuroaxonal | | | 2 0.40 | 0 0.00 |
| PERIPHERAL NERVE,SCIATIC | # EX | | 5 | 5 |
| Axonal spheroid | | | 1 0.20 | 0 0.00 |
| SPINAL CORD,MIDTHORACIC | # EX | | 5 | 5 |
| PITUITARY GLAND | # EX | | 5 | 5 |
| Cyst, pars intermedia | | | 3 0.60 | 0 0.00 |
| THYROID GLAND | # EX | | 5 | 5 |
| PARATHYROID GLAND | # EX | | 4 | 3 |
| ADRENAL GLAND | # EX | | 5 | 5 |
| SPINAL CORD,LUMBAR | # EX | | 5 | 5 |
| KIDNEY | # EX | | 5 | 5 |
| Mineralization | | | 2 0.40 | 2 0.40 |
| Tubular proteinosis | | | 0 0.00 | 1 0.20 |
| SKELETAL MUSCLE | # EX | | 5 | 5 |
| Inflammation, chronic | | | 1 0.20 | 0 0.00 |

Severity Calculated by No. of Tissues Scored (2) - 0.060 mg/kg/day CuATSM/H2ATSM
(1) - 0 mg/kg/day (vehicle control)

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## SEVERITY SUMMARY

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice
DAYS ON TEST: ALL SEX: FEMALE

| GROUP: | | 1 (1) | 3 (2) |
|---|---|---|---|
| NUMBER OF ANIMALS: | | 5 | 5 |
| | | # SEV | # SEV |
| SKIN,INJECTION SITE | # EX | 5 | 5 |
| Inflammation, heterophilic, dermis | | 2 0.40 | 0 0.00 |
| Edema, dermis | | 1 0.20 | 0 0.00 |
| Hemorrhage, acute, dermis | | 5 1.00 | 2 0.40 |
| Fibrosis, dermis | | 1 0.20 | 0 0.00 |
| URINARY BLADDER | # EX | 5 | 5 |
| Inflammation, heterophilic | | 1 0.40 | 0 0.00 |
| TRACHEA | # EX | 5 | 5 |
| Inflammation, chronic, submucosa | | 0 0.00 | 1 0.20 |
| Inflammation, heterophilic, submucosa | | 1 0.20 | 1 0.20 |
| ESOPHAGUS | # EX | 5 | 5 |
| LUNG | # EX | 5 | 5 |
| Inflammation, heterophilic, perivascular | | 5 1.40 | 4 1.00 |
| Hyperplasia, pneumocyte | | 1 0.20 | 2 0.40 |
| Intimal heterophils, pulmonary arteries | | 2 0.40 | 3 0.80 |
| Histiocytosis, alveolar | | 3 0.60 | 1 0.20 |
| Granuloma | | 1 0.40 | 0 0.00 |
| Inflammation, alveolar, heterophilic | | 0 0.00 | 1 0.20 |
| HEART | # EX | 5 | 5 |
| AORTA | # EX | 5 | 5 |
| SKIN,VENTRAL ABDOMEN | # EX | 5 | 5 |
| Inflammation, chronic, dermis | | 2 0.40 | 0 0.00 |
| MAMMARY GLAND | # EX | 3 | 3 |
| SPLEEN | # EX | 5 | 5 |

Severity Calculated by No. of Tissues Scored (2) - 0.060 mg/kg/day CuATSM/H2ATSM
(1) - 0 mg/kg/day (vehicle control)

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## SEVERITY SUMMARY

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice
DAYS ON TEST: ALL SEX: FEMALE

| GROUP: | | 1 | 3 |
|---|---|---|---|
| | | (1) | (2) |
| NUMBER OF ANIMALS: | | 5 | 5 |
| | | # SEV | # SEV |
| LIVER | # EX | 5 | 5 |
| Inflammation, chronic | | 3 0.60 | 4 0.80 |
| Fibrosis, portal | | 0 0.00 | 1 0.20 |
| Hyperplasia, bile ductule | | 0 0.00 | 1 0.20 |
| GALLBLADDER | # EX | 5 | 5 |
| SALIVARY GLAND,MANDIBULAR | # EX | 4 | 5 |
| SALIVARY GLAND,PAROTID | # EX | 5 | 4 |
| LYMPH NODE,MANDIBULAR | # EX | 5 | 5 |
| Edema | | 1 0.20 | 0 0.00 |
| Drainage of erythrocytes | | 1 0.20 | 1 0.20 |
| STOMACH | # EX | 5 | 5 |
| Inflammation, heterophilic | | 1 0.20 | 0 0.00 |
| Ectasia, gastric gland | | 1 0.20 | 0 0.00 |
| SMALL INTESTINE,DUODENUM | # EX | 5 | 5 |
| SMALL INTESTINE,ILEUM | # EX | 5 | 5 |
| LARGE INTESTINE,COLON | # EX | 4 | 5 |
| SMALL INTESTINE,JEJUNUM | # EX | 5 | 5 |
| LARGE INTESTINE,CECUM | # EX | 5 | 5 |
| PANCREAS | # EX | 5 | 5 |
| THYMUS | # EX | 5 | 5 |
| Hemorrhage, acute | | 1 0.20 | 0 0.00 |

Severity Calculated by No. of Tissues Scored (2) - 0.060 mg/kg/day CuATSM/H2ATSM
(1) - 0 mg/kg/day (vehicle control)

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## SEVERITY SUMMARY

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice
DAYS ON TEST: ALL SEX: FEMALE

| GROUP: | | 1 (1) | 3 (2) |
|---|---|---|---|
| NUMBER OF ANIMALS: | | 5 | 5 |
| | | # SEV | # SEV |
| LYMPH NODE,MESENTERIC | # EX | 5 | 5 |
| Drainage of erythrocytes | | 2 0.60 | 1 0.20 |
| OVARY | # EX | 5 | 5 |
| Corpora hemorrhagica | | 3 1.00 | 1 0.20 |
| Mineralization | | 2 0.40 | 0 0.00 |
| UTERUS,HORN | # EX | 5 | 5 |
| EYE | # EX | 5 | 5 |
| BONE,FEMUR | # EX | 5 | 5 |
| BONE MARROW,FEMORAL | # EX | 5 | 5 |
| OVIDUCT | # EX | 1 | 0 |
| Cyst | | 1 2.00 | 0 0.00 |

Severity Calculated by No. of Tissues Scored (2) - 0.060 mg/kg/day CuATSM/H2ATSM
(1) - 0 mg/kg/day (vehicle control)

LABCAT HP4.33 16-AUG-2004

SECTION IV

TABULATED ANIMAL DATA

PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## TABULATED ANIMAL DATA

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice GROUP: 1: 0 mg/kg/day (vehicle control)
DAYS ON TEST: ALL SEX: MALE

| ANIMAL ID: | 0001 | 0002 | 0003 | 0004 | 0005 |
|---|---|---|---|---|---|
| BRAIN,CEREBRAL CORTEX | - | N | - | N | N |
| Inflammation, chronic, choroid plexus | 1 | - | - | - | - |
| Gliosis | - | - | 1 | - | - |
| BRAIN,CEREBELLUM | - | - | - | N | N |
| Satellitosis, molecular layer | 1 | 1 | 1 | - | - |
| BRAIN,MEDULLA/PONS | N | N | N | N | N |
| SPINAL CORD,CERVICAL | N | N | N | N | N |
| PERIPHERAL NERVE,SCIATIC | N | N | N | N | N |
| SPINAL CORD,MIDTHORACIC | N | N | - | - | N |
| Axonal spheroid | - | - | 1 | - | - |
| Degeneration, neuroaxonal | - | - | - | 1 | - |
| PITUITARY GLAND | N | N | N | N | N |
| THYROID GLAND | N | N | N | N | N |
| PARATHYROID GLAND | N | U | N | N | N |
| ADRENAL GLAND | N | N | N | - | N |
| Congestion | - | - | - | 2 | - |
| SPINAL CORD,LUMBAR | N | N | N | N | N |
| KIDNEY | N | N | - | N | N |
| Mineralization | - | - | 1 | - | - |
| SKELETAL MUSCLE | N | N | N | N | N |
| SKIN,INJECTION SITE | - | N | - | - | - |

See Reports Code Table for Symbol Definitions

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## TABULATED ANIMAL DATA

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice GROUP: 1: 0 mg/kg/day (vehicle control)
DAYS ON TEST: ALL SEX: MALE

| ANIMAL ID: | 0001 | 0002 | 0003 | 0004 | 0005 |
|---|---|---|---|---|---|
| Inflammation, heterophilic, dermis | 2 | - | - | - | - |
| Edema, dermis | 1 | - | 1 | - | - |
| Hemorrhage, acute, dermis | 1 | - | 1 | - | - |
| Hemosiderophages, dermis | 1 | - | - | - | 1 |
| Serocellular crust | 1 | - | - | - | - |
| Inflammation, chronic, dermis | - | - | 1 | 1 | - |
| Fibrin deposition, dermis | - | - | 1 | - | - |
| URINARY BLADDER | N | N | N | N | N |
| TRACHEA | - | - | N | N | - |
| Inflammation, chronic, submucosa | 1 | - | - | - | - |
| Inflammation, heterophilic, submucosa | 1 | 1 | - | - | 1 |
| ESOPHAGUS | N | N | N | N | N |
| LUNG | - | - | - | - | - |
| Inflammation, heterophilic, perivascular | 1 | 2 | 1 | 1 | 2 |
| Hyperplasia, pneumocyte | - | 1 | 1 | - | - |
| Intimal heterophils, pulmonary arteries | - | - | 1 | 1 | 1 |
| Fibrosis, intimal, pulmonary arteries | - | - | 1 | 1 | 1 |
| Ectopic bone | - | - | - | 1 | - |
| Hypertrophy, endothelial | - | - | - | - | 1 |
| HEART | N | N | - | N | N |
| Fibrosis, epicardial | - | - | 1 | - | - |
| AORTA | N | N | N | N | N |
| SKIN,VENTRAL ABDOMEN | N | - | N | N | N |
| Inflammation, heterophilic | - | 1 | - | - | - |
| MAMMARY GLAND | U | U | U | U | U |
| SPLEEN | N | N | N | N | - |
| Hemosiderophage aggregates | - | - | - | - | 1 |

See Reports Code Table for Symbol Definitions

LABCAT HP4.33 16-AUG-2004

PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## TABULATED ANIMAL DATA

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice GROUP: 1: 0 mg/kg/day (vehicle control)
DAYS ON TEST: ALL SEX: MALE

| ANIMAL ID: | 0001 | 0002 | 0003 | 0004 | 0005 |
|---|---|---|---|---|---|
| LIVER | N | - | - | - | N |
| Inflammation, chronic | - | 1 | 1 | 1 | - |
| GALLBLADDER | N | N | N | N | N |
| SALIVARY GLAND,MANDIBULAR | N | N | N | N | N |
| SALIVARY GLAND,PAROTID | N | N | N | N | N |
| LYMPH NODE,MANDIBULAR | N | - | N | - | - |
| Edema | - | 1 | - | - | - |
| Drainage of erythrocytes | - | - | - | 1 | 1 |
| Drainage of heterophils | - | - | - | 1 | - |
| STOMACH | N | N | N | N | N |
| SMALL INTESTINE,DUODENUM | N | N | N | N | N |
| SMALL INTESTINE,ILEUM | N | N | N | - | N |
| Lymphangiectasia | - | - | - | 1 | - |
| LARGE INTESTINE,COLON | N | N | N | U | N |
| SMALL INTESTINE,JEJUNUM | N | N | - | N | N |
| Lymphangiectasia | - | - | 1 | - | - |
| LARGE INTESTINE,CECUM | N | N | N | N | N |
| PANCREAS | N | - | N | N | N |
| Necrosis, adipose with saponification | - | 1 | - | - | - |
| THYMUS | N | N | N | - | N |
| Hemorrhage, acute | - | - | - | 1 | - |
| LYMPH NODE,MESENTERIC | - | N | - | N | N |
| Drainage of erythrocytes | 1 | - | - | - | - |

See Reports Code Table for Symbol Definitions

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## TABULATED ANIMAL DATA

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice GROUP: 1: 0 mg/kg/day (vehicle control)
DAYS ON TEST: ALL SEX: MALE

| ANIMAL ID: | 0001 | 0002 | 0003 | 0004 | 0005 |
|---|---|---|---|---|---|
| Hyperplasia, paracortical | - | - | 1 | - | - |
| TESTES | N | N | N | N | N |
| EPIDIDYMIS | N | N | N | N | N |
| EYE | N | N | N | N | N |
| BONE,FEMUR | N | N | N | N | N |
| BONE MARROW,FEMORAL | N | N | N | N | N |

See Reports Code Table for Symbol Definitions

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## TABULATED ANIMAL DATA

STUDY ID : 2073-002-003 — STUDY NUMBER: 2073003
FATE: Terminal Sacrifice — GROUP: 3: 0.060 mg/kg/day CuATSM/H2ATSM
DAYS ON TEST: ALL — SEX: MALE

| ANIMAL ID: | 0033 | 0034 | 0035 | 0036 | 0037 |
|---|---|---|---|---|---|
| BRAIN,CEREBRAL CORTEX | N | N | N | N | N |
| BRAIN,CEREBELLUM | N | N | N | N | N |
| BRAIN,MEDULLA/PONS | N | N | N | N | N |
| SPINAL CORD,CERVICAL | N | N | N | N | N |
| PERIPHERAL NERVE,SCIATIC | N | N | N | N | N |
| SPINAL CORD,MIDTHORACIC | N | N | N | N | N |
| PITUITARY GLAND | N | N | N | N | N |
| THYROID GLAND | N | N | N | - | N |
| Inflammation, chronic | - | - | - | 1 | - |
| PARATHYROID GLAND | N | N | N | N | U |
| ADRENAL GLAND | N | N | N | N | N |
| SPINAL CORD,LUMBAR | N | - | N | N | N |
| Chromatolysis, neuron | - | 1 | - | - | - |
| KIDNEY | - | - | N | N | N |
| Mineralization | 1 | 1 | - | - | - |
| Fibrosis, interstitial | 2 | 1 | - | - | - |
| SKELETAL MUSCLE | N | N | N | N | N |
| SKIN,INJECTION SITE | N | - | - | - | - |
| Inflammation, heterophilic, dermis | - | 1 | - | - | - |
| Hemorrhage, acute, dermis | - | - | 1 | 1 | 2 |
| Inflammation, chronic, dermis | - | - | 1 | - | - |
| URINARY BLADDER | N | N | N | N | N |

See Reports Code Table for Symbol Definitions

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## TABULATED ANIMAL DATA

STUDY ID : 2073-002-003 — STUDY NUMBER: 2073003
FATE: Terminal Sacrifice — GROUP: 3: 0.060 mg/kg/day CuATSM/H2ATSM
DAYS ON TEST: ALL — SEX: MALE

| ANIMAL ID: | 0033 | 0034 | 0035 | 0036 | 0037 |
|---|---|---|---|---|---|
| TRACHEA | N | N | N | N | N |
| ESOPHAGUS | N | N | N | N | N |
| LUNG | - | N | - | - | - |
| Inflammation, heterophilic, perivascular | 1 | - | 2 | 2 | - |
| Hyperplasia, pneumocyte | 1 | - | - | - | - |
| Intimal heterophils, pulmonary arteries | - | - | - | 1 | 1 |
| Histiocytosis, alveolar | - | - | 1 | - | - |
| Ectopic bone | - | - | - | 1 | - |
| Fibrosis, interstitial | - | - | - | 1 | - |
| Granuloma | - | - | - | - | 2 |
| HEART | N | N | N | N | N |
| AORTA | N | N | N | N | N |
| SKIN,VENTRAL ABDOMEN | N | N | N | N | N |
| MAMMARY GLAND | U | U | U | U | U |
| SPLEEN | N | N | N | N | N |
| LIVER | - | N | - | - | N |
| Inflammation, chronic | 1 | - | 1 | 1 | - |
| GALLBLADDER | N | N | N | N | N |
| SALIVARY GLAND,MANDIBULAR | N | N | N | N | N |
| SALIVARY GLAND,PAROTID | N | N | - | N | N |
| Atrophy, acinar | - | - | 1 | - | - |
| LYMPH NODE,MANDIBULAR | N | - | N | N | U |
| Hyperplasia, paracortical | - | 1 | - | - | - |

See Reports Code Table for Symbol Definitions

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## TABULATED ANIMAL DATA

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice GROUP: 3: 0.060 mg/kg/day CuATSM/H2ATSM
DAYS ON TEST: ALL SEX: MALE

| ANIMAL ID: | 0033 | 0034 | 0035 | 0036 | 0037 |
|---|---|---|---|---|---|
| STOMACH | N | N | N | N | N |
| SMALL INTESTINE,DUODENUM | N | N | N | N | N |
| SMALL INTESTINE,ILEUM | N | N | N | N | N |
| LARGE INTESTINE,COLON | N | N | N | N | N |
| SMALL INTESTINE,JEJUNUM | N | N | N | N | N |
| LARGE INTESTINE,CECUM | N | N | N | N | N |
| PANCREAS | N | N | N | N | N |
| THYMUS | N | N | N | N | N |
| LYMPH NODE,MESENTERIC | N | N | N | N | N |
| TESTES | N | N | N | N | N |
| EPIDIDYMIS | N | N | N | N | N |
| EYE | N | N | N | N | N |
| BONE,FEMUR | N | N | N | N | N |
| BONE MARROW,FEMORAL | N | N | N | N | N |

See Reports Code Table for Symbol Definitions

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## TABULATED ANIMAL DATA

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice GROUP: 1: 0 mg/kg/day (vehicle control)
DAYS ON TEST: ALL SEX: FEMALE

| ANIMAL ID: | 0009 | 0010 | 0011 | 0012 | 0013 |
|---|---|---|---|---|---|
| BRAIN, CEREBRAL CORTEX | N | N | N | N | N |
| BRAIN, CEREBELLUM | - | N | - | N | N |
| Satellitosis, molecular layer | 1 | - | 1 | - | - |
| BRAIN, MEDULLA/PONS | N | N | N | N | N |
| SPINAL CORD, CERVICAL | N | N | N | - | - |
| Degeneration, neuroaxonal | - | - | - | 1 | 1 |
| PERIPHERAL NERVE, SCIATIC | N | N | - | N | N |
| Axonal spheroid | - | - | 1 | - | - |
| SPINAL CORD, MIDTHORACIC | N | N | N | N | N |
| PITUITARY GLAND | - | - | - | N | N |
| Cyst, pars intermedia | 1 | 1 | 1 | - | - |
| THYROID GLAND | N | N | N | N | N |
| PARATHYROID GLAND | N | N | U | N | N |
| ADRENAL GLAND | N | N | N | N | N |
| SPINAL CORD, LUMBAR | N | N | N | N | N |
| KIDNEY | N | N | - | - | N |
| Mineralization | - | - | 1 | 1 | - |
| SKELETAL MUSCLE | N | N | N | - | N |
| Inflammation, chronic | - | - | - | 1 | - |
| SKIN, INJECTION SITE | - | - | - | - | - |
| Inflammation, heterophilic, dermis | - | - | - | 1 | 1 |
| Edema, dermis | - | - | - | 1 | - |
| Hemorrhage, acute, dermis | 1 | 1 | 1 | 1 | 1 |

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14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## TABULATED ANIMAL DATA

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice GROUP: 1: 0 mg/kg/day (vehicle control)
DAYS ON TEST: ALL SEX: FEMALE

| ANIMAL ID: | 0009 | 0010 | 0011 | 0012 | 0013 |
|---|---|---|---|---|---|
| Fibrosis, dermis | 1 | - | - | - | - |
| URINARY BLADDER | N | N | N | - | N |
| Inflammation, heterophilic | - | - | - | 2 | - |
| TRACHEA | N | N | N | - | N |
| Inflammation, heterophilic, submucosa | - | - | - | 1 | - |
| ESOPHAGUS | N | N | N | N | N |
| LUNG | - | - | - | - | - |
| Inflammation, heterophilic, perivascular | 2 | 1 | 2 | 1 | 1 |
| Hyperplasia, pneumocyte | - | - | - | - | 1 |
| Intimal heterophils, pulmonary arteries | 1 | - | - | - | 1 |
| Histiocytosis, alveolar | 1 | - | 1 | - | 1 |
| Granuloma | - | - | - | - | 2 |
| HEART | N | N | N | N | N |
| AORTA | N | N | N | N | N |
| SKIN, VENTRAL ABDOMEN | - | N | N | - | N |
| Inflammation, chronic, dermis | 1 | - | - | 1 | - |
| MAMMARY GLAND | N | N | N | U | U |
| SPLEEN | N | N | N | N | N |
| LIVER | - | N | - | N | - |
| Inflammation, chronic | 1 | - | 1 | - | 1 |
| GALLBLADDER | N | N | N | N | N |
| SALIVARY GLAND, MANDIBULAR | N | U | N | N | N |
| SALIVARY GLAND, PAROTID | N | N | N | N | N |

See Reports Code Table for Symbol Definitions

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## TABULATED ANIMAL DATA

STUDY ID : 2073-002-003 — STUDY NUMBER: 2073003
FATE: Terminal Sacrifice — GROUP: 1: 0 mg/kg/day (vehicle control)
DAYS ON TEST: ALL — SEX: FEMALE

| ANIMAL ID: | 0009 | 0010 | 0011 | 0012 | 0013 |
|---|---|---|---|---|---|
| LYMPH NODE,MANDIBULAR | N | - | N | - | N |
| Edema | - | - | - | 1 | - |
| Drainage of erythrocytes | - | 1 | - | - | - |
| STOMACH | N | - | N | N | - |
| Inflammation, heterophilic | - | 1 | - | - | - |
| Ectasia, gastric gland | - | - | - | - | 1 |
| SMALL INTESTINE,DUODENUM | N | N | N | N | N |
| SMALL INTESTINE,ILEUM | N | N | N | N | N |
| LARGE INTESTINE,COLON | N | N | N | U | N |
| SMALL INTESTINE,JEJUNUM | N | N | N | N | N |
| LARGE INTESTINE,CECUM | N | N | N | N | N |
| PANCREAS | N | N | N | N | N |
| THYMUS | - | N | N | N | N |
| Hemorrhage, acute | 1 | - | - | - | - |
| LYMPH NODE,MESENTERIC | - | - | N | N | N |
| Drainage of erythrocytes | 1 | 2 | - | - | - |
| OVARY | - | - | - | - | N |
| Corpora hemorrhagica | 2 | 2 | - | 1 | - |
| Mineralization | 1 | - | 1 | - | - |
| UTERUS,HORN | N | N | N | N | N |
| EYE | N | N | N | N | N |
| BONE,FEMUR | N | N | N | - | N |
| Open physis | - | - | - | P | - |

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14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## TABULATED ANIMAL DATA

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice GROUP: 1: 0 mg/kg/day (vehicle control)
DAYS ON TEST: ALL SEX: FEMALE

| ANIMAL ID: | 0009 | 0010 | 0011 | 0012 | 0013 |
|---|---|---|---|---|---|
| BONE MARROW,FEMORAL | N | N | N | N | N |
| Non-Protocol Tissues: | | | | | |
| OVIDUCT | - | - | - | - | - |
| Cyst | - | - | - | 2 | - |

See Reports Code Table for Symbol Definitions

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## TABULATED ANIMAL DATA

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice GROUP: 3: 0.060 mg/kg/day CuATSM/H2ATSM
DAYS ON TEST: ALL SEX: FEMALE

| ANIMAL ID: | 0041 | 0042 | 0043 | 0044 | 0045 |
|---|---|---|---|---|---|
| BRAIN,CEREBRAL CORTEX | N | N | N | N | N |
| BRAIN,CEREBELLUM | - | N | - | N | N |
| Satellitosis, molecular layer | 1 | - | 1 | - | - |
| BRAIN,MEDULLA/PONS | N | N | N | N | N |
| SPINAL CORD,CERVICAL | N | N | N | N | N |
| PERIPHERAL NERVE,SCIATIC | N | N | N | N | N |
| SPINAL CORD,MIDTHORACIC | N | N | N | N | N |
| PITUITARY GLAND | N | N | N | N | N |
| THYROID GLAND | N | N | N | N | N |
| PARATHYROID GLAND | U | N | N | U | N |
| ADRENAL GLAND | N | N | N | N | N |
| SPINAL CORD,LUMBAR | N | N | N | N | N |
| KIDNEY | N | - | N | - | N |
| Mineralization | - | 1 | - | 1 | - |
| Tubular proteinosis | - | 1 | - | - | - |
| SKELETAL MUSCLE | N | N | N | N | N |
| SKIN,INJECTION SITE | N | N | N | - | - |
| Hemorrhage, acute, dermis | - | - | - | 1 | 1 |
| URINARY BLADDER | N | N | N | N | N |
| TRACHEA | N | - | N | N | N |
| Inflammation, chronic, submucosa | - | 1 | - | - | - |

See Reports Code Table for Symbol Definitions

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## TABULATED ANIMAL DATA

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice GROUP: 3: 0.060 mg/kg/day CuATSM/H2ATSM
DAYS ON TEST: ALL SEX: FEMALE

| ANIMAL ID: | 0041 | 0042 | 0043 | 0044 | 0045 |
|---|---|---|---|---|---|
| Inflammation, heterophilic, submucosa | - | 1 | - | - | - |
| ESOPHAGUS | N | N | N | N | N |
| LUNG | - | - | - | - | - |
| Inflammation, heterophilic, perivascular | 1 | - | 2 | 1 | 1 |
| Hyperplasia, pneumocyte | - | 1 | - | 1 | - |
| Intimal heterophils, pulmonary arteries | - | - | 1 | 1 | 2 |
| Histiocytosis, alveolar | - | - | - | - | 1 |
| Inflammation, alveolar, heterophilic | - | - | - | - | 1 |
| HEART | N | N | N | N | N |
| AORTA | N | N | N | N | N |
| SKIN,VENTRAL ABDOMEN | N | N | N | N | N |
| MAMMARY GLAND | N | U | N | U | N |
| SPLEEN | N | N | N | N | N |
| LIVER | - | - | - | - | N |
| Inflammation, chronic | 1 | 1 | 1 | 1 | - |
| Fibrosis, portal | - | - | 1 | - | - |
| Hyperplasia, bile ductule | - | - | 1 | - | - |
| GALLBLADDER | N | N | N | N | N |
| SALIVARY GLAND,MANDIBULAR | N | N | N | N | N |
| SALIVARY GLAND,PAROTID | N | N | U | N | N |
| LYMPH NODE,MANDIBULAR | N | N | N | - | N |
| Drainage of erythrocytes | - | - | - | 1 | - |
| STOMACH | N | N | N | N | N |

See Reports Code Table for Symbol Definitions

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## TABULATED ANIMAL DATA

STUDY ID : 2073-002-003 STUDY NUMBER: 2073003
FATE: Terminal Sacrifice GROUP: 3: 0.060 mg/kg/day CuATSM/H2ATSM
DAYS ON TEST: ALL SEX: FEMALE

| ANIMAL ID: | 0041 | 0042 | 0043 | 0044 | 0045 |
|---|---|---|---|---|---|
| SMALL INTESTINE,DUODENUM | N | N | N | N | N |
| SMALL INTESTINE,ILEUM | N | N | N | N | N |
| LARGE INTESTINE,COLON | N | N | N | N | N |
| SMALL INTESTINE,JEJUNUM | N | N | N | N | N |
| LARGE INTESTINE,CECUM | N | N | N | N | N |
| PANCREAS | N | N | N | N | N |
| THYMUS | N | N | N | N | N |
| LYMPH NODE,MESENTERIC | N | N | N | N | - |
| Drainage of erythrocytes | - | - | - | - | 1 |
| OVARY | N | N | N | N | - |
| Corpora hemorrhagica | - | - | - | - | 1 |
| UTERUS,HORN | N | N | N | N | N |
| EYE | N | N | N | N | N |
| BONE,FEMUR | N | N | N | N | N |
| BONE MARROW,FEMORAL | N | N | N | N | N |

See Reports Code Table for Symbol Definitions

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SECTION V

CORRELATION OF GROSS AND MICROSCOPIC (MICRO) FINDINGS

PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## CORRELATION OF GROSS & MICRO

STUDY ID: 2073-002-003 STUDY NUMBER: 2073003

SEX: MALE GROUP: 1: 0 mg/kg/day (vehicle control)

No Gross Observations for any animal in this group

PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## CORRELATION OF GROSS & MICRO

STUDY ID: 2073-002-003 STUDY NUMBER: 2073003
SEX: MALE GROUP: 2: 0.030 mg/kg/day CuATSM/H2ATSM

Animal ID: 0019
Animal Fate: Terminal Sacrifice Days on Test: 15

| Reference to Necropsy Record: | Related Histopathology: |
|---|---|
| SKIN,INGUINAL - ALOPECIA, 50x50 MM | SKIN,INGUINAL - Not required by protocol |
| THYROID GLAND - BILATERAL, PIGMENTATION, BLACK, MOTTLED | THYROID GLAND - Not required by protocol |

Animal ID: 0021
Animal Fate: Terminal Sacrifice Days on Test: 15

| Reference to Necropsy Record: | Related Histopathology: |
|---|---|
| LUNG - PARENCHYMA, PIGMENTATION, RED | LUNG - Not required by protocol |

Animal ID: 0023
Animal Fate: Recovery Sacrifice Days on Test: 29

| Reference to Necropsy Record: | Related Histopathology: |
|---|---|
| THYROID GLAND - LEFT, CYST, 2x2x2 MM, CLEAR | THYROID GLAND - Not required by protocol |

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## CORRELATION OF GROSS & MICRO

STUDY ID: 2073-002-003 STUDY NUMBER: 2073003
SEX: MALE GROUP: 3: 0.060 mg/kg/day CuATSM/H2ATSM

Animal ID: 0040
Animal Fate: Recovery Sacrifice Days on Test: 29

Reference to Necropsy Record:
THYMUS - PIGMENTATION, MOTTLED

Related Histopathology:
THYMUS - Not required by protocol

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## CORRELATION OF GROSS & MICRO

STUDY ID: 2073-002-003 STUDY NUMBER: 2073003
SEX: FEMALE GROUP: 1: 0 mg/kg/day (vehicle control)

Animal ID: 0009
Animal Fate: Terminal Sacrifice Days on Test: 15

| Reference to Necropsy Record: | Related Histopathology: |
|---|---|
| OVARY - BILATERAL, FOCUS, 2x2 MM, MULTIPLE, BLACK | OVARY - Corpora hemorrhagica |

Animal ID: 0010
Animal Fate: Terminal Sacrifice Days on Test: 15

| Reference to Necropsy Record: | Related Histopathology: |
|---|---|
| OVARY - BILATERAL, FOCUS, 2x2 MM, MULTIPLE, BLACK (Found at trim) | OVARY - Corpora hemorrhagica |

Animal ID: 0012
Animal Fate: Terminal Sacrifice Days on Test: 15

| Reference to Necropsy Record: | Related Histopathology: |
|---|---|
| OVARY - BILATERAL, FOCUS, 2x2 MM, MULTIPLE, BLACK (Found at trim) | OVARY - Corpora hemorrhagica |
| OVIDUCT - CYST, 2x2 MM, TWO, CLEAR (Found at trim) | OVIDUCT - Cyst |

Animal ID: 0015
Animal Fate: Recovery Sacrifice Days on Test: 29

| Reference to Necropsy Record: | Related Histopathology: |
|---|---|
| OVARY - RIGHT, CYST, 2x2x2 MM, RED | OVARY - Not required by protocol |

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## CORRELATION OF GROSS & MICRO

STUDY ID: 2073-002-003 STUDY NUMBER: 2073003
SEX: FEMALE GROUP: 2: 0.030 mg/kg/day CuATSM/H2ATSM

Animal ID: 0027
Animal Fate: Terminal Sacrifice Days on Test: 15

| Reference to Necropsy Record: | Related Histopathology: |
|---|---|
| OVARY - BILATERAL, FOCUS, 2x2 MM, MULTIPLE, BLACK | OVARY - Not required by protocol |

Animal ID: 0029
Animal Fate: Terminal Sacrifice Days on Test: 15

| Reference to Necropsy Record: | Related Histopathology: |
|---|---|
| LUNG - RIGHT CARDIAC LOBE, DEFORMITY, PALE | LUNG - Not required by protocol |

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PATHOLOGY ASSOCIATES DIVISION OF CHARLES RIVER LABORATORIES, INC.
14-DAY TOXICITY STUDY OF CuATSM/H2ATSM (NSC-D729307) IN RABBITS
IIT RESEARCH INSTITUTE PROJECT NUMBER 2073-002-003

## CORRELATION OF GROSS & MICRO

STUDY ID: 2073-002-003 STUDY NUMBER: 2073003
SEX: FEMALE GROUP: 3: 0.060 mg/kg/day CuATSM/H2ATSM

Animal ID: 0045
Animal Fate: Terminal Sacrifice Days on Test: 15

| Reference to Necropsy Record: | Related Histopathology: |
|---|---|
| OVARY - RIGHT, FOCUS, 1x1 MM, MULTIPLE, BLACK | OVARY - Corpora hemorrhagica |
| THYROID GLAND - RIGHT, FOCUS, 2x1 MM, MULTIPLE, RED | THYROID GLAND - No corresponding lesion |

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SECTION VI

QUALITY ASSURANCE STATEMENT

**QUALITY ASSURANCE STATEMENT**

This histopathology project was inspected and audited by the Pathology Associates Quality Assurance Unit (QAU) as required by the Good Laboratory Practice (GLP) standards promulgated by the U.S. Food and Drug Administration. The following table is a record of the inspections/audits performed and reported by the QAU:

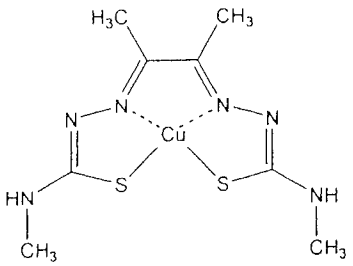
| Date of Inspection | Phase Inspected | Date Findings Reported to Management and Study Pathologist | Date Findings Reported to Study Director and Study Director Facility Management |
|---|---|---|---|
| 06/10/04 | Coverslipping & Staining | 06/16/04 | 06/16/04 |
| 08/12,13/04 | Individual Animal Data | 08/16/04 | 08/16/04 |
| 08/12,13/04 | Draft Pathology Report | 08/16/04 | 08/16/04 |
| 09/22/04 | 2nd Draft Pathology Report | 09/22/04 | 09/22/04 |
| 12/07/04 | Final Pathology Report | 12/07/04 | 12/07/04 |

Enosha Simmons
Enosha Simmons
Quality Assurance Unit
Pathology Associates Illinois Division

12/7/2004
Date

Appendix E. Test Article Compound Data Sheets and Control Article Certificates of Analysis

## Cu-ATSM




**Elemental Analysis;**

| | C | H | N | S |
|---|---|---|---|---|
| Expected; Calc for $CuC_8H_{14}S_2N_6$ | 29.85 | 4.38 | 26.11 | 19.92 |
| Found (Cu JSL(1)) | 29.83 | 4.54 | 25.92 | 20.04 |
| Found (Cu JSL(2)) | 29.54 | 4.50 | 25.66 | 20.00 |
| Found (Cu JSL(3)) | 29.74 | 4.55 | 25.95 | 19.86 |

**Mass Spectra;**

*LRFAB:* Peak match to $[M + H]^+$ m/z = 321.9855

*HRFAB:* Peak match to $[M + H]^+$ m/z = 322.0095

*ESI +ve:* A 1 mg/ml solution of Cu-ATSM (M) was made up by dissolving 1 mg of material into 1 mL of ethanol. Of this freshly prepared solution 20 µL was removed and added to 200 µL of a 1:1 mixture of water and methanol. This was then directly infused at a flow rate of 10 µL/min into the water ZQ 4000 mass spectrometer. The conditions of the mass spectrometer were then adjusted to generate a signal of maximum intensity. Data was then collected using an ESI probe operating in the positive mode for a time frame of 2 minutes over the M/Z range of 150-600 Da. The major peak was observed at 321.88 Da which corresponds to $C_8H_{15}N_6S_2Cu$ or $[M + H]^+$. The isotopic distribution pattern around this peak matched exactly the theoretical pattern generated by Cu-ATSM.

# GALBRAITH LABORATORIES, INC.

## LABORATORY REPORT

Dr Jason Lewis
Washington Univ
School of Med CB8225
510 S Kingshwy Blvd
St Louis MO 63110

Report Date: 06/11/03

Purchase Order #: 68600P

Fax Number: 314-362-9940

| SAMPLE ID | LAB ID | ANALYSIS | RESULT(S) | |
|---|---|---|---|---|
| Cu JSL(1) | Q-4455 | Sulfur | 20.04 | % |
| | | Carbon | 29.83 | % |
| | | Hydrogen | 4.54 | % |
| | | Nitrogen | 25.92 | % |
| Cu JSL(2) | Q-4456 | Sulfur | 20.00 | % |
| | | Carbon | 29.54 | % |
| | | Hydrogen | 4.50 | % |
| | | Nitrogen | 25.66 | % |
| Cu JSL(3) | Q-4457 | Sulfur | 19.86 | % |
| | | Carbon | 29.74 | % |
| | | Hydrogen | 4.55 | % |
| | | Nitrogen | 25.95 | % |

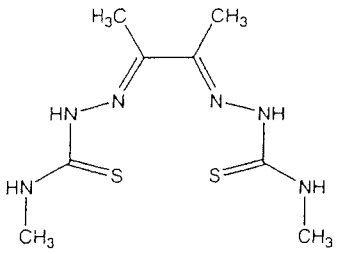




2323 Sycamore Drive
Knoxville, TN 37921-1700
TOLL FREE 877.449.8797

P.O. Box 51610
Knoxville, TN 37950-1610
FAX 865.546.7209

$H_2ATSM$



**Elemental Analysis;**

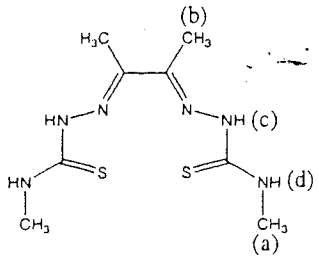
| | C | H | N |
|---|---|---|---|
| Expected; Calc for $C_8H_{16}S_2N_6.¼H_2O$ | 36.40 | 6.30 | 31.83 |
| Found (JSL 3697) | 36.48 | 6.23 | 31.33 |
| Found (JSL 3697 (b)) | 36.59 | 6.15 | 31.77 |

I have a large number of elemental analysis results, shown above are two representative samples. The results from an identical sample run twice do vary. This leads to the assumption that water is present. When calculated for different amounts of water present the elemental analysis result for all samples are consistent. The presence of water is confirmed by the NMR spectra (see below).

**Mass Spectra;**
*HRFAB:* Peak match to $[M + H]^+$ m/z = 261.0956

*HREI:* Molecular Ion Peak m/z = 260.0878

**NMR δ(ppm), in DMSO-$d_6$;**
The $^1$H-NMR is somewhat difficult to interpret due to the tautomeric nature of the ligand.




2.203 (s, C<u>H</u>$_3$ (b), 6H); 3.011-3.026 (d, C<u>H</u>$_3$ (a), 6H); Doublet at 8.365 and singlet at 10.214 are not possible to assign due to tautomeric nature, however, they do correspond to the N<u>H</u> and intergrate for (C) and (d) as 4H consistent with the structure. Water is prensent in the NMR (confirming elemental analysis) at 3.338 ppm.

The $^{13}$-NMR is very clean and consistent with structure. 11.657 (s, <u>C</u>H$_3$ (b)); 31.207 (s, <u>C</u>H$_3$ (a)); 147.977 (<u>C</u>=S); 178.471 (<u>C</u>=N).

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## LABORATORY REPORT

Jason Lewis
Washington University
510 South Kingshighway Blvd
Campus Box 8225
St Louis MO 63110

Report Date: 03/24/97
Sample Received: 03/14/97
Purchase Order #: 60678R

| SAMPLE ID | LAB ID | ANALYSIS | RESULTS | |
|---|---|---|---|---|
| JSL 3697 | S-9796 | Carbon | 36.48 | % |
| | | Hydrogen | 6.23 | % |
| | | Nitrogen | 31.33 | % |

ICP:sc
D9

1996 Tennessee Quality Commitment Award
Building Partnerships for Continuous Improvement

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# GALBRAITH® LABORATORIES, INC.

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## LABORATORY REPORT

Jason Lewis
Washington University
510 South Kingshighway Blvd
Campus Box 8225
St Louis MO 63110

Report Date: 04/03/97
Sample Received: 03/25/97
Purchase Order #: 61782R

| SAMPLE ID | LAB ID | ANALYSIS | RESULTS | |
|---|---|---|---|---|
| JSL 3697(b) | T-1071 | Carbon | 36.59 | % |
| | | Hydrogen | 6.15 | % |
| | | Nitrogen | 31.77 | % |

ICP:le
A8

Tennessee Quality Commitment Award 1996 Building Partnerships for Continuous Improvement

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Tel: (423) 546-1335 · Fax: (423) 546-7209

SIGMA-ALDRICH

# Certificate of Analysis

| | |
|---|---|
| **Product Name** | Dimethyl sulfoxide |
| **Product Number** | D1435 |
| **CAS Number** | 67-68-5 |
| **Molecular Formula** | $C_2H_6OS$ |
| **Molecular Weight** | 78.13 |

| TEST | SPECIFICATION | LOT 033K0640 RESULTS |
|---|---|---|
| **IDENTITY** | PASS | PASS |
| **SPECIFIC GRAVITY** | 1.095 TO 1.101 | 1.099 |
| **CONGEALING TEMPERATURE** | NLT 18.3 DEG C INDICATING NLT 99.9% C2H6OS | 18.4 DEG C |
| **REFRACTIVE INDEX** | 1.4755 TO 1.4775 | 1.4761 |
| **ACIDITY** | PASS | PASS |
| **WATER CONTENT BY KARL FISCHER** | NMT 0.1% | 0.017% |
| **UV ABSORBANCE** | PASS | PASS |
| **SUBSTANCES DARKENED BY POTASSIUM HYDROXIDE** | PASS | PASS |
| **LIMIT OF DIMETHYL SULFONE** | NMT 0.1% | PASS |
| **LIMIT OF NONVOLATILE RESIDUE** | PASS | PASS |
| | | ALL RESULTS SUPPLIER DATA |
| | | MEETS CURRENT USP REQUIRMENTS |
| **SHELF LIFE SOP QC-12-006** | 2 YEARS | MARCH 2005 |
| **QC ACCEPTANCE DATE** | | MARCH 2003 |

Lori Schulz, Manager
Analytical Services

**Note:** The data contained in this report are confidential and the property of the U.S. Government. It is not to be disclosed to a third party, used in an IND or used in any other publications without the written permission of the Toxicology & Pharmacology Branch, DTP, DCTD, NCI.

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PRODUCTS INC

# CERTIFICATE OF ANALYSIS
## ETHYL ALCOHOL 200 PROOF, ABSOLUTE
## ACS/USP GRADE

LOT # PS5520
Q.C. # 0303124
Date / Date of Manufacture: 03/19/03
Current Catalog #: 111000200, 111USP200,
Old Cat#112000200, 112USP200, 111ACS200, or 112ACS200

| TEST | SPECIFICATION | RESULT |
|---|---|---|
| Assay (ACS) (v/v) | NLT 99.5% | 99.98% |
| Water (ACS) (v/v) | NMT 0.2% | 0.07% |
| Proof @ 20C | NLT 199 | 199.9 |
| Specific Gravity @ 20C | 0.7900-0.7932 | 0.7906 |
| Color (APHA) (ACS) | NMT 10 | <10 |
| Solubility in Water (ACS) | To Pass Test | Pass |
| Nonvolatile Residue (ACS) | NMT 0.001% | <0.001% |
| Nonvolatile Residue (USP) | NMT 0.0025% | <0.001% |
| Acetone/IPA (ACS, USP) | To Pass Tests | Pass |
| Titrable Acid (ACS) | NMT 0.0005 meq/g | Pass |
| Titrable Base (ACS) | NMT 0.0002 meq/g | Pass |
| Acidity (USP) | To Pass Test | Pass |
| Methanol (ACS) | NMT 0.1% | <0.1% |
| Methanol (USP) | To Pass Test | Pass |
| Substances Darkened by Sulfuric Acid (ACS) | To Pass Test | Pass |
| Substances Reducing Permanganate (ACS) | To Pass Test | Pass |
| ID Test A (USP) | To Pass Test | Pass |
| ID Test B (USP) | To Pass Test | Pass |
| Specific Gravity @ 15.56°C | NMT 0.7962 | 0.7937 |
| Water Insoluble Substances | To Pass Test | Pass |
| Aldehydes and Other Foreign Organic Substances | To Pass Test | Pass |
| Amyl Alcohol/Nonvolatile, Carbonizable Substances | Not Detected | Pass |
| Ultraviolet Absorbance @ 240 nm (USP) | NMT 0.08 | 0.068 |
| Ultraviolet Absorbance @ 270-340 nm (USP) | NMT 0.02 | 0.006 |
| Ultra Violet Absorbance (ACS 9th ed.) | To Pass Test | Pass |

Form: Ethanol, Pure, 200, ACS/USP, #101, Rev 2.3, 07/28/02

Approved by: R. Diaz, Technician

For Industrial, Pharmaceutical, Flavor & Fragrance or Lab Use. Not intended as an active substance in Food or Drug. Not to be considered a Medical Device. Not intended for use as a Disinfectant as defined by the EPA. The expiration date of this product is three years from the date of manufacture. (Rev. # disclaimer only: Rev 3.2 12/19/02 PD)

*This document has been electronically generated and is therefore not signed. A signed copy can be obtained from Pharmco's Quality Control office.*

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Hwy 221 N PO Box 1390
Marion N.C. 28752
Telephone: (828) 756-4151
Fax: (828) 756-4821

# Certificate of Analysis

**Product:** 0.9% Sodium Chloride, USP

**Lot #:** C604942

**Code:** 2B1323Q

**Manufactured Date:** 02/04/04

**Expiry:** 05/2005

| TEST | LIMIT | RESULT |
|---|---|---|
| NaCl (g/L) | 8.55 - 9.45 g/L | 8.96 g/L |
| Sodium ID | Positive | Positive |
| Sodium ID- Flame | Positive | Positive |
| pH at 25 deg. C | 4.5 - 7.0 | 5.6 |
| Particle Analysis | NMT 25 ≥ 10 um | NMT 25 |
| Particle Analysis | NMT 3 ≥ 25 um | NMT 3 |
| Sterility | Pass Parametric Release | Pass |
| Endotoxin | Pass | Pass |

This is to certify that this product was manufactured according to current GMP and fulfills the requirements of the Master Production Document.

M. LaRue 3-31-04
Prepared By / Date

Nancy P Barton 3-31-04
Verified By / Date

L. Lopez 3/31/04
Quality Management Approval