REPORT

FINAL REPORT

CARDIOVASCULAR AND PULMONARY SAFETY TESTING OF CuATSM/H_2ATSM (NSC-D729307) IN BEAGLE DOGS

To

Toxicology and Pharmacology Branch

National Cancer Institute

November, 2004

Battelle
The Business of Innovation

Battelle Study Number: G465535A

FINAL REPORT

on the

CARDIOVASCULAR AND PULMONARY SAFETY TESTING OF CuATSM/H_2ATSM (NSC-D729307) IN BEAGLE DOGS

(G465535A)

by

Craig R. Hassler, Jeffrey J. Wallery, Robert A. Lordo,
Patricia J. Tosca, and Irma M. Grossi

Contract No.: N01-CM-87028

November, 2004

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for

Toxicology and Pharmacology Branch
Developmental Therapeutics Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20892

Study Number: G465535A

Title: Cardiovascular and Pulmonary Safety Testing of CuATSM/H_2ATSM (NSC-D729307) in Beagle Dogs

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Sponsoring Organization Name and Address:
Toxicology and Pharmacology Branch
Developmental Therapeutics Program
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National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20892

ABSTRACT

The objective of this study was to evaluate the cardiovascular and pulmonary safety of CuATSM/H_2ATSM (NSC-D729307) when administered as a single intravenous bolus dose in beagle dogs. Doses of 0 (vehicle) and 0.3 mg/kg were administered. Each dose group utilized two male and two female dogs. Clinical observations, body temperatures, body weights, clinical pathology, cardiovascular data (systemic arterial blood pressures, heart rate, ECG waveforms and ECG interval measurements) and pulmonary data (respiratory rate, tidal volume and minute volume) were all evaluated.

There were no test article-related changes associated with the clinical observations, body temperatures, body weights or clinical pathology.

The hemodynamic parameters, systemic arterial blood pressures (systolic, diastolic, and mean) and heart rate, appeared to increase for the first 10-minute post-dosing period for all animals in both test article and vehicle groups. The 10-minute average pressures increased 10 to 15 mmHg and heart rates increased 15 to 30 BPM as compared to baseline. Pressures returned to near baseline by the second 10-minute interval whereas heart rates returned towards baseline slower. Similar pressure and rate increases in both test article and vehicle groups indicate that a component present in the vehicle was responsible for these elevations. When both sexes were considered, there were no differences between the test article and vehicle groups for first 4.5 hours when the animals were "in-slings" for simultaneous pulmonary determinations. Following the 4.5 hours post-dosing period, animals were returned to their home cages and cardiovascular monitoring continued until 72 hours post-dosing. For the 6 to 72 hour "in-cage" post-dosing period, there were no statistically significant differences between the test article and vehicle groups. No alterations in ECG intervals, rhythm or morphology were noted that could be attributed to the test article. No statistically significant alterations in the pulmonary parameters (respiratory rate, tidal volume, and minute volume) were observed.

Thus, there were no alterations in the blood pressure, heart rate, ECG or pulmonary parameters that could be attributed to the administration of CuATSM/H_2ATSM. The acute blood pressure and heart alterations seen in both test article and vehicle groups, are likely a response to the DMSO component of the formulations.

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November, 2004

C R. Hassler — 11/22/04

Craig R. Hassler, Ph.D.
Study Director — Date

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Jeffrey J. Wallery, M.S.
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Robert A. Lordo — 11/22/04

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Irma M. Grossi, Ph.D.
Senior Program Manager — Date

GOOD LABORATORY PRACTICES COMPLIANCE STATEMENT

Study Title: Cardiovascular and Pulmonary Safety Testing of CuATSM/H_2ATSM (NSC-D729307) in Beagle Dogs

Battelle Study Number: G465535A

This study was conducted in compliance with the Food and Drug Administration (FDA) Good Laboratory Practice Regulations (21 CFR, Part 58) with the exception of the formulated test article stability. Results from this study are intended for possible submission to the FDA in support of IND/NDA applications. The data generated accurately reflect the results of the study.

C. R. Hassler — 11/22/04

Craig R. Hassler, Ph.D. — Date

QUALITY ASSURANCE STATEMENT

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

Phase Inspected	Date Inspected	Date Reported to Study Director/ Management
Protocol review	1/22/2004	1/22/2004
Training records review	1/22/2004	2/27/2004
Body temperature determination	1/27/2004	1/28/2004
Cardiovascular data collection	1/27/2004	2/27/2004
Catheter placement	1/27/2004	2/27/2004
Formulation preparation	1/27/2004	2/27/2004
Pulmonary data collection	1/27/2004	2/27/2004
Sling restraint time	1/27/2004	1/28/2004
Test system identification	1/27/2004	2/27/2004
Test article administration - intravenous	1/27/2004	2/27/2004
Randomization	1/27/2004	2/27/2004
Clinical observations	1/27/2004	2/27/2004
Protocol amendment review	2/4/2004	2/4/2004
Infrared spectroscopy analysis	2/23/2004	2/24/2004
Audit study file	3/9/2004	3/9/2004
Audit study file	9/13/2004	9/13/2004
Audit study file	11/5/2004	11/5/2004
Audit draft final report	11/11/2004	11/11/2004
Audit final report	11/22/2004	11/22/2004

Shara D. Shook — Quality Assurance Unit

1/22/04 — Date

CONTENTS

APPENDICES

APPENDIX A

Protocol, Amendment, and Deviations

APPENDIX B

Individual Animal In-Life Data

APPENDIX C

Clinical Pathology Data

APPENDIX D

Statistical Analysis

APPENDIX E

Qualitative ECG Evaluation

SUMMARY

Purpose: The objective of this study was to evaluate the cardiovascular and pulmonary safety of CuATSM/H_2ATSM when administered as a single intravenous bolus dose in beagle dogs.

Test Article: Copper-diacetyl-bis(N4-methylthiosemicarbazone)/diacetyl-bis(N4-methylthiosemicarbazone) (CuATSM/H_2ATSM; NSC-D729307)

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

Target Test Article Concentration: 0 and 0.03 mg/mL

Target Test Article Dose Level: 0 and 0.3 mg/kg

Target Dose Volumes: 10 mL/kg

Route of Administration: Intravenous (slow bolus or push)

Experimental Design:

Species: Beagle dogs implanted with telemetry transmitters, which have blood pressure, heart rate and ECG data collection capabilities.
Sex: Male and Female
Body Weight Range: 6 to 15 kg
Number of Animals: 8 (4/sex)

Animal Numbers (Sex)	Group	Dose Level (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)
101, 102 (Males) 151, 152 (Females)	1 (Vehicle)	0	0	10
201, 202 (Males) 251, 252 (Females)	2 (CuATSM/ H_2ATSM)	0.3	0.03	10

Measurements

Clinical Observations: Animals were observed daily during pretest, at least twice on the day of dosing, and once daily thereafter or more often as clinical signs warranted through Day 4.

Body Temperatures: Body temperatures (rectal) were taken on Days -1 (baseline), 1 (between 4 and 5 hours after dosing when the animals were removed from the restraint slings), and 4.

Body Weights: Body weights were recorded on Day -1.

Clinical Pathology: Blood was collected for clinical pathology analysis on Days -1 and 4.

Cardiovascular Data Collection: Blood pressure (systolic, diastolic, and mean), heart rate, and ECG waveforms were collected via implanted telemetry transmitters from at least 12 hours before dosing to at least 72 hours following dosing.

Periodic ECG waveform tracings were produced on the day of dosing (Day 1) at the following targeted time points: prior to dosing (i.e., two "in-cage" baselines and two "in-sling" baselines) and at 10 and 30 minutes and 1, 2, 4, and 8 hours post-dose. Additionally, an am and a pm time point was selected for each of the next two days (Days 2 and 3). The ECG waveform strips were qualitatively evaluated for rhythm and morphology alterations by a board-certified veterinary cardiologist.

ECG intervals (PR, RR, QRS, and QT) were measured on the ECG waveform tracings produced at selected time intervals determined by the Study Director. The QT interval was normalized for changes in heart rate by conversion to the corrected QT (QTc) interval using Fridericia's formula $QTc = QT/(RR)^{1/3}$. The ECG interval data were evaluated by the Study Director.

Pulmonary Data Collection: Before dosing, each animal was placed in a restraint sling and fitted with an air dam and a head dome for pulmonary function monitoring. All animals were allowed to acclimate to the sling and head dome apparatus for at least 30 minutes to allow baseline values to become consistent with the experimental environment. Following this initial 30-minute period, baseline data were collected for at least 30 minutes. All animals were monitored for at least 4 to 5 hours post-exposure. Pulmonary parameters measured and evaluated were: respiratory rate, tidal volume and minute volume.

Results

Clinical Observations: All vehicle treated animals were normal throughout the study with the exception of female dog 152 (vehicle), which exhibited salivation during the dosing period. Male dog 201 (0.3 mg/kg) exhibited salivation during dosing, but was normal for the remainder of the study. One instance of emesis (female 252, 0.3 mg/kg) was reported on Day 3. None of the abnormal clinical observations were considered to be test article-related. However, the excessive salivation observed in vehicle and test article animals was probably due to the DMSO component of the formulations.

Body Temperatures: Prestudy (Day -1) body temperatures (rectal) ranged from 38.3 to 39.9°C. Body temperatures recorded on Day 1 (4 to 5 hours after dosing when the dogs were removed from the sling) ranged from 36.9 to 38.8°C. On Day 4, body temperatures ranged from 38.5 to 40.5°C. There were no significant fluctuations in body temperatures that could be attributed to test article or vehicle administration.

Body Weights: Body weights recorded on Day -1 (used for dose volume determinations) ranged from 11.14 to 14.43 kg for the males and 6.39 to 9.83 kg for the females.

Clinical Pathology: When capturing baseline values (Day-1) to post-dosing values (Day 4), no changes in hematology or serum chemistry parameters were observed that could be attributed to test article administration.

Hemodymamic Evaluation: Blood pressures (systolic, diastolic, and mean) and heart rate appeared to increase for the first 10-minute post-dosing period for all animals in both the test article and vehicle groups. The 10-minute group mean average pressures increased 10 to 15 mmHg and heart rates increased 15 to 30 BPM as compared to baseline. Pressures returned to near baseline by the second 10-minute interval, whereas, heart rates returned towards baseline gradually over 1.5 hours post-dose. The individual animal plots indicate that peak values for pressures and rate occurred within the first 10-minutes post-dosing. Similar pressure and heart rate increases in both test article and vehicle groups indicate that a component, possibly DMSO which was present in the vehicle, was responsible for these elevations. When both sexes were considered, no differences between the test article and vehicle groups were observed for the first 4.5 hours post-dosing. Blood pressures in the female animals trended marginally higher for the test article groups as compared to vehicle. For the first 4.5 hours post-dosing, no statistically significant differences between the test article and vehicle groups occurred. Following the 4.5 hours post-dosing period, animals were returned to their home cages and monitoring continued until at least 72 hours post-dosing. Pressures trended marginally lower than vehicle for the test article group. This trend appeared to be primarily due to the females. Heart rates for the test article group did not appear to differ from vehicle. For the 6 to 72 hour "in-cage" post-dosing period, no statistically significant differences were observed between the test article and vehicle groups.

ECG Interval Evaluation: There were no ECG interval alterations that could be attributed to the test article.

Qualitative ECG Evaluation: There were no changes in the ECG rhythms or morphologies that could be attributed to test article administration.

Pulmonary Evaluation: No test article-related trends were apparent in respiratory rate, tidal volume, or minute volume. Statistical evaluation of the pulmonary data indicated that there were no statistically significant alterations for the males or females dosed with test article as compared to vehicle.

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1.0 INTRODUCTION

The National Cancer Institute (NCI), Developmental Therapeutics Program is responsible for the identification, development, and evaluation of drugs and vaccines for the treatment of cancer. As part of the program established by the NCI to meet these objectives, potential drugs are screened for antitumor activity and vaccines for their ability to induce immunogenetic responses. Drugs demonstrating such activity are tested in animal models to profile their toxicity. Drugs which successfully complete a preclinical safety evaluation are then introduced into clinical trials.

CuATSM is a positron emission tomography (PET) agent for hypoxia, as well as, a potential therapeutic agent and H_2ATSM is a parent ligand. For imaging, CuATSM can be labeled with a number of isotopes of copper (Cu).

This study was conducted under Contract N01-CM-87028 with the Toxicology and Pharmacology Branch, Developmental Therapeutics Program (DTP), Division of Cancer Treatment and Diagnosis (DCTD) of the National Cancer Institute (NCI). The study was conducted according to the study protocol (Appendix A) at Battelle's Columbus, Ohio laboratories under the direction of Craig R. Hassler, Ph.D. The study was initiated on January 27, 2004 (Day 1) and the in-life was completed on January 31, 2004.

2.0 MATERIALS AND METHODS

2.1 Test Article and Vehicle

2.1.1 Test Article

The test article, CuATSM/H_2ATSM (NSC-D729307), was received and stored at room temperature on January 22, 2004 (one 8-mL amber glass vial containing 40 mg).

2.1.2 Vehicle

The vehicle was 100% ethanol in 0.9% sodium chloride for injection, USP and dimethyl sulfoxide (DMSO). Ethanol (100%, USP) was purchased from Aldrich (Lot Number: M013204L0, expire: March, 2007), DMSO was purchased from Sigma (Lot Number: 71K0043, expire: October, 2007), and 0.9% sodium chloride for injection, USP was purchased from Baxter (Lot Number: C576553, expire: July, 2004).

2.1.3 Dose Preparation

The test article was dissolved in DMSO to produce a stock solution. The stock solution was diluted with 100% ethanol and saline to produce a dosing solution with final concentrations of test article, DMSO, ethanol and saline of 0.03 mg/mL, 0.3% (v/v), 7% (v/v) and 92.7% (v/v), respectively. The stock solution and dosing solution were both prepared on January 27, 2004 (Day 1, the day of dose administration).

An adequate quantity of the dosing mixture was retained and stored at -70 ± 10°C for possible analysis until at least 30 days after completion of in-life.

2.2 Test System

2.2.1 Animal Source and Arrival

Purebred male and female beagle dogs were used for this study. All dogs were originally received from Covance Research Products, Inc. for previous studies and were between 16 and 36 months of age at study initiation (Day 1). The dog is an acceptable species to support safety studies of compounds used or intended for use in humans.

2.2.2 Quarantine and Animal Care

The dogs were individually housed in stainless-steel cages during the quarantine and study periods and were observed during quarantine for signs of disease or other abnormalities that would make them unfit for study. All dogs were quarantined and accepted in accordance with facility Standard Operating Procedures. Hematology and serum chemistry screens were performed on Day -1.

The dogs were identified by a tattoo and a cage card. The dogs were provided with Harlan Teklad Global Diet once daily. The ration was sufficient to meet nutritional requirements. Water from the Columbus municipal system was used without further treatment and supplied to the cage, *ad libitum*, via a watering bowl. Copies of the feed and water analyses are maintained under the direction of Battelle. There were no known contaminants in the feed or water which would interfere with the purpose or outcome of this study.

2.3 Experimental Design

Eight dogs (4 males/4 females) were administered the vehicle or CuATSM/H_2ATSM as a bolus intravenous injection on Day 1. The dose groups are shown below:

Animal Numbers (Sex)	Group	Dose Level (mg/kg)	Dose Concentration (mg/mL)	Dose Volume (mL/kg)
101, 102 (Males) 151, 152 (Females)	1 (Vehicle)	0	0	10
201, 202 (Males) 251, 252 (Females)	2 (CuATSM/ H_2ATSM)	0.3	0.03	10

On Day 1, each animal was removed from its home cage, placed in a restraint sling, and fitted with an air dam and a head dome for pulmonary monitoring. "In-sling" cardiovascular data collection began after the animals were placed in the slings. Each animal was allowed to acclimate to the sling and head dome apparatus for at least 30 minutes to allow pulmonary baseline values to become consistent with the experimental environment. Following this initial 30-minute period, baseline data were collected for at least 30 minutes. Following the baseline period, the animals were dosed and monitored for at least 4 to 5 hours post-exposure. The animals were then returned to their home cages and "in-cage" cardiovascular data collection was resumed.

2.3.1 Clinical Observations

The animals were observed daily during pretest, at least twice on Day 1, and at least once daily thereafter or more often as clinical signs warranted through Day 4.

2.3.2 Body Temperatures

Rectal body temperatures were recorded on Days -1, 1 (between 4 and 5 hours after dose administration when the animals were removed from the restraint slings) and 4.

2.3.3 Body Weights

Body weights were recorded on Day -1 for dose volume determinations.

2.3.4 Clinical Pathology

Blood (fasted) was collected for clinical pathology evaluation on Days -1 and 4. Parameters (with corresponding unit designations) evaluated are listed below:

Hematology:

Erythrocyte count (RBC) - $10^6/mm^3$
Hemoglobin (HGB) - g/dL
Hematocrit (HCT) - %
Mean corpuscular volume (MCV) - fL
Mean corpuscular hemoglobin (MCH) - pg
Mean corpuscular hemoglobin concentration (MCHC) - g/dL
Platelet count (PLT) - $10^3/mm^3$
Reticulocyte count (RET) - $10^5/mm^3$
Total leukocyte count (WBC) - $10^3/mm^3$
Differential leukocyte count - $10^3/mm^3$ (SEG, TLYM, MON, EOS, BAS, LYM, LUC)
Nucleated red blood cell count (nRBC) - #/100 WBC

Serum Chemistry:

Blood urea nitrogen (BUN) - mg/dL
Serum aspartate aminotransferase (AST) - U/L
Serum alanine aminotransferase (ALT) - U/L
Alkaline phosphatase (ALP) - U/L
Gamma glutamyl transferase (GGT) - U/L
Serum glucose (GLU) - mg/dL
Lactate Dehydrogenase (LDH) - U/L
Creatinine (CREA) - mg/dL
Creatine Kinase (CK) - U/L
Total protein (TP) - g/dL
Total, direct, and indirect bilirubin (TBIL, DBIL, IBIL) - mg/dL
Albumin - (ALB) - g/dL
Globulin - (GLOB; by calculation) - g/dL
A/G ratio (AGR)
Sodium (NA) - meq/L
Potassium (K) - meq/L
Chloride (CL) - meq/L
Calcium (CA) - mg/dL
Phosphorous (PHOS) - mg/dL
Amylase (AMYL) - U/L
C-reactive protein - mg/L
Serum amyloid A - μg/mL
Troponin T (TnT)- ng/mL

A separate blood sample was collected for C-reactive protein, serum amyloid A, and troponin T analyses. The blood samples were allowed to clot at room temperature and centrifuged for separation of serum. The harvested serum samples were dispensed into tubes and placed on dry ice until stored in a freezer set to maintain a temperature of -20 ± 10°C. The serum samples were shipped to AniLytics, Inc. for analyses.

2.3.5 Cardiovascular Data Collection

Systemic arterial blood pressures (systolic, diastolic, and mean), heart rate, and ECG data were collected using the PhysioTel Telemetry System, utilizing the Dataquest A.R.T. data acquisition and analysis software (Data Sciences International, St. Paul, MN). Each animal's home cage and restraint sling was equipped with a Data Sciences International radiotelemetry receiver, which collected the signal transmitted by the animal's surgically implanted radiotelemetry transmitter. The data were collected continuously except when the animals were out of range of the receivers for study-driven activities. Data collection began on Day -1 (January 26, 2004) and ended on Day 4 (January 30, 2004).

Periodic ECG waveform tracings were generated using ECGAUTO software (EMKA Technologies, Paris, France). ECG waveform tracings of approximately 30 seconds in duration were produced on the day of dose administration (Day 1) at the following targeted time points: predose (i.e., two "in-cage" baselines and two "in-sling" baselines), 10 and 30 minutes post-dose and 1, 2, 4 and 8 hours post-dose. Additionally, an am and pm time point was selected for each of the next two days (Days 2 and 3). A board-certified veterinary cardiologist, Robert L. Hamlin, D.V.M., Ph.D., D.A.C.V.I.M. (Cardiology/Internal Medicine), qualitatively assessed these periodic ECG waveform tracings for rhythm and morphology alterations.

ECG interval measurements (PR, RR, QRS, and QT) were made on the ECG waveform tracings produced at each of the time points designated above using the ECGAUTO software. The measurements were the average data obtained from approximately 20 ECG complexes at each time point. Additionally, rate-corrected QT (referred to as QTc) intervals were calculated for each animal using the rate-correction method of Fridericia (Mann *et al.*, 1994), which involved dividing the QT interval by the cubed root of the RR interval.

2.3.6 Pulmonary Data Collection

On the day of dosing (Day 1), pulmonary data (respiratory rate, tidal volume, and minute volume) were collected using the Buxco BioSystem XA Data Acquisition System (Buxco Electronics, Inc., Wilmington, NC). During pulmonary data collection, each animal was placed in a restraint sling and fitted with an air dam and a head dome. A controlled flow of fresh breathing air was supplied to the head domes, which was connected via appropriate instrumentation to the Buxco System. The animals

were allowed to acclimate to the experimental environment for at least 30 minutes to allow their pulmonary parameters to return to appropriate baseline values. Then, at least 30 additional minutes of baseline pulmonary data were collected prior to dosing. Following the baseline data collection period, each animal was dosed via slow intravenous push. Pulmonary data collection continued for four to five hours following the start of dosing. At the conclusion of the respiratory monitoring period, the animals were returned to their home cages. Pulmonary data were only collected when the dogs were in the restraint slings.

2.3.7 Necropsy

None of the animals required necropsy. All animals were removed from study and returned to Battelle's holding pool of animals on Day 5.

2.4 Statistical Analysis of Data

Statistical analyses were performed using the SAS System for Windows. Animals were analyzed by sex. Further, "in-cage" and "in-sling" data were analyzed separately where appropriate. All references to statistical significance are at the 0.05 level unless specified otherwise. Detailed descriptions of the statistical materials and methods are located in Appendix D.

Statistical analysis was conducted on data for the following parameters:

- systolic blood pressure (mmHg)
- diastolic blood pressure (mmHg)
- mean arterial blood pressure (mmHg)
- heart rate (BPM)
- four selected ECG interval measures: PR, RR, QRS, QT (msec)
- QT interval corrected for heart rate by dividing QT by the cubed root of RR (i.e., QTc)
- three pulmonary parameters: respiratory rate (breaths/min), tidal volume (mL/breath/kg), and minute volume (mL/min/kg).

The primary objectives for the statistical analysis performed on these data were as follows:

1. For the blood pressure, heart rate, and pulmonary parameters, determine whether significant differences existed among dose groups on a 10-minute interval basis immediately following dosing when animals were in the restraint slings.

2. For the blood pressure and heart rate parameters, determine whether significant differences existed among dose groups on an hourly basis during the period following dosing when animals were in their home cages.

3. For the ECG interval parameters, determine whether significant differences existed among dose groups at specified time points following dosing, both when animals were in the restraint slings and in their home cages.

3.0 RESULTS

3.1 Clinical Observations

Individual animal abnormal clinical observations are presented in Appendix B. All vehicle treated animals were normal throughout the study with the exception of female dog 152, which had salivation during the dosing period. Male dog 201 (0.3 mg/kg) also had salivation during dosing, but was normal for the remainder of the study. Prior to being dosed (Days -2 and -1) and continuing through Day 2, female dog 251 (0.3 mg/kg) had clear eye discharge and reddening and swelling of the muzzle and inner ears. The swelling subsided by Day 3, but the eye discharge and reddening continued through Day 4. One instance of emesis occurred in female 252 (0.3 mg/kg) on Day 3. None of the abnormal clinical observations were considered to be test article-related. However, the salivation observed in animals 152 and 201 may have been due to the DMSO component of the formulations.

3.2 Body Temperatures

Individual animal body temperatures (rectal) are presented in Appendix B. Prestudy (Day -1) body temperatures ranged from 38.3 to 39.9°C. Body temperatures recorded on Day 1 (4 to 5 hours after dosing when the dogs were removed from the sling) ranged from 36.9 to 38.8°C, and those recorded on Day 4 ranged from 38.5 to 40.5°C. There were no significant fluctuations in body temperatures that could be attributed to test article or vehicle administration.

3.3 Body Weights

Individual animal body weights are presented in Appendix B. Body weights recorded on Day -1 ranged from 11.14 to14.43 kg for the males and 6.39 to 9.83 kg for the females.

3.4 Clinical Pathology

Individual animal clinical pathology data are presented in Appendix C.

3.4.1 Hematology

The hematology results did not suggest any test article-related effects.

3.4.2 Serum Chemistry

The serum chemistry did not suggest any test article-related effects.

3.4.3 C-Reactive Protein, Serum Amyloid A, and Troponin T Levels

C-reactive protein, serum amyloid A, and troponin T levels did not suggest any test article-related effects.

3.5 Cardiovascular and Pulmonary Evaluations

Analyses of the hemodynamic, ECG interval, and pulmonary data are presented in Appendix D (Figures 1 through 63 and U-1 through U-63; Tables 1 through 52). Figures 1 to 63 contain the "in-sling"/"in-cage" baseline adjusted data, whereas, Figures U-1 to U-63 contain the "in-sling"/"in-cage" unadjusted data. The individual animal figures are also presented in Appendix D.

3.5.1 Hemodynamic Evaluation

Blood pressures (systolic, diastolic, and mean) and heart rate appeared to increase for the first 10-minute post-dosing period for the vehicle and the test article animals (Figures 1 to 4). During this 10-minute period, pressures increased approximately 10 to 15 mmHg and heart rates increased approximately 15 to 30 BPM as compared to baseline. On the average, pressures returned to near baseline values by the second 10-minute interval, whereas, heart rates gradually returned to baseline values over the first 1.5 hours post-dose. The individual animal figures indicate that all animals (vehicle and test article) exhibited immediate increased blood pressures and heart rates to some degree (Figures 0-1a to 0-1h). Peak values for pressures and heart rate occurred within the first ten minutes post-dosing. Similar average pressure and heart rate increases in both test article and vehicle groups

indicate that a component present in the vehicle (possibly DMSO) was likely responsible for these elevations.

When the "in-sling" data were analyzed by sex, blood pressures in the female animals trended marginally higher for the test article animals as compared to vehicle (Figures 9 to 11). For the first 4.5 hours post-dosing, there were no statistically significant differences between the test article and vehicle groups (Tables 5 to 12). Following the 4.5 hours post-dosing period, animals were returned to their home cages and monitored for at least 72 hours post-dosing. "In-cage" (combined sex) pressures trended marginally lower than vehicle for the test article group (Figures 13 to 15). This trend appeared to be primarily due to lower pressures observed in the females (Figures 21 to 23). "In-sling"/"in-cage" heart rate data for the test article group did not appear to differ from vehicle (Figures 16, 20, 24) and there were no statistically significant differences between the test article and vehicle groups (Tables 13 to 20).

3.5.2 ECG Interval Evaluation

When the ECG interval data were analyzed collectively by sex, there were no trends suggesting a difference between test article and vehicle (Figures 25 to 54). There were also no statistically significant alterations in the test article group as compared to vehicle (Tables 25 to 44).

3.5.3 Qualitative ECG Evaluation

Dr. Robert Hamlin's qualitative assessment of the ECG waveform tracings for rhythm and morphology alterations is presented in Appendix E. His assessment revealed that there were no alterations in ECG rhythm or morphology that could be attributed to the test article.

3.5.4 Pulmonary Evaluation

There were no apparent alterations in any of the pulmonary parameters (respiratory rate, tidal volume, and minute volume) for either sex (Figures 55 to 63), and there were no statistically significant alterations in any of the pulmonary parameters for either sex (Tables 47, 49, and 51).

4.0 DISCUSSION AND CONCLUSIONS

There were no abnormal clinical observations during this study that were considered to be related to CuATSM/H_2ATSM administration. Although one vehicle and one test article dog exhibited salivation during the dosing procedure, this was probably due to the DMSO component of the formulations. Further, there were no abnormal clinical pathology or body temperature findings.

There were no statistically significant alterations in blood pressures, heart rate, ECG or pulmonary parameters that could be attributed to the administration of CuATSM/H_2ATSM. The acute blood pressure and heart rate alterations observed in both test article and vehicle groups following dosing, are likely a response to the DMSO component of the formulations.

5.0 SPECIMEN STORAGE AND RECORD ARCHIVES

Records of test article receipt, methods, analysis, and other written information pertinent to the conduct of this study are contained in appropriately labeled binders. These and all other raw data (including the electronic data) collected at Battelle for this study will be maintained under the direction of Battelle, along with a copy of the protocol and final report. In addition, all raw data generated outside of Battelle will be the responsibility of the Sponsor.

6.0 ACKNOWLEDGMENTS

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

Participant	Title
Craig R. Hassler, Ph.D.	Study Director
Jeffrey J. Wallery, M.S.	Safety Pharmacology Study Coordinator
Robert A. Lordo, Ph.D.	Study Statistician
Patricia J. Tosca, B.S.	Toxicology Study Coordinator
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Irma M. Grossi, Ph.D.	Principal Investigator

APPENDIX A

PROTOCOL, AMENDMENT, AND DEVIATIONS

CARDIOVASCULAR AND PULMONARY SAFETY TESTING OF CuATSM / H_2ATSM (NSC-D729307) IN BEAGLE DOGS

SPONSOR: Toxicology & Pharmacology Branch
Developmental Therapeutics Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20892

PROJECT OFFICER: Elizabeth R. Glaze, Ph.D.

CONTRACT NUMBER: NO1-CM-87028

CONTRACTOR: Battelle Memorial Institute
505 King Avenue
Columbus, Ohio 43201-2693

PRINCIPAL INVESTIGATOR: Irma M. Grossi, Ph.D.

STUDY DIRECTOR: Craig R. Hassler, Ph.D.

SAFETY PHARMACOLOGY STUDY COORDINATOR: Jeffrey J. Wallery, M.S.

STUDY COORDINATOR: Patricia J. Tosca, B.S.

PROPOSED IN-LIFE PHASE:

Start: January 27, 2004

Finish: January 30, 2004

I. OBJECTIVE

The objective of this study is to evaluate the cardiovascular and pulmonary safety of CuATSM/H_2ATSM when administered as a single intravenous bolus injection dose in beagle dogs.

II. MATERIALS AND METHODS

A. Test Article and Vehicle

1. Name of Test Articles:

Copper-diacetyl-bis(N4-methylthiosemicarbazone) / diacetyl-bis(N4-methylthiosemicarbazone (CuATSM/H_2ATSM; NSC-D729307)

2. Name of Vehicle:

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 Articles:

Compound identity, strength, stability and purity as well as documentation of methods of synthesis, fabrication, or derivation are the responsibility of the NCI. Confirmation of identity will be done upon receipt of each new lot of the compound. Sufficient quantity of drug shall be reserved for a retention sample from each lot used. Remaining test article will be disposed of or returned to the Sponsor.

b. Vehicle:

Characterization of DMSO, ethanol and saline may be made by recording all pertinent information provided on the container label or by retaining the container label as raw data.

4. **Stability and Storage:**

   a. **Test Articles:**

      The test article will be stored at controlled room temperature (approximately 17 to 25°C).

   b. **Vehicle:**

      The DMSO, 100% ethanol and saline will be stored at controlled room temperature (approximately 17 to 25°C). The vehicles are stable unopened through the date of expiration as provided by the manufacturer/supplier.

5. **Formulation Preparation, Stability and Storage:**

   The test article will be dissolved in DMSO to produce a stock solution. When not in use, the test article stock solution will be stored in the dark at controlled room temperature (approximately 17 to 25°C). On the day of dosing, 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 0.03 mg/mL, 0.3% (v/v), 7% (v/v) and 92.7% (v/v), respectively.

6. **Dose Concentration Analyses:**

   An adequate quantity of each dosing mixture will be retained and stored at -70°F (±10°F) for possible analysis until 30 days after completion of in-life. Homogeneity analysis will not be required, since homogeneity has been previously demonstrated.

B. **Test System**

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

   Purebred beagles from Covance, Inc. will be used in this study. This is an accepted species to support studies of compounds used or intended for use in humans.

2. **Initial Age, Sex, and Weight:**

   Male and female dogs will be approximately 8 to 40 months of age and approximately 5 to 16 kg at study initiation.

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). The dogs will be housed individually in stainless steel cages. Environmental parameters will be set to maintain conditions specified in the facility SOPs. Environmental conditions will be within specified limits of at least 90 percent of scheduled observations. All animal cages will be rinsed with water twice daily and changed, washed, and sanitized approximately on a regular schedule.

All dogs on study will not be exercised during the cardiovascular data collection periods for scientific reasons. Cardiovascular data can only be collected when the animals are in their cages or the restraint slings, therefore, if the animals are removed from their cages, important cardiovascular data may be missed. Further, the exercise activity may confound the data analyses.

4. **Diet and Water Supply:**

A certified, commercial, dry chow or meal will be used. The quantity of the daily ration will be sufficient to meet nutritional requirements. The water source will be the public supply given *ad libitum*. No contaminants will be present in the feed or water which could interfere and affect the results of the study.

5. **Quarantine:**

All dogs were quarantined and accepted in accordance with facility standard operating procedures. The dogs selected for study will be in good physical condition.

6. **Animal Identification:**

Dogs will be uniquely identified by ear tattoo number or letter combination. Positive identification will be required at least after every cage change, blood sampling, and dosing.

C. **Experimental Design**

1. **Group Assignments:**

All animals were recently conditioned to the restraint sling and a head dome apparatus on a previous study. On Day 1, each animal will be restrained in a sling and fitted with an air dam and a head dome. Each animal will then be administered either vehicle or formulated test article as

per the table below. The total restraint time will not exceed 6 hours. Note that the animals may be in slings for up to an additional 15 minutes beyond 6 hours to allow for a sufficient amount of time to return them to their home cages.

Treatment	No. of Dogs (M + F)	CuASTM / H_2ASTM Dose Level (mg/kg)	CuASTM / H_2ASTM Dose Concentration (mg/mL)	Dose Volume (mL/kg)
Vehicle	2+2	0	0	10
CuASTM / H_2ASTM	2+2	0.3	0.03	10

2. Route of Administration and Reason for Choice:

The test article will be given intravenously (slow bolus) because this is the intended route of administration of this compound in humans.

3. Dosing Procedure:

The test article will be administered as a single intravenous dose on Day 1. Dogs in the vehicle group will receive a volume of vehicle equivalent to the greatest volume administered on a mL/kg basis. Dose calculations will be based on each animal's most recent body weight. All calculations will be checked by a second individual who will initial and date the verification.

D. Surgical Procedure for Implantation of Telemetry Transmitters

Five male and five female dogs were previously surgically implanted with Data Sciences International telemetry transmitters, which have systemic arterial blood pressure, heart rate and ECG data collection capabilities. Four dogs per sex will be selected for dosing and one dog per sex will be used as replacement animals, if needed. A blood pressure catheter was placed into a muscular branch of the femoral artery (or equivalent) and ECG leads were placed beneath the skeletal musculature in a configuration emulating a standard Lead II electrocardiogram. A detailed account of the surgical procedure will be included in the study documentation.

E. Cardiovascular and Respiratory Data Collection

Each animal's home cage and restraint sling apparatus will be equipped with a Data Sciences International telemetry receiver. The transmitters, receivers, data matrices, ambient pressure monitors, cabling and computers which run the Dataquest A.R.T. data acquisition and analysis software are all components of the PhysioTel Telemetry System. The Dataquest A.R.T. telemetry software will

collect systemic arterial blood pressures (systolic, diastolic and mean), heart rate and ECG data continuously (except when the animals are out of range of the receivers for study-driven activities) at least 12 hours before dosing until at least 72 hours following dosing. Cardiovascular data will be collected when the animals are in their cages or in their sling apparatus. A detailed account of the cardiovascular data collection procedure will be included in the study documentation.

F. Pulmonary Data Collection

Before each dosing, each animal will be placed in a restraint sling and fitted with an air dam and a head dome. A controlled flow of fresh breathing air will be supplied to the head dome. The head dome will be connected via appropriate instrumentation to a Buxco BioSystem XA Data Acquisition System. Pulmonary parameters to be measured and evaluated will include: respiratory rate, tidal volume and minute volume. Pulmonary data will only be collected when the dogs are in the sling apparatus.

For exposure monitoring, all animals will be allowed to acclimate to the sling and head dome apparatus for at least 30-minutes to allow for baseline values to become consistent with the experimental environment. Following this initial 30-minute period, baseline data will be collected for at least 30-minutes. Finally, all animals will be monitored for at least 4 to 5 hours post-exposure. The animals will then be returned to their home cages and in-cage telemetry data collection will be resumed. A detailed account of the cardiovascular and respiratory data collection procedure will be included in the study documentation.

G. Measurements

1. Clinical Signs and Body Temperatures:

PRETEST - Observe dogs daily and record any abnormal clinical signs. Baseline rectal body temperatures will be taken on Day -1.

TEST - Clinical observations will be recorded at least twice on Day 1 and at least once daily thereafter or more often as clinical signs warrant. Rectal body temperature will be measured and recorded between 4 and 5 hours after dosing (when the animals are removed from the restraint slings) and on Day 4.

2. Body Weight:

Body weights will be recorded on Day -1.

3. **Clinical Pathology:**

PRETEST - All dogs will be fasted overnight and bled for clinical pathology on Day -1. Dogs that have aberrant values will not be used.

TEST - All dogs will be fasted overnight and have blood drawn on Day 4. The procedures will be performed according to the facility SOP, but in no case will dogs be bled from the treatment site. An attempt will be made to obtain a blood sample prior to necropsy from each dog sacrificed in a moribund condition.

Hematology:

Erythrocyte count (RBC) - $10^6/mm^3$
Hemoglobin (HGB) - g/dL
Hematocrit (HCT) - %
Mean corpuscular volume (MCV) - fL
Mean corpuscular hemoglobin (MCH) - pg
Mean corpuscular hemoglobin concentration (MCHC) - g/dL
Platelet count (PLT) - $10^3/mm^3$
Reticulocyte count (RETIC) - $10^5/mm^3$
Total leukocyte count (WBC) - $10^3/mm^3$
Differential leukocyte count - $10^3/mm^3$
Nucleated red blood cell count (nRBC) - nRBC/100 WBC

Clinical Chemistry:

Urea nitrogen (BUN) - mg/dL
Serum aspartate aminotransferase (AST) - I.U./L
Serum alanine aminotransferase (ALT) - I.U./L
Alkaline phosphatase (ALP) - I.U./L
Gamma glutamyl transferase (GGT) - I.U./L
Glucose (GLU) - mg/dL
Lactate Dehydrogenase (LDH) - I.U./L
Creatinine (CREA) - mg/dL
Creatine Kinase (CK) - I.U./L
Total protein (TP) - g/dL
Total, direct and indirect bilirubin (TBIL, DBIL, IBIL) - mg/dL
Albumin - (ALB) - g/dL
Globulin - (GLOB; by calculation) - g/dL
A/G ratio
Sodium (Na) - meq/L
Potassium (K) - meq/L
Chloride (Cl) - meq/L
Calcium (Ca) - mg/dL
Phosphorous (PHOS) - mg/dL
Amylase

C-reactive protein
Serum amyloid A
Troponin T (TnT)

A separate blood sample will be collected for C-reactive protein, serum amyloid A and Troponin T analyses into a 3 mL blood tube without anticoagulant. Nominally, 2 to 3 mL of whole blood will be collected from each animal and allowed to clot at room temperature. The blood samples will be centrifuged for 10 to 15 minutes for separation of serum. The serum samples will be harvested and dispensed into labeled 1.5 mL tubes and placed on dry ice until stored in a freezer set to maintain a temperature of -20 ± 10°C. The serum samples will be shipped to AniLytics, Inc. for analyses.

4. **Frozen Tissue and Serum Samples for Toxomic or Other Specialized Analyses:**

Animals in moribund condition will have five (5) samples of serum (approximately 0.5 mL each) collected immediately prior to sacrifice. Five (5) samples will be collected from each of the following tissues targeting 100 mg per sample: brain, heart, kidney, liver, lung and target tissues will also be collected from moribund animals during necropsy and obtained adjacent to sections used for histopathology. In addition, bone marrow will be collected from the femur during necropsy of moribund animals. The tissues will be flash-frozen and the serum and tissues will be stored at -70 ± 5°C. The tissues potentially may be used for any of the following analyses: biomarker or molecular target measurement, biodistribution of test article (i.e., PCR amplification), genomic or proteomic analysis, *in situ* hybridization or immunohistochemistry.

Since speed is of the essence in order to prevent degradation or other alteration of the sample, the required tissues MUST be collected rapidly following animal sacrifice and immediately frozen.

5. **Gross Necropsy**

All surviving animals will not be necropsied. Animals will be removed from study on Day 5 and transferred to a subsequent NCI study.

UNSCHEDULED SACRIFICE - Moribund animals will be sacrificed to minimize the degree of postmortem autolysis. The authorization to sacrifice moribund dogs will be made by the Study Director or other qualified individual after examination of the dogs. If a dog is found dead outside of normal working hours, the dog will be necropsied as soon as possible with the carcass refrigerated (not frozen) in the interim period (not to exceed 24 hours). Body weight will be taken and tissues will not be discarded because of postmortem autolysis.

All dogs that die or are sacrificed moribund will have a complete necropsy. At each necropsy, tissue samples will be collected for toxomic or other specialized analyses as indicated in Section "e" above. These samples should be obtained adjacent to sections used for histopathology. Antemortem observations will be recorded for each dog and commented on or confirmed at necropsy. Dogs that are clinically normal will also be indicated. A pathologist will be available to examine any unusual findings.

The tissues listed below will be examined, sampled and fixed in 10% neutral buffered formalin.

Bone marrow, sternum
Brain
Cecum
Colon
Duodenum
Gall bladder
Heart
Ileum
Jejunum
Kidneys (2)
Liver
Lungs
Lymph nodes (bronchial, mandibular, mesenteric)
Sciatic nerve
Skin: 1. Ventral abdomen 2. Injection site
Spinal cord, thoracolumbar (cervical and posterior lumbar spinal cord examined if nervous system signs present)
Spleen
Thymus

The identification mark from the dog will be preserved in fixative.

All fixed tissues will be retained for possible future histopathology evaluation.

H. Data Analysis

1. Hemodynamic and Pulmonary Evaluations

Group mean and individual animal plots will be produced for the systemic arterial blood pressures (systolic, diastolic and mean), heart rate, respiratory rate, tidal volume and minute volume. These plots will be assessed by the Study Director and included in the report.

2. **Electrocardiographic Evaluation**

Periodic ECG waveform tracings will be generated using ECGAUTO software (EMKA Technologies). The ECG waveform strips will be qualitatively assessed for rhythm and morphology alterations at appropriate time intervals by a board-certified veterinary cardiologist.

ECG intervals (PR, RR, QRS and QT) will be measured on the ECG waveform tracings generated at time points to be determined by the Study Director. The QT interval will be normalized for changes in heart rate by conversion to the corrected QT (QTc) interval using Fridericia's formula $QTc = QT/(RR)^{1/3}$, described by Mann *et al.* These ECG interval data will be assessed by the Study Director and included in the report.

3. **Statistical Analysis**

Data collected via the PhysioTel Telemetry System and the Buxco System will be electronically transferred to the Battelle statistics group for analysis. Between group statistical analysis will be performed on systemic arterial blood pressures (systolic, diastolic and mean), heart rate, ECG intervals, respiratory rate, tidal volume and minute volume data. An analysis of variance (ANOVA) using repeated measure techniques will be used to identify daily differences across the dose levels. An appropriate multiple comparison technique such as Dunnett's test will be applied within the ANOVA's when significant dose level effects are noted, in order to identify where significant differences are present. Specific statistical analysis methods will be documented in the study documentation.

I. **Computer Systems for Data Management and Analysis**

The Xybion PATH/TOX System will be used for the assignment of study specific animal numbers, and for the capture, storage and summarization of all appropriate animal-derived in-life data (clinical observations and body weights). The PhysioTel Telemetry System with Dataquest A.R.T. software, the ECGAUTO software and the Buxco BioSystem XA Data Acquisition System will be used for the capture, storage and summarization of all appropriate animal-derived cardiovascular and respiratory data. Statistical summaries and analyses will be performed on the cardiovascular and respiratory data using the SAS System for Personal Computers.

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 a protocol change may be granted by the NCI Project Officer, but a written amendment will follow.

D. Records

All records necessary to reconstruct this study will be maintained. A list of records to be maintained will include, but will not necessarily be limited to the following:

- a list of key personnel participating in the study
- copies of the approved study protocol, amendments, and deviations
- test article receipt and identification
- test article inventory and use records
- animal transfer records
- quarantine and health screening records
- animal identification records
- records of animal disposal and disposition
- treatment room location and environmental conditions
- food log
- all body weight records
- all records of clinical observations
- treatment and dosing records for each animal
- all clinical pathology records
- all physiologic data
- copy of final report (if available)

IV. REPORTING AND DISCUSSION OF DATA

A. Progress Reports

Status reports summarizing the progress of the study will be provided at monthly intervals. This report will detail the status of the study on the reporting date, any problems encountered and a proposed means of resolution. These unaudited reports will be kept on file with the Principal Investigator and will not be included in the study file.

B. Final Report

In order to maximize output in the final months of this contract, the contractor can submit an abbreviated study report. This abbreviated report will include: (a) a cover page which will include the title, contract number, authors, laboratory name and address, dates of initiation and completion, and sponsor; (b) a table of contents; (c) all individual animal data and appropriate summary tables for the following: cardiovascular and pulmonary data, mortality, body weights, clinical observations, hematology, clinical chemistry, and any other pertinent data; and (d) the signature of the Study Director and any others deemed necessary. In addition to the appropriate number of paper copies of the 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: _____ 23 Jan 04
Date

Principal Investigator: _____ 26 Jan 04
Date

NCI Project Officer: _____ 2-2-04
Date

G465535A
PROTOCOL AMENDMENT NUMBER 1
Document Number: NO1-CM-87028-35(A)
Effective Date: January 27, 2004

To: CARDIOVASCULAR AND PULMONARY SAFETY TESTING OF CuATSM / H_2ATSM (NSC-D729307) IN BEAGLE DOGS

1. Part to be changed/added. II. Materials and Methods. A. Test Article and Vehicle. 6. Dose Concentration Analyses.

Change the storage conditions from -70°F (±10°F) to -70°C (±10°C).

Reason for change: Typographical error.

2. Part to be changed/added. II. Materials and Methods. C. Experimental Design. 1 Group Assignments.

Change the total restraint time will not exceed 6 hours to the total restraint time will not exceed 7 hours.

Reason for change: The length of the dosing period extended the total restraint time of the dogs.

3. Part to be changed/added. II. Materials and Methods. C. Experimental Design. 1. Group Assignments.

Change the name of the compounds in the table headers from CuASTM / H_2ASTM to CuATSM / H_2ATSM.

Reason for change: Typographical error.

4. Part to be changed/added. II. Materials and Methods. G. Measurements. 3. Clinical Pathology.

Change the serum tubes from 1.5 mL tubes to 1.8 mL tubes.

Reason for change: Only 1.8 mL tubes were available.

Approved By:

C. R. Hassler 2/4/04
Craig R. Hassler, Ph.D. Date
Study Director

04Feb04
Irma M. Grossi, Ph.D. Date
Principal Investigator

2/9/04
Elizabeth R. Glaze, Ph.D. Date
Project Officer

DEVIATION REPORT

G465535A

Cardiovascular and Pulmonary Safety Testing of
CuATSM / H_2ATSM (NSC-D729307) in Beagle Dogs

Type of Deviation: Protocol

Date of Deviation: January 22, 2004

Nature of Deviation: Section II.A.3a. of the protocol states that confirmation of identity will be done upon receipt of each shipment of the compound. The test article was received on January 22, 2004, however, confirmation of identity (i.e., IR analysis) was not performed until February 23, 2004.

Cause of Deviation: Since there was a limited supply of compound, IR analysis was not performed until after the test article formulation was completed to ensure that there was a sufficient amount of test article available for dosing.

Impact of Deviation on Study: None. A sufficient amount of test article was available following the formulation to perform the IR analysis.

Corrective Action: None required.

Prepared By (Study Coordinator): Jeffrey J. Wallery, M.S.

Approved By: C R. Hansen Date: 3/16/04
(Study Director)

DEVIATION REPORT

G465535A

Cardiovascular and Pulmonary Safety Testing of
CuATSM/H_2ATSM (NSC-D729307) in Beagle Dogs

Type of Deviation: Protocol

Date of Deviation: January 26, 2004

Nature of Deviation: Dog tattoos CSMBDL and CTVAUK were not fasted the night prior to the Day -1 clinical pathology blood collection.

Cause of Deviation: Section II.G.3. of the protocol indicates that all dogs were to be fasted overnight and bled for clinical pathology on Day -1; however, food for two animals was not removed the night before the clinical pathology bleeds.

Impact of Deviation on Study: None. The animals were fasted at 7:15 a.m. (three hours and 33 minutes prior to the initiation of blood collection). Further, these animals were not selected for dosing, therefore no further blood collection or analyses occurred for these dogs.

Corrective Action: None required.

Prepared By (Study Coordinator): Jeffrey J. Wallery, M.S.

Approved By: C R. Hasler Date: 10/6/04
(Study Director)

DEVIATION REPORT

G465535A

Cardiovascular and Pulmonary Safety Testing of
CuATSM/H_2ATSM (NSC-D729307) in Beagle Dogs

Type of Deviation: Protocol

Date of Deviation: January 26 and 30, 2004

Nature of Deviation: A 5-mL blood tube without anticoagulant was used to collect blood samples for C-reactive protein, serum amyloid A and Troponin T analyses.

Cause of Deviation: Section II.G.3. of the protocol indicates that a 3-mL blood tube without anticoagulant was to be used for collection; however, only 5-mL blood tubes were available at the time of collection.

Impact of Deviation on Study: None. Appropriate blood samples were collected for C-reactive protein, serum amyloid A and Troponin T analyses.

Corrective Action: None required.

Prepared By (Study Coordinator): Jeffrey J. Wallery, M.S.

Approved By: C R. Hazelton Date: 10/6/04
(Study Director)

DEVIATION REPORT

G465535A

Cardiovascular and Pulmonary Safety Testing of
CuATSM / H_2ATSM (NSC-D729307) in Beagle Dogs

Type of Deviation: Protocol

Date of Deviation: January 27, 2004

Nature of Deviation: The rectal body temperature for animal number 101 was measured and recorded approximately 5 hours and 10 minutes after dosing instead of the protocol required between 4 and 5 hours after dosing.

Cause of Deviation: The protocol required the rectal body temperatures to be measured and recorded when the animals were removed from the restraint slings. However, the length of the dosing period extended the total restraint time of the dogs, thus extending the time that the body temperature was measured and recorded.

Impact of Deviation on Study: None. The animal's rectal body temperature was measured and recorded and found to be normal.

Corrective Action: None required.

Prepared By (Study Coordinator): Jeffrey J. Wallery, M.S.

Approved By: _____ Date: 2/4/04
(Study Director)

DEVIATION REPORT

G465535A

Cardiovascular and Pulmonary Safety Testing of
CuATSM/H_2ATSM (NSC-D729307) in Beagle Dogs

Type of Deviation: Protocol

Date of Deviation: January 27, 2004

Nature of Deviation: The storage conditions of the vehicle components (DMSO, 100% ethanol and saline) could not be verified (the conditions were not recorded by the technician performing dose formulation).

Cause of Deviation: Section II.A.4.b. of the protocol indicates that the DMSO, 100% ethanol and saline were to be stored at controlled room temperature (approximately 17 to 25°C).

Impact of Deviation on Study: None.

Corrective Action: The storage conditions of vehicle components will be recorded for future NCI studies.

Prepared By (Study Coordinator): Jeffrey J. Wallery, M.S.

Approved By: _____ Date: 7/23/04
(Study Director)

APPENDIX B

INDIVIDUAL ANIMAL IN-LIFE DATA

Abnormal Clinical Observations

Cage #	Animal Number	Sex	Group/ Subgroup	Date and Time Data was Entered	Phase Day/time Data was Taken	Oper. #	Clinical Observations	*Sev. Grade
3	201	M	2/1	17-Nov-04 12:38	1 / 11:02	38	DIGESTIVE SYSTEM / SALIVATION	+
6	152	F	1/1	17-Nov-04 12:23	1 / 10:57	38	DIGESTIVE SYSTEM / SALIVATION	+
7	251	F	2/1	27-Jan-04 16:16	1 / 16:16	66	EYES / DISCHARGE-CLEAR/EYE(S)	+
							SWELLING / NOSE/MUZZLE	+
							EARS / REDDENED/EAR(S)	+
							clear discharge both eyes	
							both inner ears and muzzle reddened	
							and slightly swollen	
				28-Jan-04 08:45	2 / 08:45	41	EYES / DISCHARGE-CLEAR/EYE(S)	+
							SWELLING / NOSE/MUZZLE	+
							EARS / REDDENED/EAR(S)	+
							clear discharge both eyes	
							both inner ears and muzzle reddened	
							and slightly swollen	
				29-Jan-04 07:13	3 / 07:13	59	EYES / DISCHARGE-CLEAR/EYE(S)	+
							EARS / REDDENED/EAR(S)	+
							clear discharge both eyes	
							both inner ears reddened	
				30-Jan-04 07:07	4 / 07:07	59	EYES / DISCHARGE-CLEAR/EYE(S)	+
							EARS / REDDENED/EAR(S)	+
							clear discharge both eyes	
							both inner ears reddened	
8	252	F	2/1	29-Jan-04 07:14	3 / 07:14	59	DIGESTIVE SYSTEM / EMESIS	+
							white foamy emesis	

* Key to severity grade: + or 1 = not graded; 2 = mild; 3 = moderate; 4 = marked; 5 = severe
Note: Data for Study Phase

Body Weights (kg)

Animal	Group		Day of Phase 1
		Male	Animals
101	1		11.89
102			11.14
		(n)	2
		Means	11.51
201	2		14.43
202			12.82
		(n)	2
		Means	13.63
		Female	Animals
151	1		6.39
152			8.20
		(n)	2
		Means	7.29
251	2		8.21
252			9.83
		(n)	2
		Means	9.02

Note: Data for Prestudy Phase

Body Temperatures (°C)

Animal Number	Dose Level (mg/kg)	Day -1	Day 1	Day 4
101	0	39.7	36.9	39.1
102	0	39.7	37.6	38.5
201	0.3	39.4	37.3	40.5
202	0.3	39.4	37.9	39.5
151	0	38.3	37.7	38.7
152	0	39.7	38.2	39.4
251	0.3	39.9	38.8	39.1
252	0.3	38.7	38.3	39.2

APPENDIX C

CLINICAL PATHOLOGY DATA

Hematology

Animal Number	Sex	Group/ Subgrp	Day/week of Phase	Sesn #	Entry Type	WBC K/UL	RBC M/UL	HGB G/DL	HCT %	MCV FL	MCH PG	MCHC G/DL	PLT K/UL	SEG K/UL
101	M	1/1	1/1!	S 1	Onl	9.18	7.90	16.8	50.6	64.1	21.3	33.2	189	6.17
			4/1"	S 1	Onl	8.34	7.91	16.8	51.0	64.5	21.3	33.0	206	4.99
102	M	1/1	1/1!	S 1	Onl	12.74	7.34	16.5	48.1	65.5	22.5	34.3	281	8.18
			4/1"	S 1	Onl	12.08	7.10	15.9	46.4	65.3	22.5	34.4	268	8.20
201	M	2/1	1/1!	S 1	Onl	11.68	7.33	16.0	47.6	65.0	21.8	33.5	267	8.45
			4/1"	S 1	Onl	9.89	7.14	15.6	46.2	64.7	21.8	33.8	267	7.23
202	M	2/1	1/1!	S 1	Onl	13.58	7.87	16.5	48.5	61.5	21.0	34.1	543	8.46
			4/1"	S 1	Onl	12.37	7.87	16.2	48.4	61.5	20.6	33.5	495	7.87
151	F	1/1	1/1!	S 1	Onl	8.07	6.73	14.8	43.8	65.2	22.0	33.8	468	4.62
			4/1"	S 1	Onl	10.26	6.67	14.5	43.5	65.1	21.7	33.3	496	6.72
152	F	1/1	1/1!	S 1	Onl	12.97	8.45	18.0	53.0	62.7	21.3	34.0	385	9.75
			4/1"	S 1	Onl	10.83	7.89	16.8	49.2	62.4	21.3	34.2	367	8.06
251	F	2/1	1/1!	S 1	Onl	11.44	7.36	16.0	46.9	63.7	21.8	34.2	395	7.22
			4/1"	S 1	Onl	10.39	7.09	15.1	45.1	63.6	21.4	33.6	364	6.93
252	F	2/1	1/1!	S 1	Onl	21.95	6.83	14.9	43.6	63.9	21.8	34.1	458	15.47
			4/1"	S 1	Onl	13.66	7.00	15.2	44.5	63.6	21.7	34.1	486	8.66

Note: ! = Prestudy Phase; " = Study Phase

Hematology

Animal Number	Sex	Group/ Subgrp	Day/week of Phase	Sesn #	Entry Type	TLYM K/UL	MON K/UL	EOS K/UL	BAS K/UL	LYM K/UL	LUC K/UL	RET K/UL	NRBC #/100WB
101	M	1/1	1/1!	S 1	Onl	2.06	0.27	0.63	0.04	2.02	0.04	33.50	0
			4/1"	S 1	Onl	2.23	0.41	0.67	0.03	2.22	0.01	24.50	0
102	M	1/1	1/1!	S 1	Onl	3.63	0.35	0.54	0.03	3.60	0.03	27.40	0
			4/1"	S 1	Onl	3.04	0.39	0.43	0.02	3.01	0.03	25.90	0
201	M	2/1	1/1!	S 1	Onl	2.20	0.47	0.54	0.03	2.17	0.03	34.10	0
			4/1"	S 1	Onl	1.83	0.29	0.52	0.02	1.81	0.02	89.00	0
202	M	2/1	1/1!	S 1	Onl	3.87	0.68	0.51	0.07	3.83	0.04	70.50	0
			4/1"	S 1	Onl	3.46	0.70	0.30	0.05	3.41	0.05	74.10	0
151	F	1/1	1/1!	S 1	Onl	2.64	0.36	0.42	0.02	2.59	0.05	26.60	0
			4/1"	S 1	Onl	2.81	0.33	0.36	0.04	2.76	0.05	25.80	0
152	F	1/1	1/1!	S 1	Onl	2.32	0.53	0.31	0.06	2.28	0.04	37.80	0
			4/1"	S 1	Onl	1.92	0.49	0.30	0.06	1.87	0.05	33.10	0
251	F	2/1	1/1!	S 1	Onl	2.97	0.42	0.80	0.04	2.94	0.03	60.50	0
			4/1"	S 1	Onl	2.46	0.34	0.65	0.01	2.44	0.02	59.00	0
252	F	2/1	1/1!	S 1	Onl	4.81	1.21	0.37	0.10	4.73	0.08	29.00	0
			4/1"	S 1	Onl	3.94	0.58	0.45	0.05	3.89	0.05	29.70	0

Note: ! = Prestudy Phase; " = Study Phase

Serum Chemistry

Animal Number	Sex	Group/ Subgrp	Day/week of Phase	Sesn #	Entry Type	ALP U/L	AST U/L	ALT U/L	GGT U/L	TBIL MG/DL	DBIL MG/DL	TP G/DL	ALB G/DL	GLU MG/DL
101	M	1/1	1/1!	S 1	Onl	40	28	43	4	0.10	0.03	6.0	3.8	91
			4/1"	S 1	Onl	41	27	41	5	0.13	0.02	6.2	4.1	98
102	M	1/1	1/1!	S 1	Onl	33	39	101	3	0.11	0.04	5.7	3.2	86
			4/1"	S 1	Onl	32	34	77	4	0.17	0.05	6.0	3.5	89
201	M	2/1	1/1!	S 1	Onl	53	22	27	4	0.10	0.03	6.2	3.5	88
			4/1"	S 1	Onl	53	24	26	3	0.15	0.04	6.6	3.7	91
202	M	2/1	1/1!	S 1	Onl	80	82	42	5	0.13	0.04	6.3	3.5	78
			4/1"	S 1	Onl	80	81	48	4	0.13	0.04	6.8	3.8	88
151	F	1/1	1/1!	S 1	Onl	37	24	38	5	0.06	0.02	5.9	3.5	87
			4/1"	S 1	Onl	37	26	33	5	0.08	0.02	6.1	3.7	96
152	F	1/1	1/1!	S 1	Onl	65	35	32	6	0.19	0.05	6.6	4.1	89
			4/1"	S 1	Onl	73	28	32	5	0.21	0.07	6.7	4.1	98
251	F	2/1	1/1!	S 1	Onl	55	30	42	5	0.12	0.04	5.7	3.6	92
			4/1"	S 1	Onl	58	29	31	5	0.10	0.05	6.0	3.7	107
252	F	2/1	1/1!	S 1	Onl	29	37	30	5	0.07	0.04	6.3	3.3	92
			4/1"	S 1	Onl	32	32	28	5	0.12	0.04	7.0	3.5	94

Note: ! = Prestudy Phase; " = Study Phase

Serum Chemistry

Animal Number	Sex	Group/ Subgrp	Day/week of Phase	Sesn #	Entry Type	BUN MG/DL	CREA MG/DL	CA MG/DL	PHOS MG/DL	CK U/L	LDH U/L	NA MEQ/L	K MEQ/L	CL MEQ/L
101	M	1/1	1/1!	S 1	Onl	14	0.9	10.6	3.4	130	64	147	4.4	111
			4/1"	S 1	Onl	15	1.0	11.0	3.4	113	84	150	4.4	112
102	M	1/1	1/1!	S 1	Onl	20	1.1	10.7	4.1	134	94	148	4.3	113
			4/1"	S 1	Onl	18	1.0	11.1	4.2	92	73	149	4.3	114
201	M	2/1	1/1!	S 1	Onl	11	0.8	10.3	3.8	98	55	147	4.0	113
			4/1"	S 1	Onl	10	0.8	10.8	4.1	135	76	150	4.4	115
202	M	2/1	1/1!	S 1	Onl	15	1.0	10.8	4.1	143	119	147	4.5	111
			4/1"	S 1	Onl	16	0.9	11.3	4.1	170	219	150	4.6	113
151	F	1/1	1/1!	S 1	Onl	17	0.7	10.6	4.5	131	46	145	4.8	110
			4/1"	S 1	Onl	20	0.7	11.2	4.7	138	82	147	5.1	112
152	F	1/1	1/1!	S 1	Onl	14	0.7	10.7	3.4	176	104	149	4.0	113
			4/1"	S 1	Onl	15	0.8	11.5	3.2	126	96	151	4.1	116
251	F	2/1	1/1!	S 1	Onl	16	0.8	11.2	4.4	141	48	146	4.7	110
			4/1"	S 1	Onl	16	0.8	11.7	4.8	137	59	150	4.4	113
252	F	2/1	1/1!	S 1	Onl	14	0.9	10.3	3.8	205	52	146	4.0	114
			4/1"	S 1	Onl	16	0.9	10.7	3.9	118	69	150	4.1	114

Note: ! = Prestudy Phase; " = Study Phase

Serum Chemistry

Animal Number	Sex	Group/ Subgrp	Day/week of Phase	Sesn #	Entry Type	GLOB G/DL	AGR	IBIL MG/DL	AMYL U/L
101	M	1/1	1/1!	S 1	Onl	2.2	1.73	0.07	689
			4/1"	S 1	Onl	2.1	1.95	0.11	700
102	M	1/1	1/1!	S 1	Onl	2.5	1.28	0.07	776
			4/1"	S 1	Onl	2.5	1.40	0.12	787
201	M	2/1	1/1!	S 1	Onl	2.7	1.30	0.07	571
			4/1"	S 1	Onl	2.9	1.28	0.11	526
202	M	2/1	1/1!	S 1	Onl	2.8	1.25	0.09	730
			4/1"	S 1	Onl	3.0	1.27	0.09	720
151	F	1/1	1/1!	S 1	Onl	2.4	1.46	0.04	796
			4/1"	S 1	Onl	2.4	1.54	0.06	848
152	F	1/1	1/1!	S 1	Onl	2.5	1.64	0.14	603
			4/1"	S 1	Onl	2.6	1.58	0.14	550
251	F	2/1	1/1!	S 1	Onl	2.1	1.71	0.08	595
			4/1"	S 1	Onl	2.3	1.61	0.05	616
252	F	2/1	1/1!	S 1	Onl	3.0	1.10	0.03	1054
			4/1"	S 1	Onl	3.5	1.00	0.08	957

Note: ! = Prestudy Phase; " = Study Phase

C-Reactive Protein, Serum Amyloid A, and Troponin T

Animal Tattoo/Sex	Animal Number	C-Reactive Protein (mg/L)	Serum Amyloid A (μg/mL)	Troponin T (ng/mL)
January 26, 2004 (Day -1)				
CSRACA/M	101	0.02	0.00	0.00
CTVADF/M	102	0.00	1.43	0.00
CTWAMK/M	201	0.00	0.92	0.00
CTVAMB/M	202	0.00	0.13	0.00
CSMBDL/M	NA	0.02	0.17	0.00
CTWBAT/F	151	0.04	2.58	0.00
CTVAVV/F	152	0.00	0.00	0.00
CTVALZ/F	251	0.01	0.12	0.00
CTVAMK/F	252	0.00	0.34	0.00
CTVAUK/F	NA	0.00	4.04	0.00
January 30, 2004 (Day 4)				
CSRACA/M	101	0.07	0.18	0.00
CTVADF/M	102	0.00	1.23	0.00
CTVAMB/M	201	0.00	0.30	0.00
CTWAMK/M	202	0.00	0.06	0.00
CSMBDL/M	NA	-	-	--
CTWBAT/F	151	0.00	1.26	0.00
CTVAVV/F	152	0.00	0.00	0.00
CTVALZ/F	251	0.01	0.17	0.00
CTVAMK/F	252	0.00	0.00	0.00
CTVAUK/F	NA	-	-	-

11/16/04 G465535A

CARDIOVASCULAR AND PULMONARY SAFETY TESTING
OF Cu ATSM/H_2 ATSM (NSC-D729307) IN BEAGLE DOGS

CLINICAL PATHOLOGY

Hematology

None of the hematology results of the study indicated any drug treatment effects.

Clinical Chemistry

None of the clinical chemistry results of the study indicted any drug treatment effects.

Special Clinical Chemistry

None of the C-reactive protein, amyloid A, or troponin T results indicated any drug treatment effects.

Michael J. Ryan 11/16/04

Michael J. Ryan, D.V.M., Ph.D., D.A.B.T. Date
Diplomate, A.C.V.P.
Clinical Pathologist

11-16-04

Allen W. Singer, D.V.M., D.A.B.T. Date
Diplomate, A.C.V.P.
Technical Review

APPENDIX D

STATISTICAL ANALYSIS

Statistical Methods and Results

Statistical analysis was conducted on data for the following parameters:

- systolic blood pressure (mmHg)
- diastolic blood pressure (mmHg)
- mean arterial blood pressure (mmHg)
- heart rate (BPM)
- four selected ECG interval measures: PR, RR, QRS, QT (msec)
- QT interval corrected for heart rate by dividing QT by the cubed root of RR (i.e., QTc)
- three pulmonary parameters: respiratory rate (breaths/min), tidal volume (mL/breath/kg) and minute volume (mL/min/kg).

These parameters were selected for statistical analysis and interpretation to characterize the cardiovascular and pulmonary effects of a single intravenous bolus injection of test article [CuATSM/ H_2ATSM (NSC-D729307)] on the study animals (conscious beagle dogs). Two dogs of each sex were assigned randomly to either the vehicle or the test article dose group.

The primary objectives for the statistical analysis performed on these data were as follows:

1. For the blood pressure, heart rate, and pulmonary parameters, determine whether significant differences existed among dose groups on a 10-minute interval basis immediately following dosing when animals were in the restraint slings.
2. For the blood pressure and heart rate parameters, determine whether significant differences existed among dose groups on an hourly basis during the period following dosing when animals were in their home cage.
3. For the ECG interval parameters, determine whether significant differences existed among dose groups at specified time points following dosing, both when animals were in the restraint slings and in their home cages.

Study Data

Blood pressure and heart rate data collected via radiotelemetry were stored in SAS datasets for statistical summary and analysis. Data values outside of the following intervals were not considered in these summaries and analyses:

- systolic blood pressure: 50 mmHg to 210 mmHg.
- diastolic blood pressure: 20 mmHg to 140 mmHg.
- mean arterial blood pressure: 30 mmHg to 160 mmHg.
- heart rate: 20 BPM to 240 BPM.

If data were unavailable for any of the four blood pressure and heart rate parameters in a given data record, then no data from that record were included in either the statistical summaries or analyses.

Baseline averages for blood pressure and heart rate were calculated for each animal, using data collected prior to dosing when animals were not subjected to dosing effects. Because blood pressure and heart rate could be affected by whether the animal is in the restraint sling or its home cage, and because these data were collected post-dosing under both conditions, separate baseline averages were calculated for "in-sling" and "in-cage" conditions. The method for calculating these baseline averages and the post-dosing endpoints used in the statistical summary and analysis is as follows:

- "In-sling" data: Each animal's "in-sling" baseline average was calculated by averaging data collected during the 30-minute interval from 10 to 40 minutes prior to dosing (see **Table 1**). "Unadjusted" 10-minute averages were obtained by partitioning the 4.5-hour period immediately following dosing when animals were in the restraint slings into 27 10-minute intervals and averaging the measured data within each interval. Each animal's "in-sling" baseline average was then subtracted from each of its unadjusted post-dosing 10-minute averages, resulting in "baseline-adjusted" 10-minute averages.

- "In-cage" data: Each animal's "in-cage" baseline average was calculated by averaging data collected within the one-hour interval from 5 am to 6 am, prior to dosing (see **Table 2**). "Unadjusted" hourly averages were obtained by partitioning the 66-hour period starting at approximately 6 hours post-dosing, after the animals had been returned to their home cages, into 66 hourly intervals and averaging the measured data within each hourly interval. Each animal's "in-cage" baseline average was then subtracted from each of its unadjusted post-dosing hourly averages, resulting in "baseline-adjusted" hourly averages.

ECG interval measurements (PR, RR, QRS, and QT, along with corrected QT) associated with the following time points were considered for the statistical analysis:

- at 20 and 40 minutes prior to dosing, at 10 minutes post-dosing, and at 0.5, 1, 2, and 4 hours post-dosing, when animals were in the restraint slings.

- between either 4 am and 5 am, prior to dosing (vehicle animals) or 5 am and 6 am, prior to dosing (test article animals), and at 8, 20, 32, 44, and 56 hours post-dosing, when animals were in their home cages. [Note that the 8, 20, 32, 44 and 56 hour target time points were considered acceptable if they were within ±1 hour of the target.]

On each dosing day, as with the blood pressure and heart rate data, separate "in-sling" and "in-cage" baseline averages were calculated for each animal as the average of the reported measurements taken during the "in-sling" and "in-cage" pre-dosing time points, respectively (see **Table 21** and **Table 22**). For a given environment, the baseline average associated with that environment was subtracted from the animal's reported measurements during the post-dosing time points on that day within that environment. The results were "baseline-adjusted" post-dosing measurements for both the in-sling and in-cage environments.

Pulmonary data (respiratory rate, tidal volume and minute volume) were collected when the animals were in the restraint slings. Any data records having a value for respiratory rate above 60 breaths per minute were omitted from the analysis of pulmonary data. Tidal volume and minute volume were adjusted by body weight prior to analysis.

For each animal, the period from one-hour prior to dosing through four hours post-dosing were partitioned into 30 10-minute intervals and the measured data were averaged within each interval, resulting in "unadjusted" 10-minute averages. Then, baseline averages were calculated for each animal by averaging data collected during the 30-minute interval from 10 to 40 minutes prior to dosing (see **Table 45**). An animal's baseline average was then subtracted from each of its 10-minute averages within the four-hour post-dosing period, resulting in "baseline-adjusted" 10-minute averages.

Statistical Method

The statistical approaches taken to address the statistical objectives are given below. Statistical analyses were performed separately for each parameter and for "in-sling" and "in-cage" conditions. All references to statistical significance are at the 0.05 level unless specified otherwise.

Comparison of Baseline Averages between Two Dose Groups

The following analysis of variance (ANOVA) model (model (1)) was fitted to the baseline averages using the MIXED procedure in the SAS® System:

$$Y_{ijk} = \mu + Sex_i + Dose_j + (Sex*Dose)_{ij} + A_k + \varepsilon_{ijk} \quad (1)$$

where Y_{ijk} was the baseline average for the k^{th} animal of sex i in the j^{th} dose group (i, j, k=1, 2), μ was an overall constant, Sex_i was the (fixed) effect of sex, $Dose_j$ was the fixed effect of dose group, $(Sex*Dose)_{ij}$ was the interaction effect between sex and dose group, A_k is the (random) animal effect, and ε_{ijk} was random error left unexplained by the model. The error term ε_{ijk} was assumed to follow a normal distribution with zero mean. If the effect of sex and the interaction effect between sex and dose group were not significant at the 0.05 level, then comparisons of baseline averages between dose groups were made across all animals. Otherwise, comparisons between dose groups were made separately by sex within the fitted model using F-tests (by applying the SLICE option within an LSMEANS statement in the MIXED procedure).

Comparison of Baseline-Adjusted Post-Dosing Data between the Two Dose Groups

The following repeated measures ANOVA model (model (2)) was fitted to the baseline-adjusted post-dosing data using the MIXED procedure in the SAS® System:

$$Y_{ijkm} = \mu + Sex_i + Dose_j + T_m + (Sex*Dose)_{ij} + (Dose*T)_{jm} + (Sex*Dose*T)_{ijm} + A_k + \varepsilon_{ijkm} \quad (2)$$

where Y_{ijkm} was the baseline-adjusted value at the m^{th} time point for the k^{th} animal of sex i in the j^{th} dose group (i, j, k=1, 2; m=1, 2, ..., M), μ was an overall constant, Sex_i was the (fixed) effect of sex, $Dose_j$ was the (fixed) effect of dose group, T_m was the (fixed) effect of a particular time point within the specified post-dosing period, $(Sex*Dose)_{ij}$ was the interaction effect between sex and dose group, $(Dose*T)_{jm}$ was

the interaction effect between dose group and time point, $(Sex*Dose*T)_{ijm}$ was the interaction effect between sex, dose group and time point, and A_k was the (random) animal effect. The term ε_{ijkm} was random error left unexplained by the model and was assumed to have a covariance structure which permitted a nonzero correlation to exist in errors associated with the same animal; these errors were allowed to have higher correlation as the time points for which they were associated were closer together. When the time points involved in the analysis were equidistant (i.e., blood pressure, heart rate, and pulmonary parameters), a first autoregressive (AR(1)) covariance structure was used, while in other cases, a spatial power covariance structure in time was used (i.e., for ECG interval parameters). In this ANOVA model, M corresponds to the number of post-dosing intervals included in the analysis (i.e., M=27 for analysis of "in-sling" blood pressure and heart rate; M=66 for "in-cage" blood pressure and heart rate data; M=24 for pulmonary data; and M=5 for both "in-sling" and "in-cage" ECG interval data).

For each parameter, significant differences between the two dose groups were tested at each time point within the fitted model using F-tests (by applying the SLICE option within an LSMEANS statement in the MIXED procedure). If the sex effect, interaction effect between sex and dose group, or interaction effect between sex, dose group and time point were significant at the 0.05 level, then significant differences between the two dose groups were tested at each time point separately for each sex within the fitted model. Otherwise, dose group comparisons were made across all study animals. Conclusions of significant differences between the two dose groups at each of the M time points were based on significance levels that were adjusted using the Benjamini and Hochberg method within the MULTTEST procedure in SAS to ensure that the false positive rate for the M comparisons between the two dose groups was not higher than 0.05.

Results

Analysis of baseline averages for the blood pressure and heart rate data: For each of the four blood pressure and heart rate parameters, each animal's "in-sling" and "in-cage" baseline averages are presented in **Table 1** and **Table 2**, respectively. **Table 3** and **Table 4** present dose group averages and standard errors of the "in-sling" and "in-cage" baseline averages, respectively, when calculated across animals for each sex, as well as across all animals. The results of fitting model (1) to the baseline averages indicated that significant differences between dose groups were present at the 0.05 level only for mean arterial pressure in the "in-sling" condition for both males and females (**Table 3**). The direction of these differences in the baseline average mean arterial pressure differed between the two sexes, with males in the test article group having a higher baseline average than in the vehicle group, and vice versa for females.

Analysis of post-dosing averages for the "in-sling" blood pressure and heart rate data: **Table 5** through **Table 12** (two tables per parameter, one overall and one grouped by sex) present means and standard errors for each dose group of the unadjusted and baseline-adjusted 10-minute averages during the 4.5-hour period immediately following dosing when animals were in the restraint slings. These baseline-adjusted dose group means are plotted (with +/- standard error bars) versus time in **Figure 1** to **Figure 4** where means are calculated across all study animals, in **Figure 5** through **Figure 8** where data for only male animals are considered, and **Figure 9** through **Figure 12** where data for only female animals are considered. In each set of plots, one figure corresponds to each parameter.

When model (2) was fitted to the 10-minute "in-sling" baseline-adjusted averages by parameter, no significant differences between the two dose groups were observed within any 10-minute interval for any parameter. For each parameter, dose group comparisons were made across all study animals, as the dose group effect did not interact significantly with the sex effect.

Analysis of post-dosing averages for the "in-cage" blood pressure and heart rate data: **Table 13** through **Table 20** (two tables per parameter, one overall and one grouped by sex) present means and standard errors for each dose group of the unadjusted and baseline-adjusted hourly averages

during the 66-hour period starting when animals were returned to their home cages following dosing. These baseline-adjusted dose group means are plotted (with +/- standard error bars) versus time in **Figure 13** to **Figure 16** where means are calculated across all study animals, in **Figure 17** through **Figure 20** where data for only male animals are considered, and **Figure 21** through **Figure 24** where data for only female animals are considered. In each set of plots, one figure corresponds to each parameter.

When model (2) was fitted to the hourly "in-cage" baseline-adjusted averages by parameter, no significant differences between the two dose groups were observed within any 10-minute interval for any parameter. As with the "in-sling" data analysis, comparisons were made across all study animals, as the dose group effect did not interact significantly with the sex effect.

Analysis of baseline averages for the ECG interval parameters: For each of the five ECG interval parameters, each animal's "in-sling" baseline averages for each dosing day are presented in **Table 21**, and the "in-cage" baseline averages are presented in **Table 22**. **Table 23** and **Table 24** present dose group averages and standard errors of the "in-sling" and "in-cage" baseline averages, respectively, when calculated across animals for each sex, as well as across all animals. Upon fitting model (1) to the baseline averages, significant differences between dose groups were observed at the 0.05 level in the following two cases: 1) for QT interval in female animals during "in-sling" conditions (**Table 23**), and 2) for RR interval in male animals during "in-cage" conditions (**Table 24**). In both cases, the test article animals averaged lower baselines than the vehicle animals. Note that both cases are sex-specific, because the sex/dose group interaction was significant.

Analysis of post-dosing averages for the ECG interval data (both "in-sling" and "in-cage"): **Table 25** through **Table 34** (two tables per parameter, one overall and one grouped by sex) present means and standard errors for each dose group of the unadjusted and baseline-adjusted post-dosing ECG interval measurements at each time point following dosing when the intervals were measured during the "in-sling" period. The same set of tables exists for the "in-cage" ECG interval data within **Table 35** through **Table 44**. These baseline-adjusted dose group means are plotted (with +/- standard error bars) versus time in **Figure 25** through **Figure 39** for "in-sling" data and **Figure 40** through **Figure 54** for "in-

cage" data, with separate plots existing for each ECG interval parameter/sex combination, as well as for each parameter in which all study animals are represented.

When model (2) was fitted to the baseline-adjusted ECG interval measurements, separately for "in-sling" and "in-cage" data, no significant differences were observed between dose groups at any time point for any parameter. Dose group comparisons were made across all study animals, as dose group effects did not interact significantly with sex effects.

Analysis of baseline averages for the pulmonary parameters: For each of the three pulmonary parameters, each animal's baseline averages are presented in **Table 45. Table 46** presents dose group averages and standard errors of the baseline averages when calculated across animals for each sex, as well as across all animals. When fitting model (1) to the baseline averages, no significant differences were observed at the 0.05 level between the two dose groups for any respiratory parameter. Dose group comparisons were made across all animals, as the dose group effect did not interact significantly with the sex effect at the 0.05 level.

Analysis of post-dosing averages for the pulmonary data: Table 47 through **Table 52** (two tables per parameter, one overall and one grouped by sex) present means and standard errors for each dose group of the unadjusted and baseline-adjusted 10-minute averages. These baseline-adjusted dose group means are plotted (with +/- standard error bars) versus time in **Figure 55** to **Figure 57** where means are calculated across all study animals, in **Figure 58** through **Figure 60** where data for only male animals are considered, and **Figure 61** through **Figure 63** where data for only female animals are considered. In each set of plots, one figure corresponds to each parameter.

When model (2) was fitted to the baseline-adjusted 10-minute averages by parameter, no significant differences were observed at the 0.05 level between the two dose groups within any 10-minute interval for any parameter. Dose group comparisons were made across all study animals, as the dose group effect did not interact significantly with the sex effect at the 0.05 level.

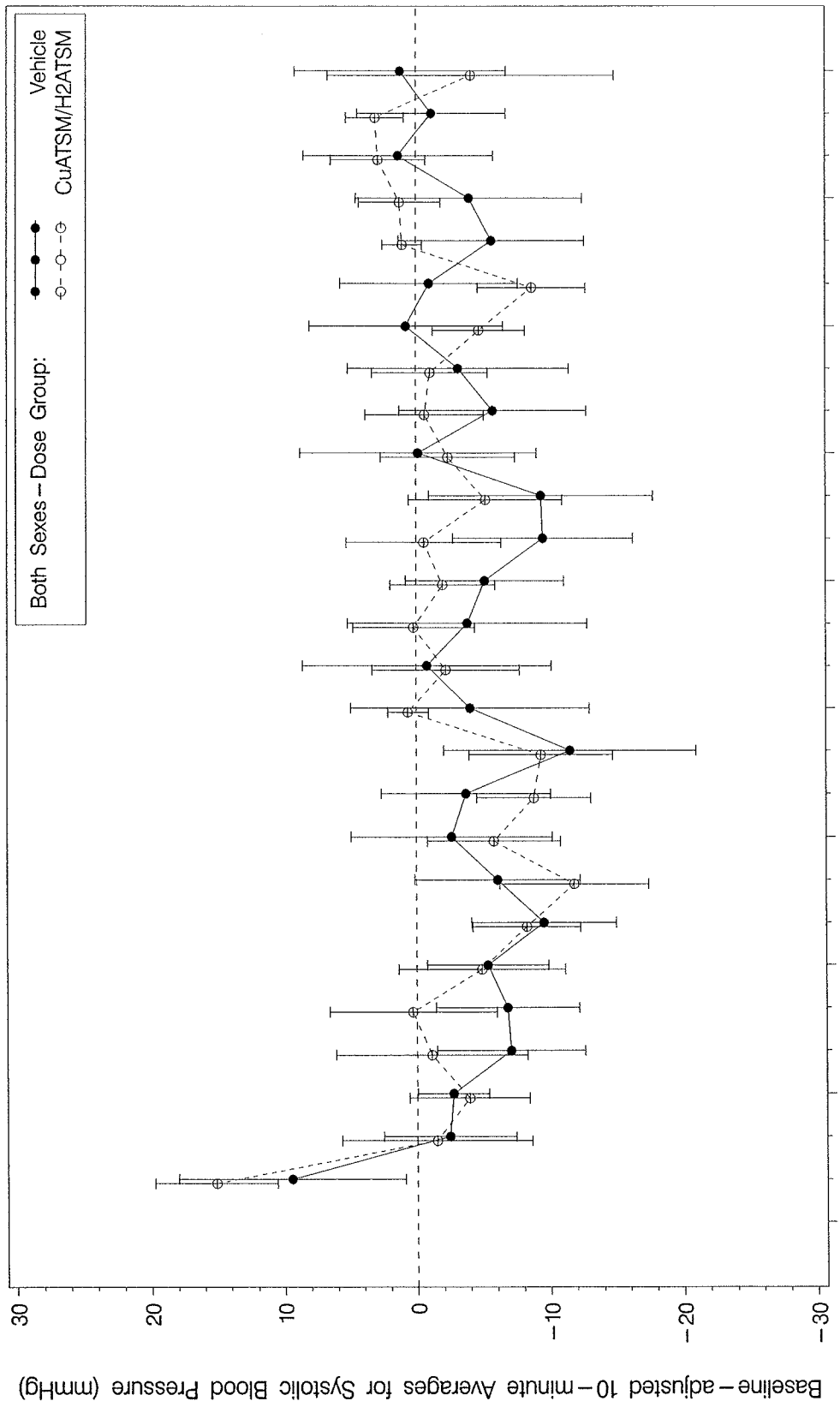


Figure 1. **Systolic Blood Pressure (mmHg), Both Sexes, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

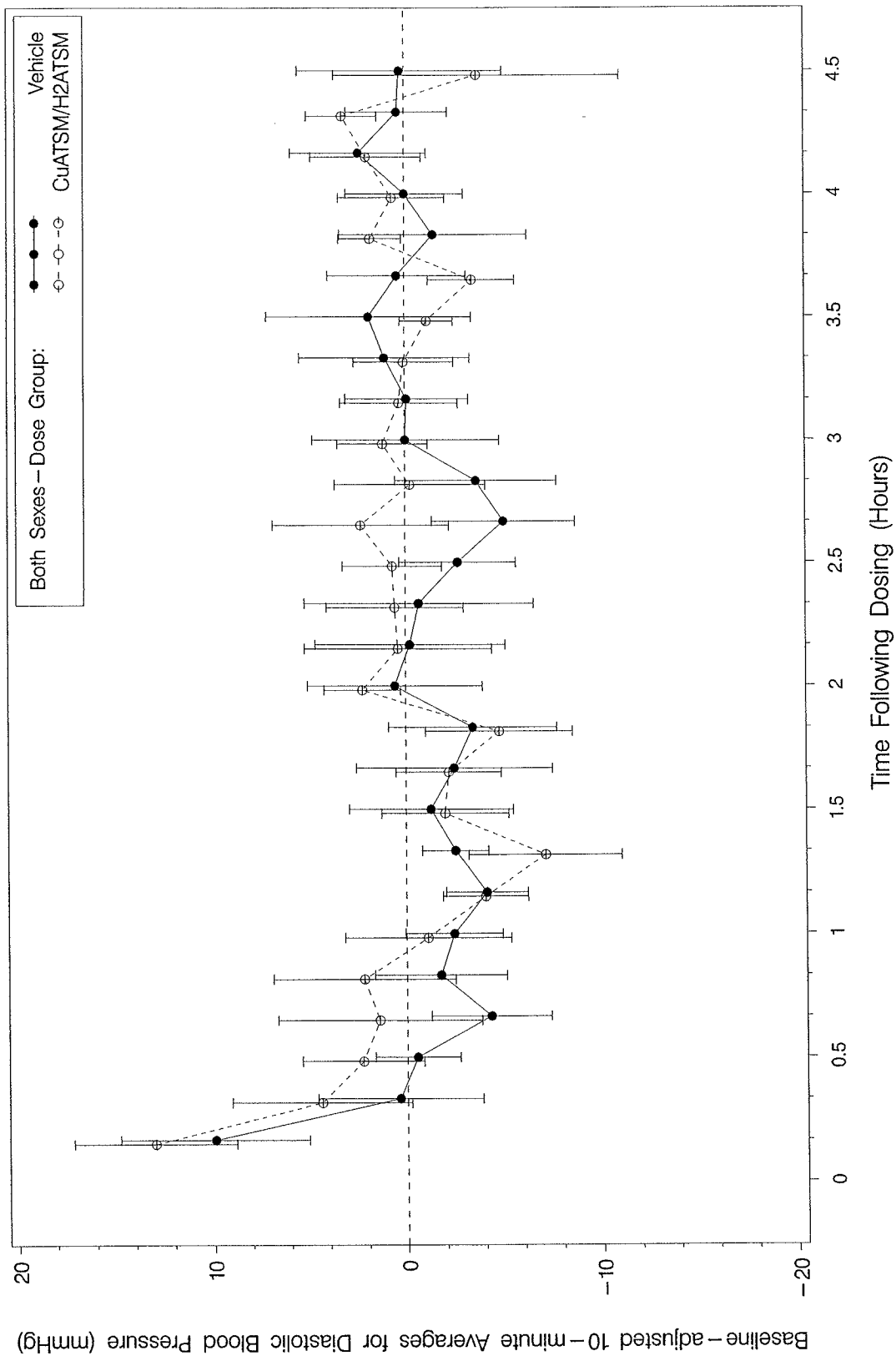


Figure 2. **Diastolic Blood Pressure (mmHg), Both Sexes, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

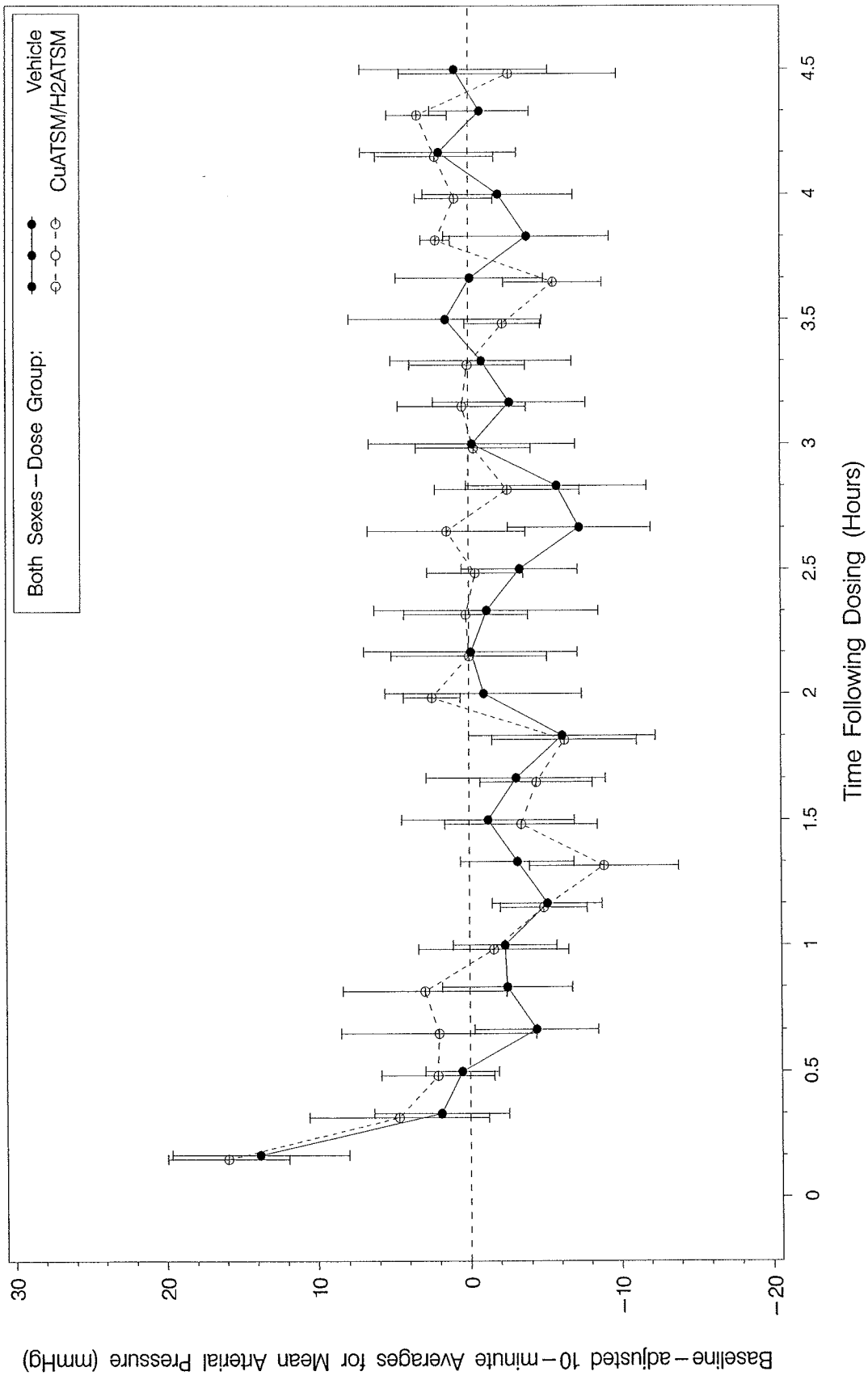


Figure 3. **Mean Arterial Pressure (mmHg), Both Sexes, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

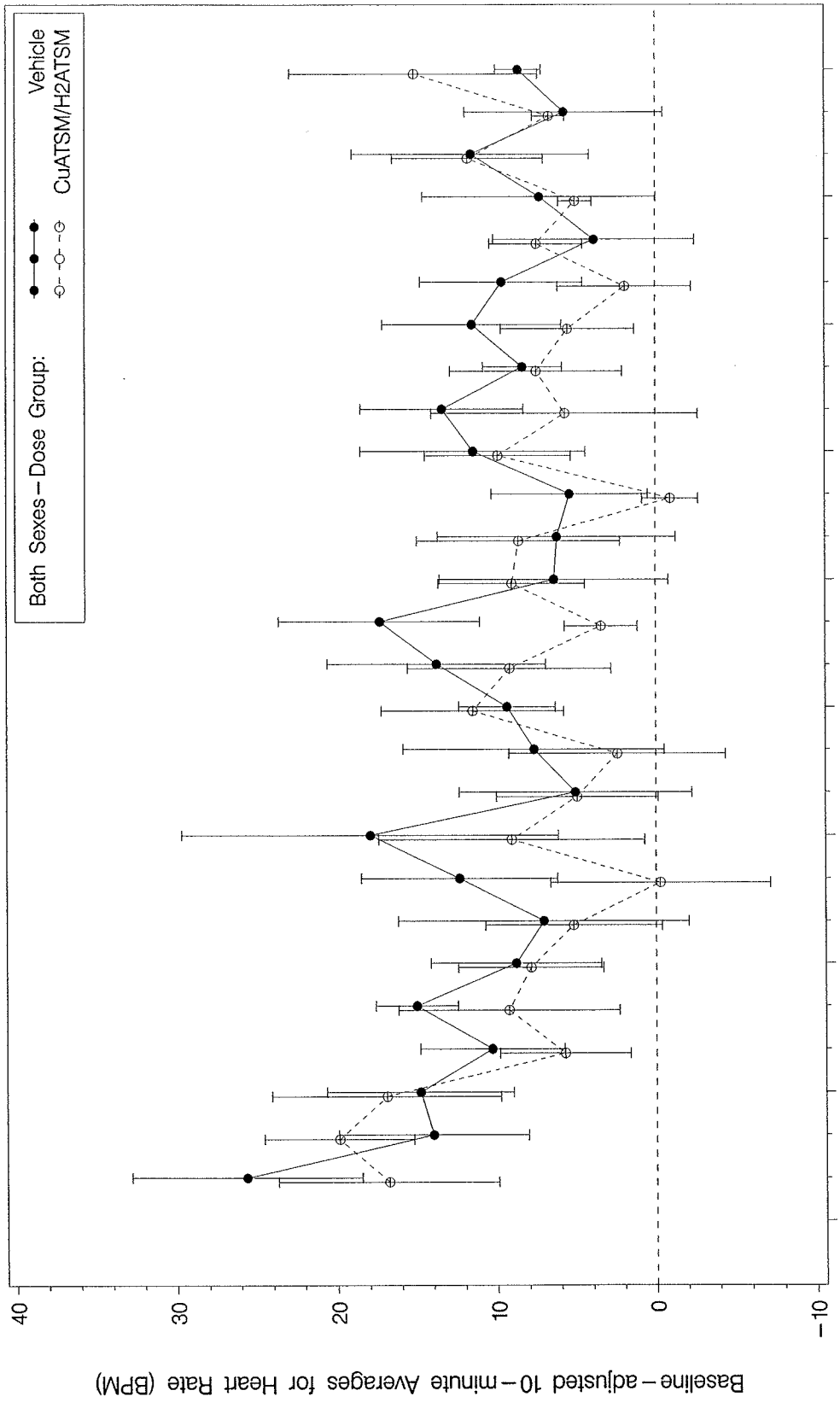


Figure 4. **Heart Rate (BPM), Both Sexes, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

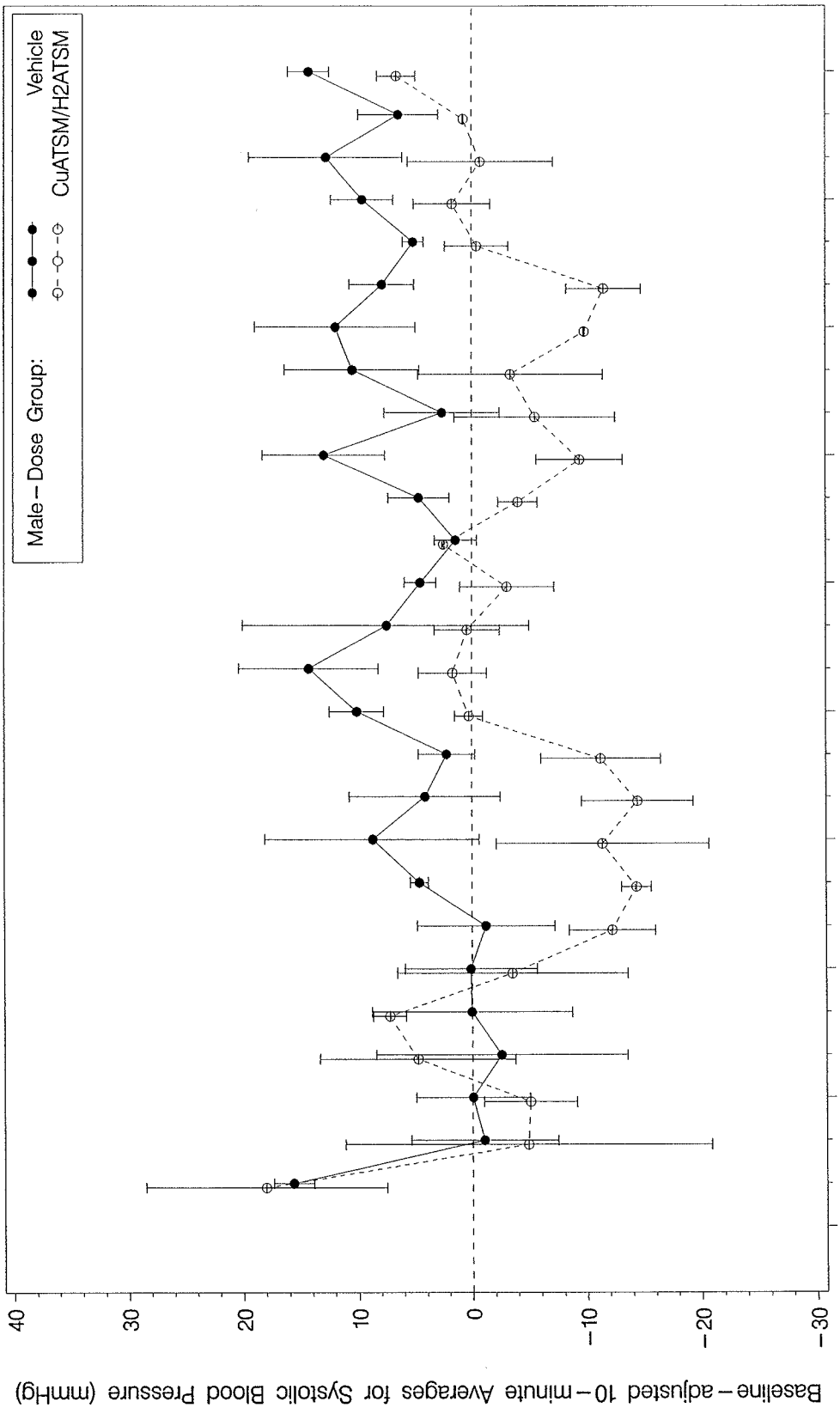


Figure 5. **Systolic Blood Pressure (mmHg), Male Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

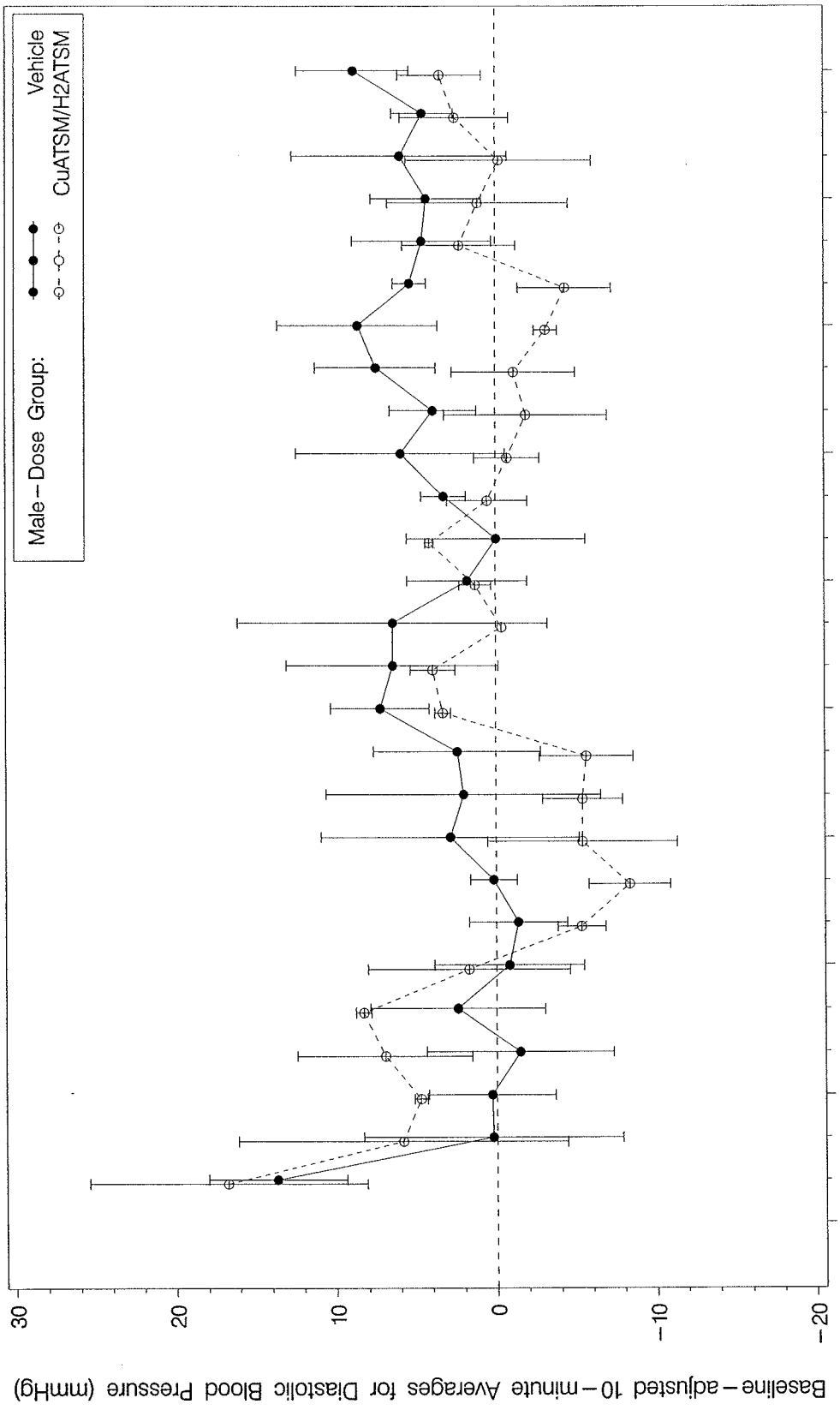


Figure 6. **Diastolic Blood Pressure (mmHg), Male Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with $CuATSM/H_2ATSM$ or Vehicle**

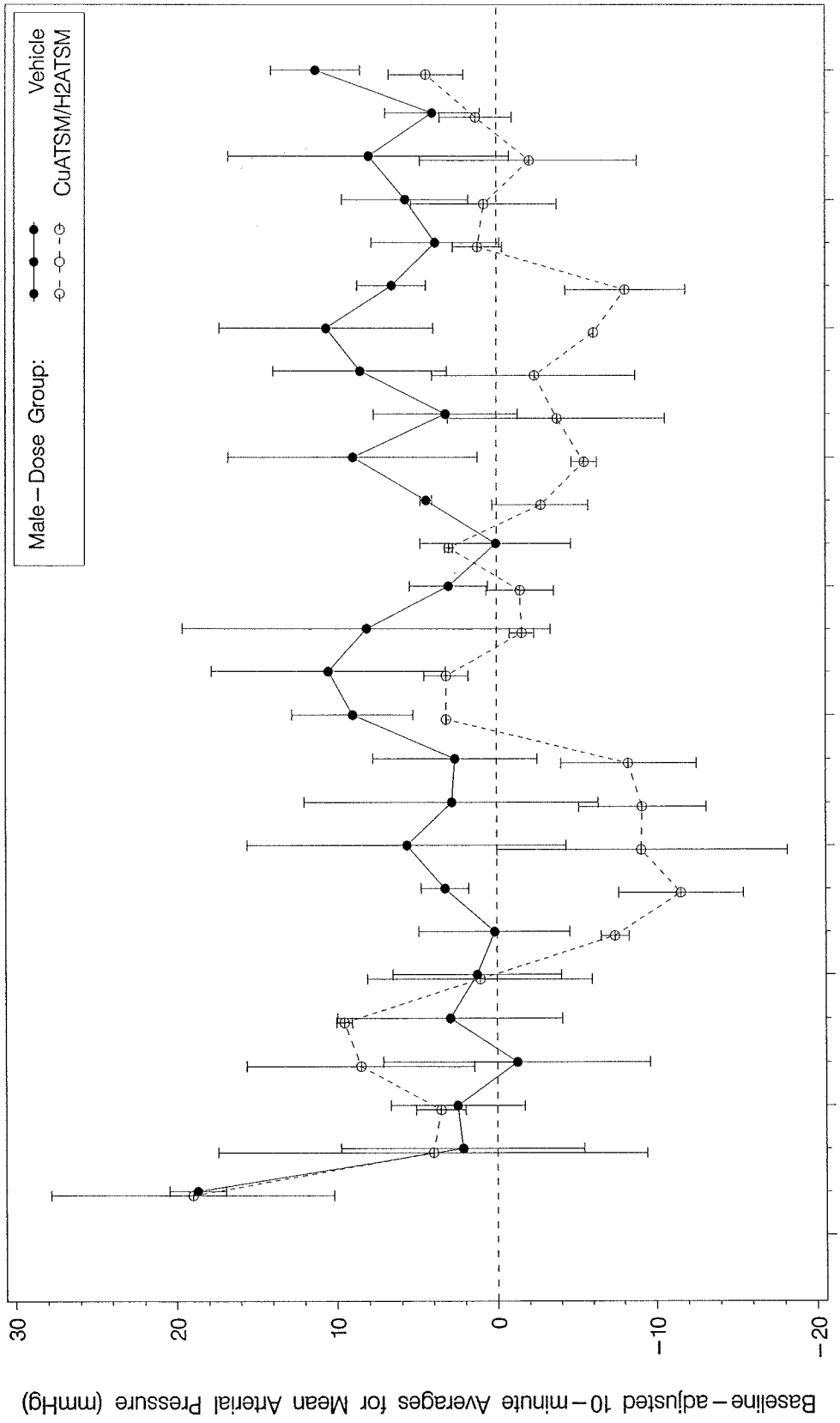


Figure 7. **Mean Arterial Pressure (mmHg), Male Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

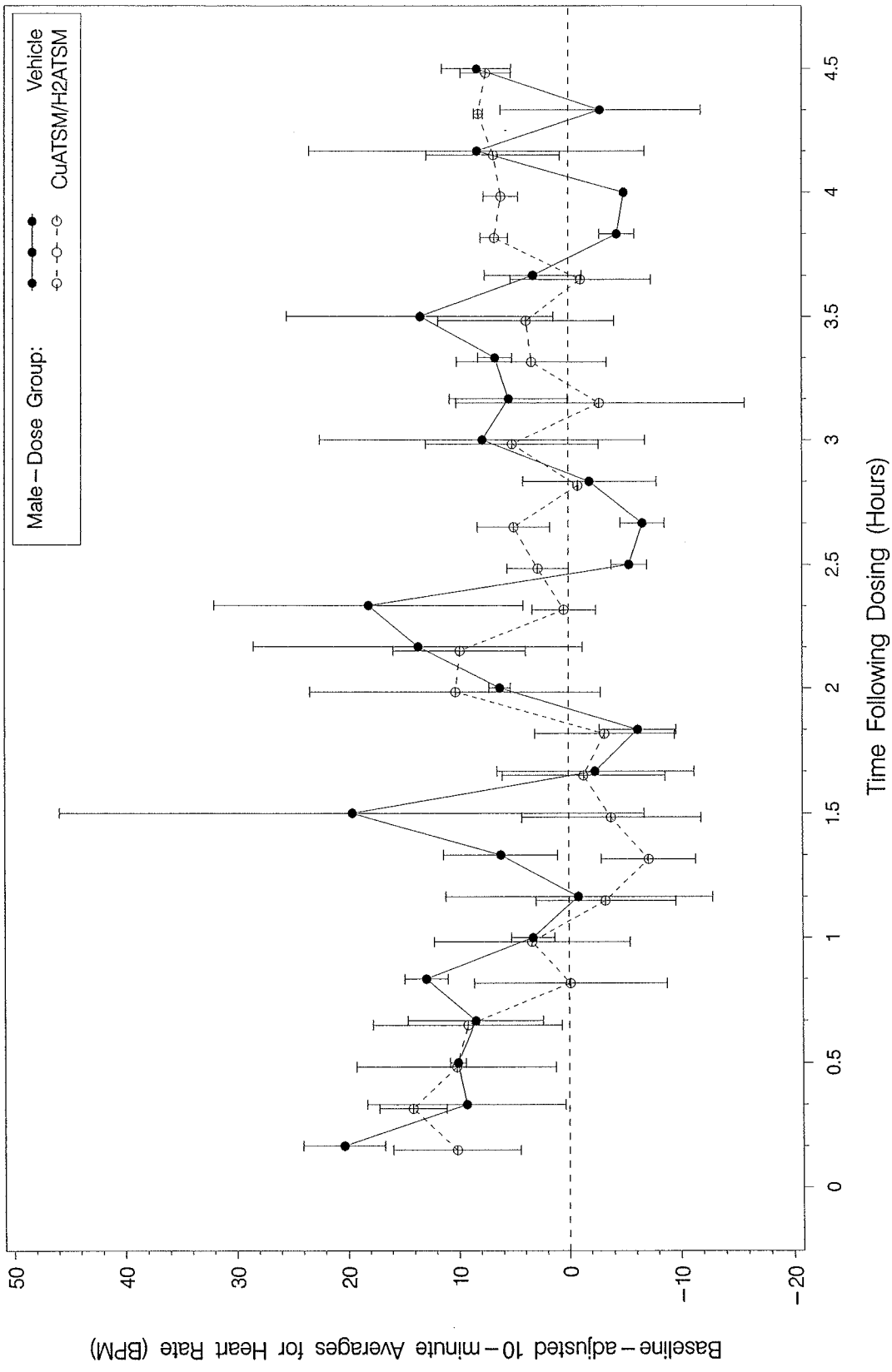


Figure 8. **Heart Rate (BPM), Male Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

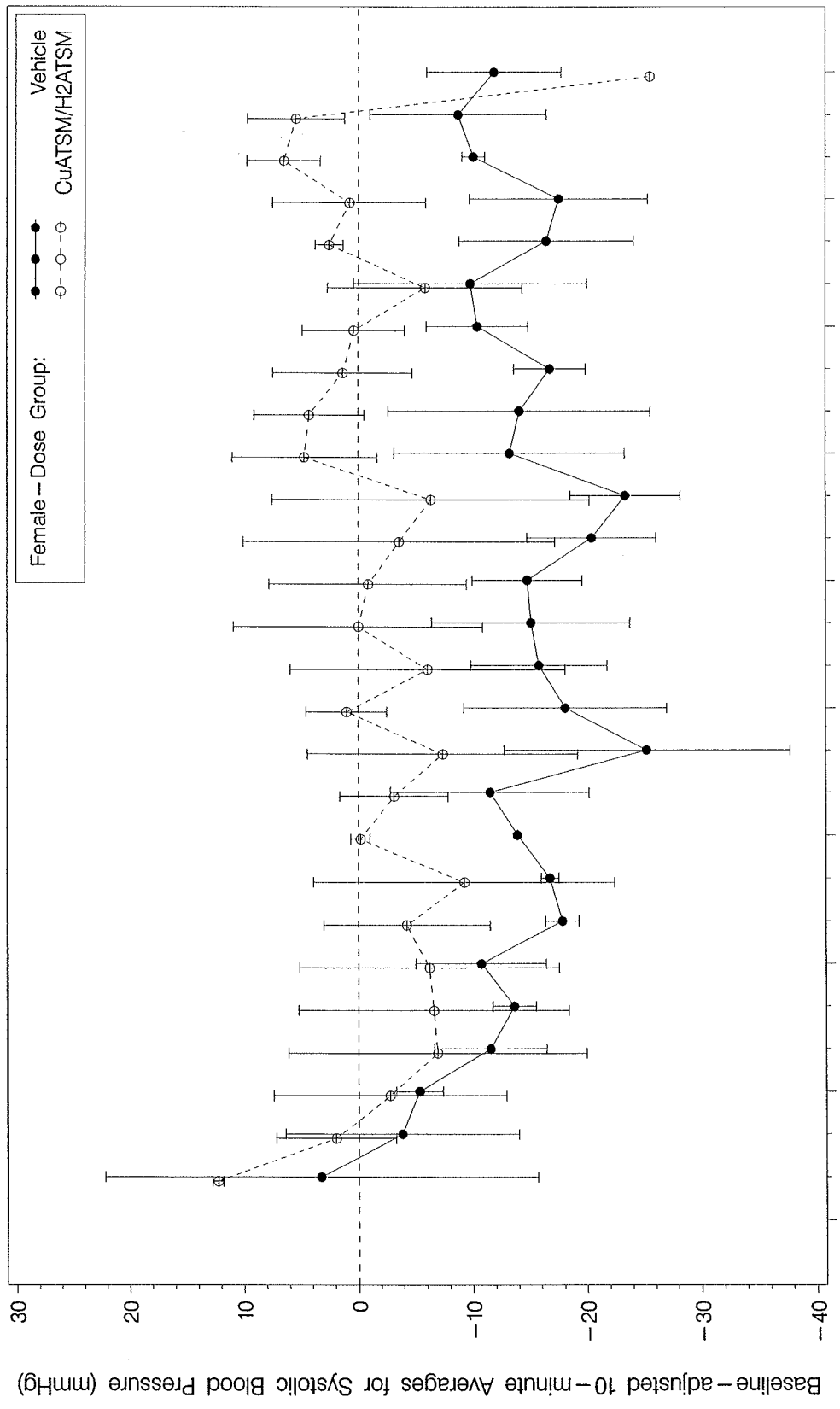


Figure 9. **Systolic Blood Pressure (mmHg), Female Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

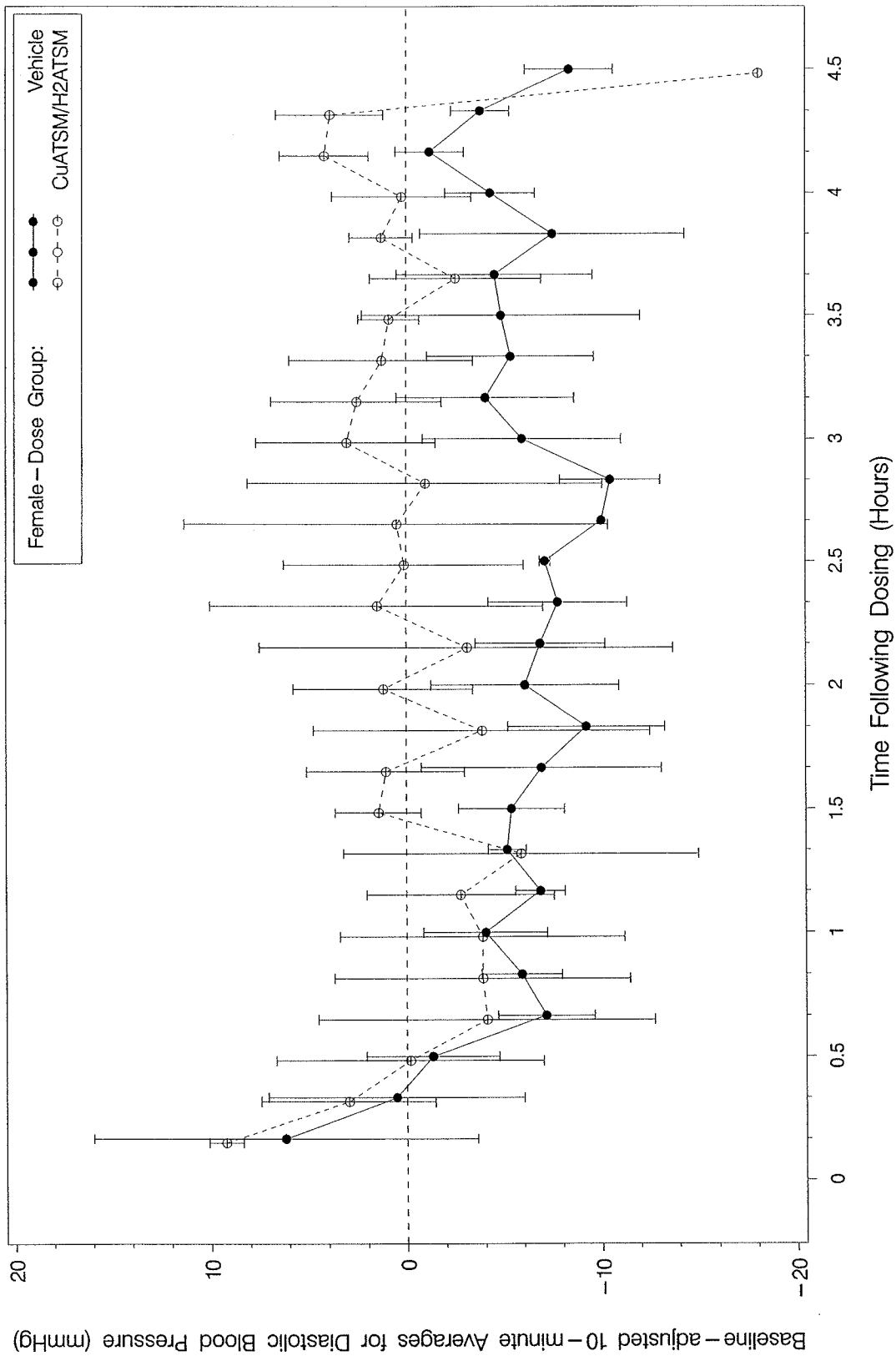


Figure 10. **Diastolic Blood Pressure (mmHg), Female Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

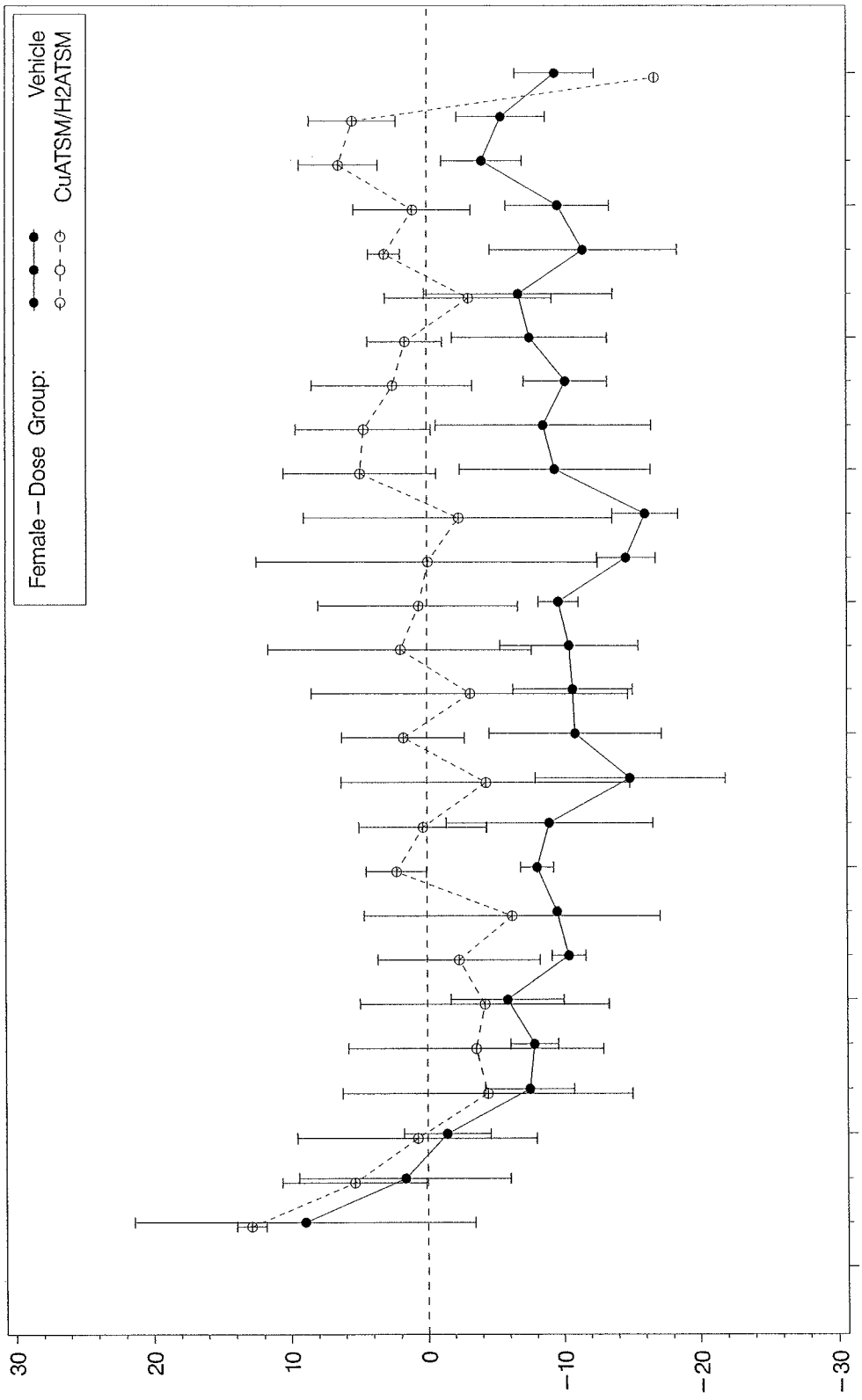


Figure 11. **Mean Arterial Pressure (mmHg), Female Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with $CuATSM/H_2ATSM$ or Vehicle**

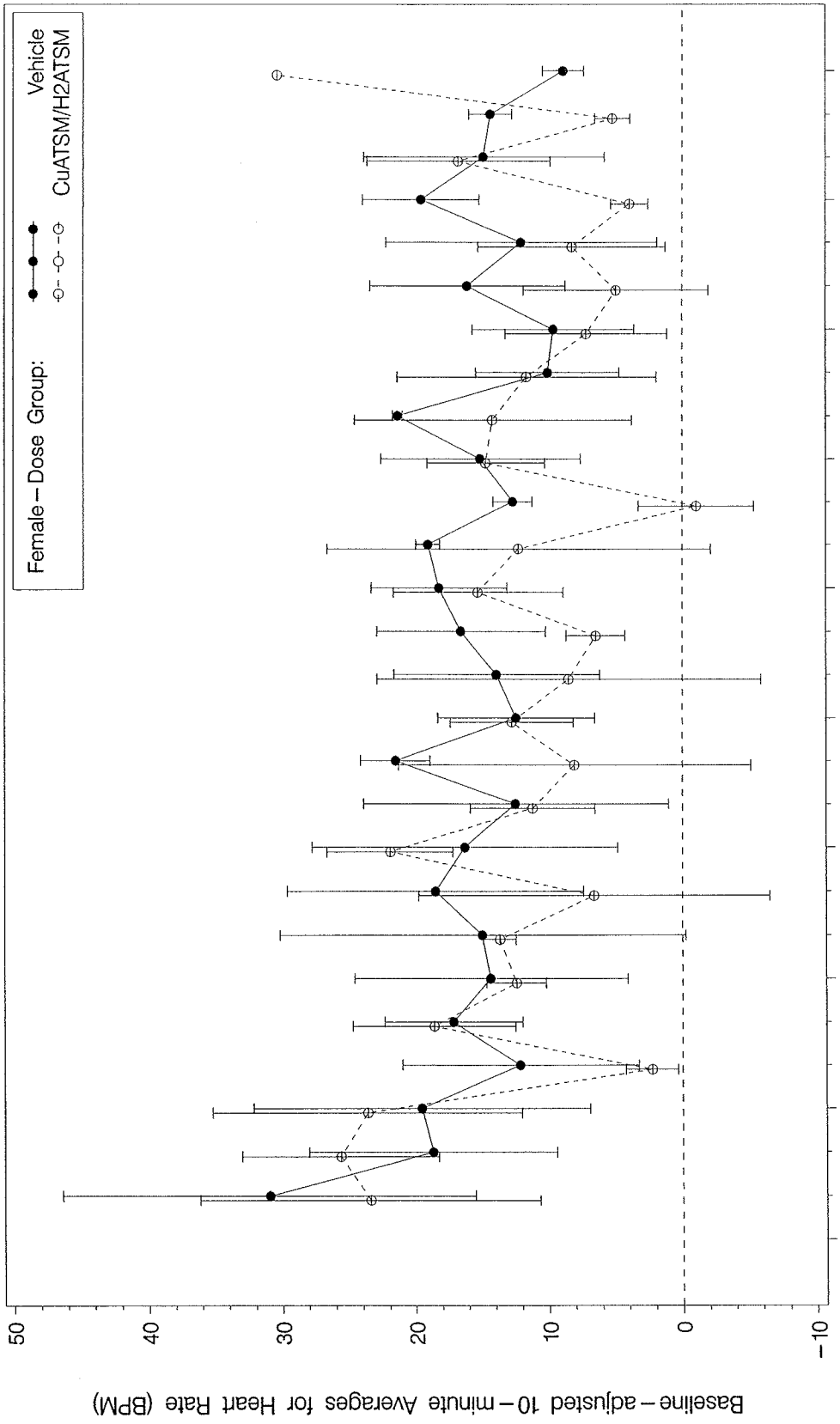


Figure 12. Heart Rate (BPM), Female Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

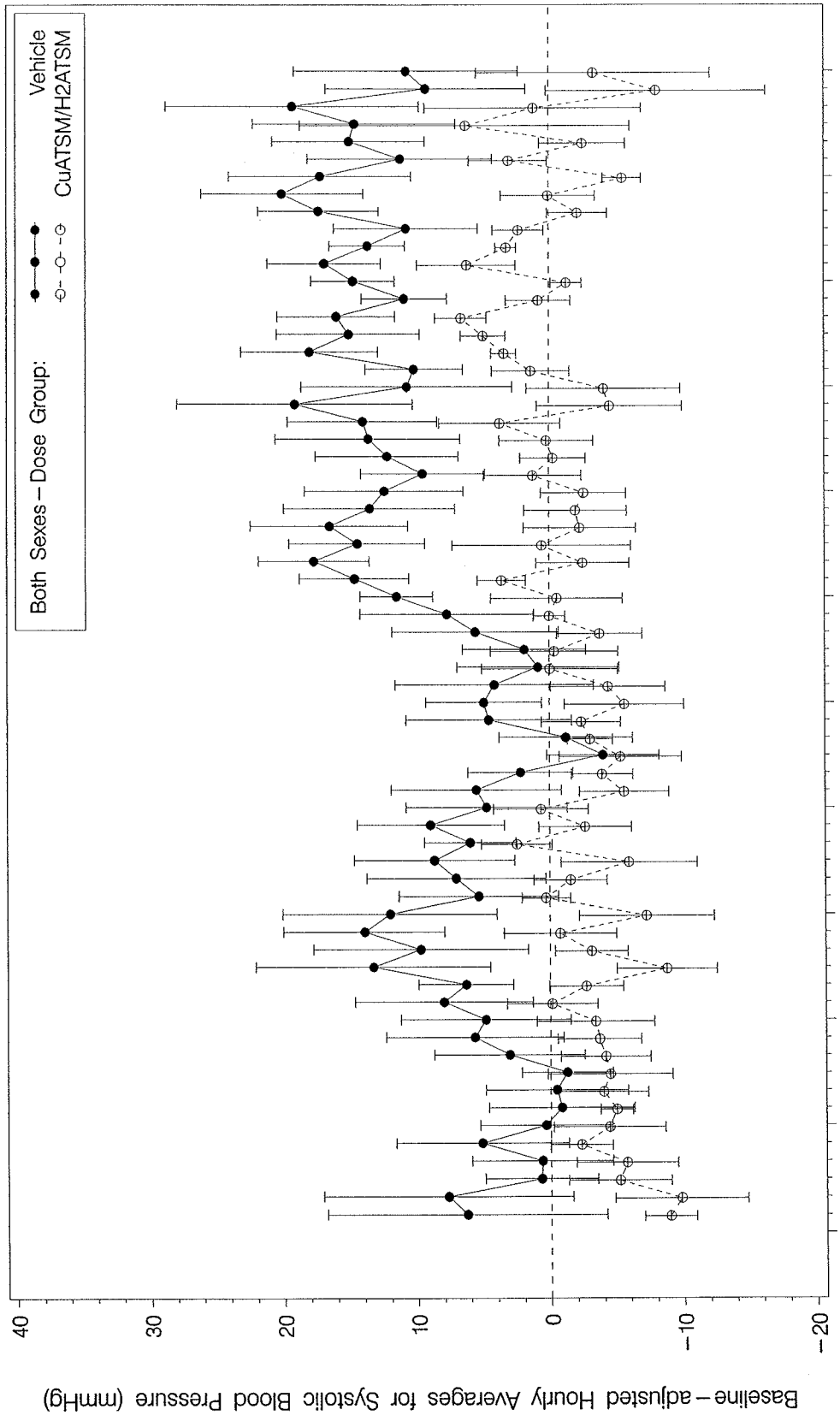


Figure 13. **Systolic Blood Pressure (mmHg), Both Sexes, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle**

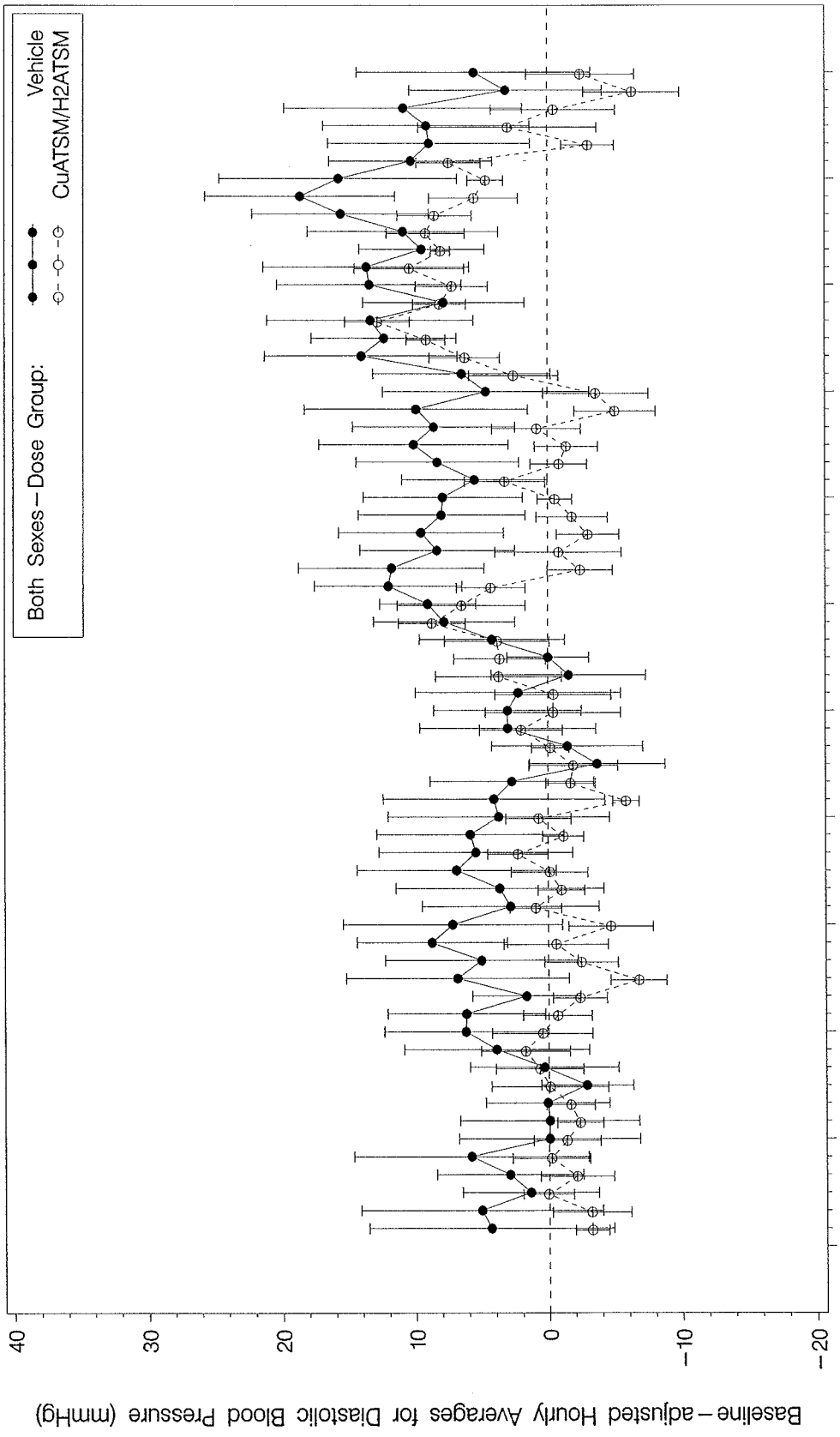


Figure 14. **Diastolic Blood Pressure (mmHg), Both Sexes, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle**

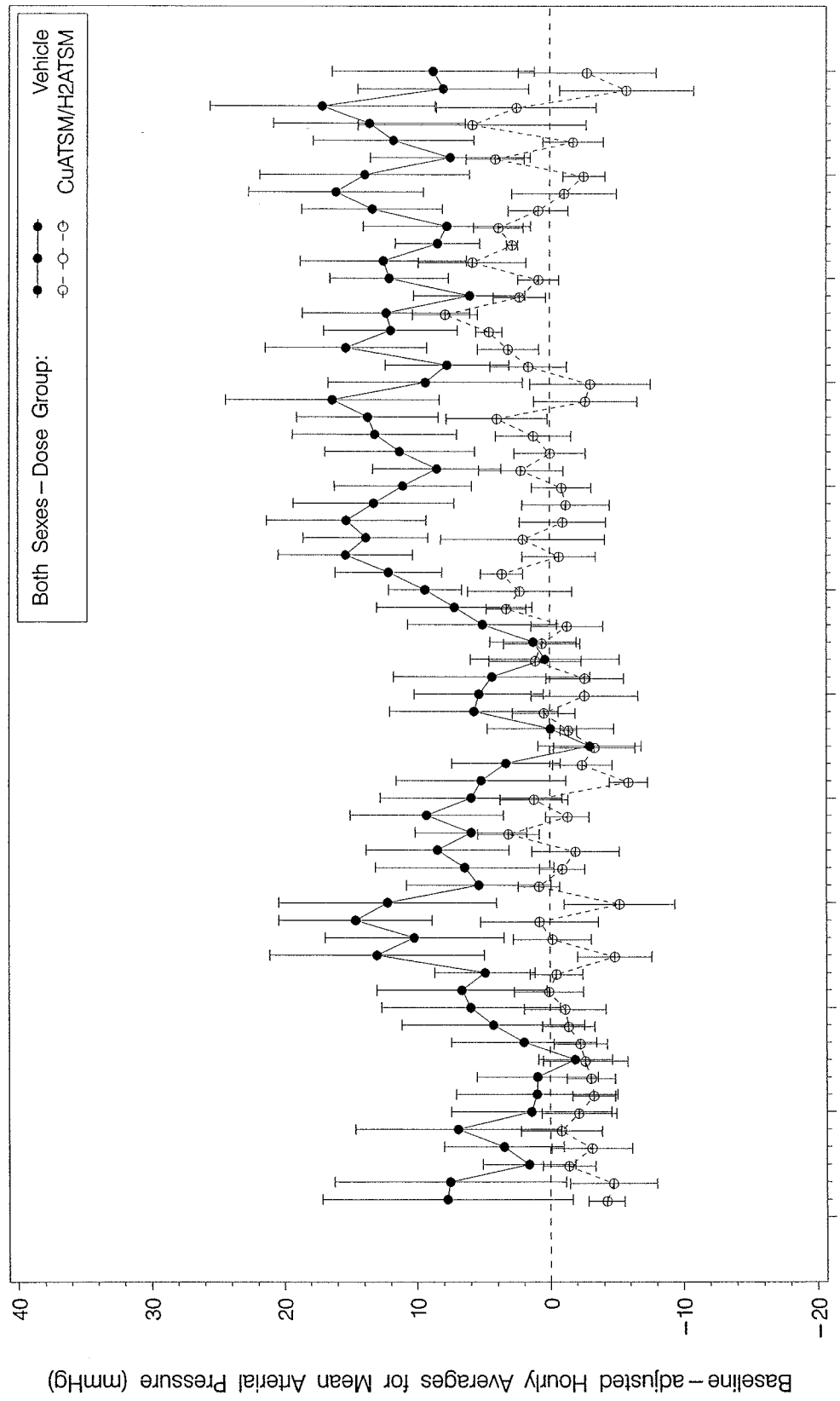


Figure 15. **Mean Arterial Pressure (mmHg), Both Sexes, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H$_2$ATSM or Vehicle**

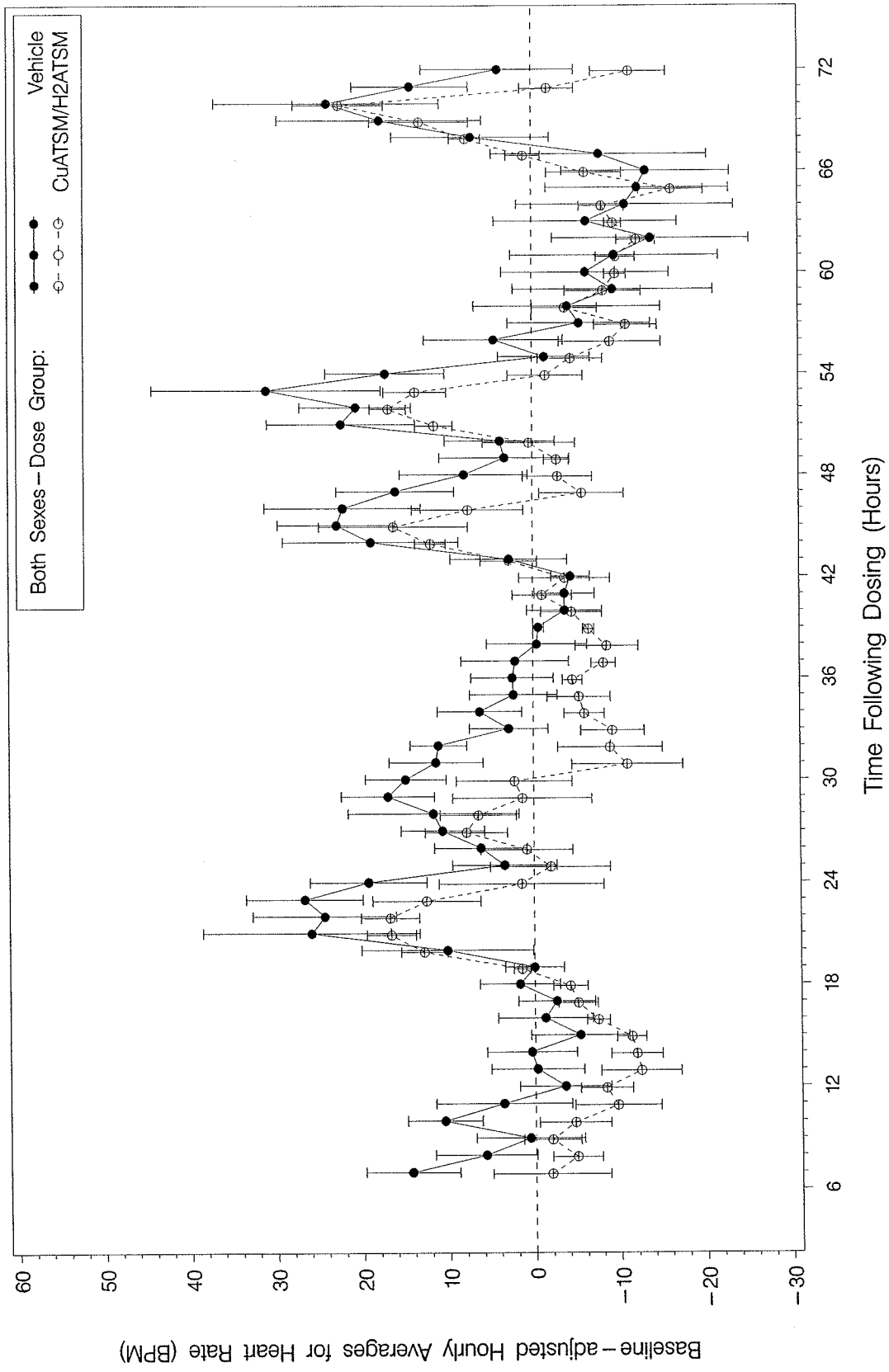


Figure 16. Heart Rate (BPM), Both Sexes, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle

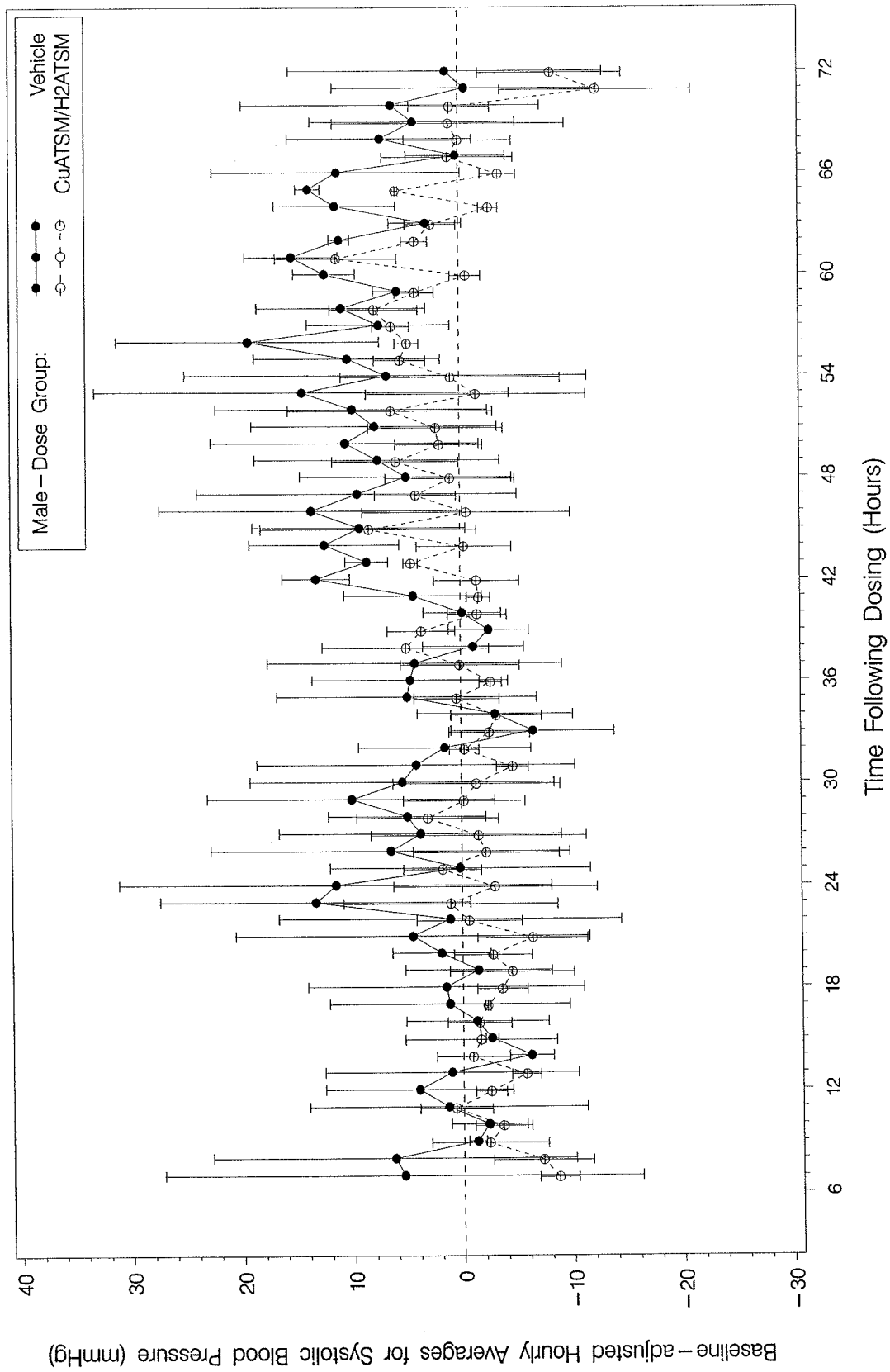


Figure 17. **Systolic Blood Pressure (mmHg), Male Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle**

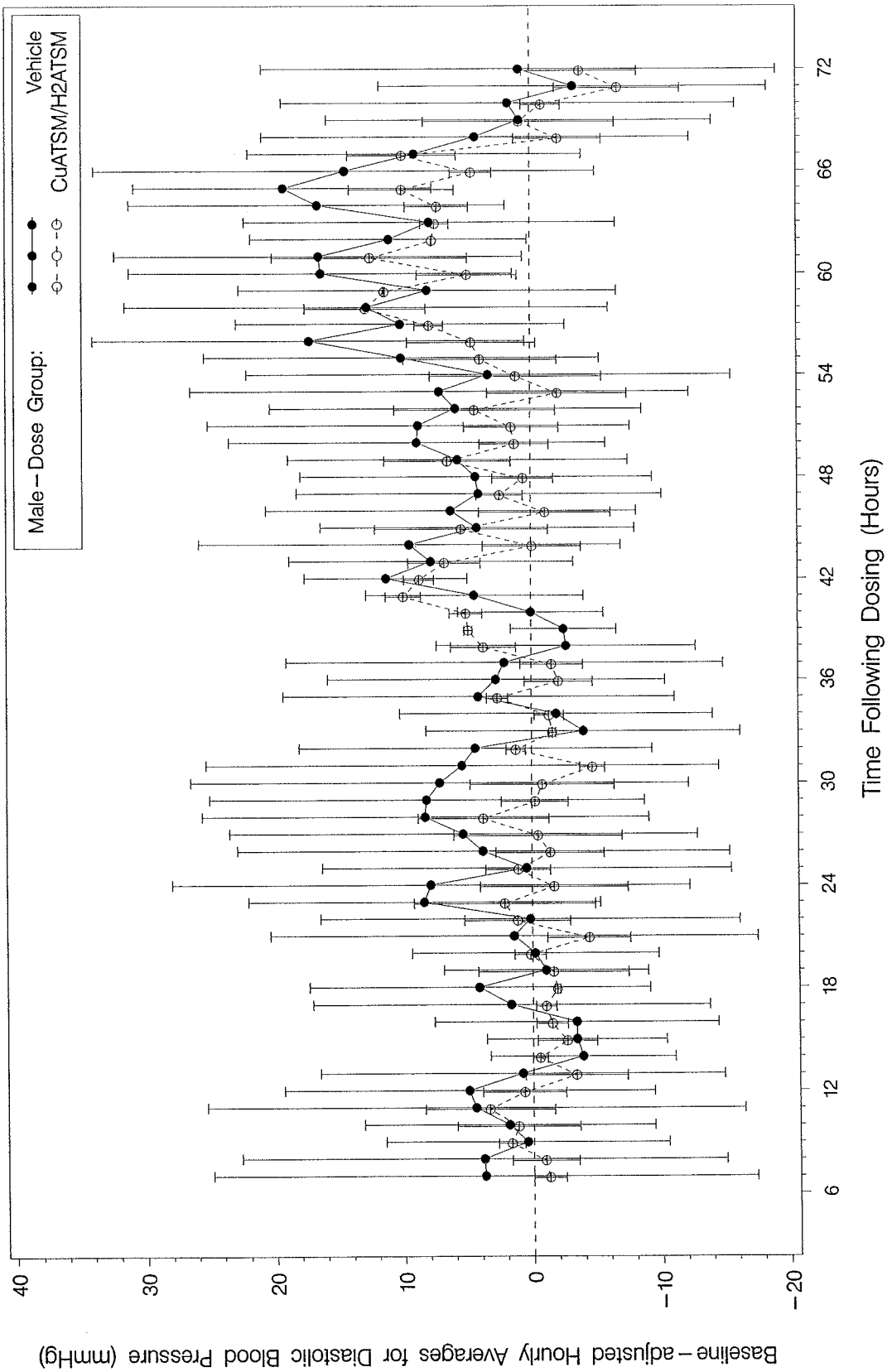


Figure 18. **Diastolic Blood Pressure (mmHg), Male Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle**

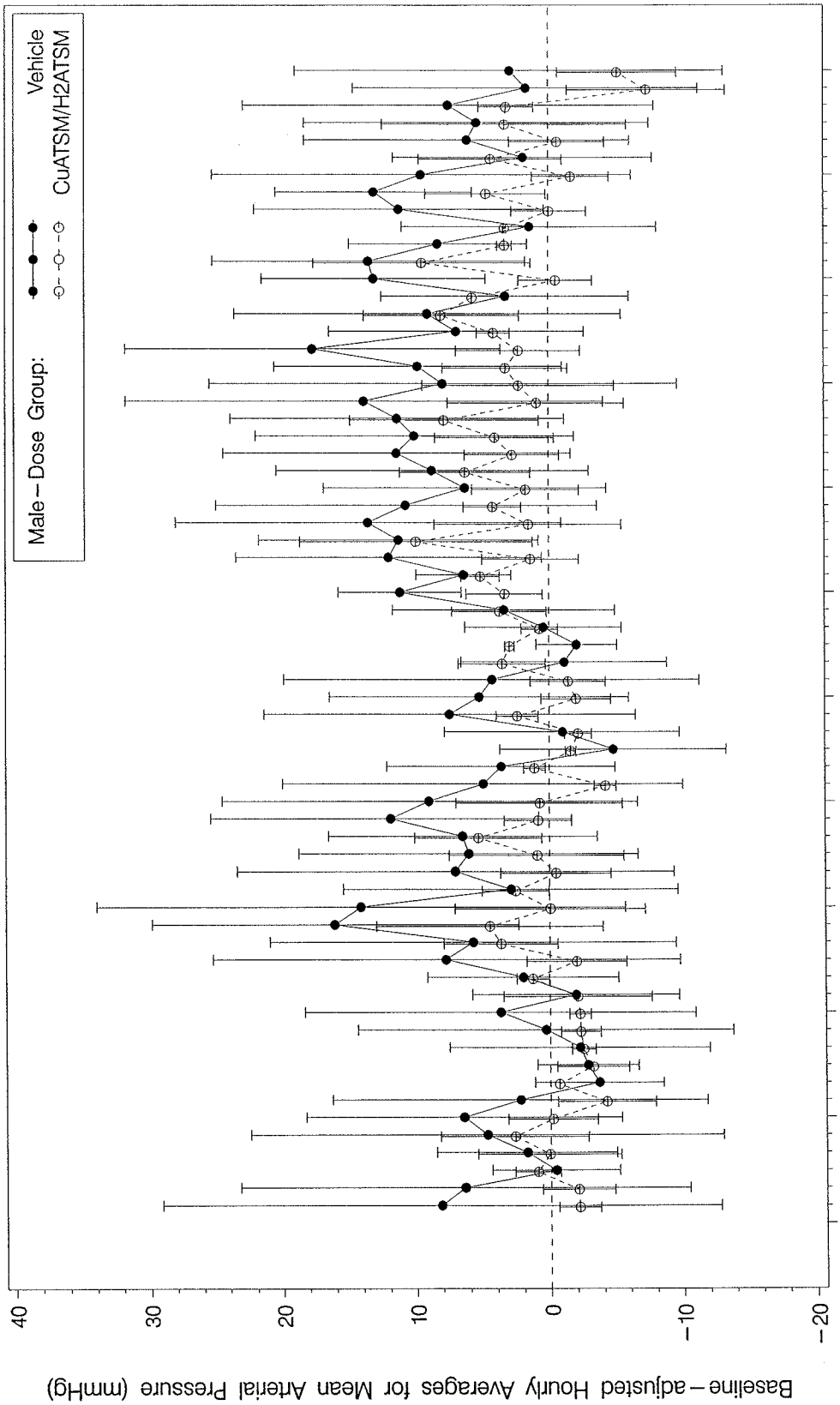


Figure 19. **Mean Arterial Pressure (mmHg), Male Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle**

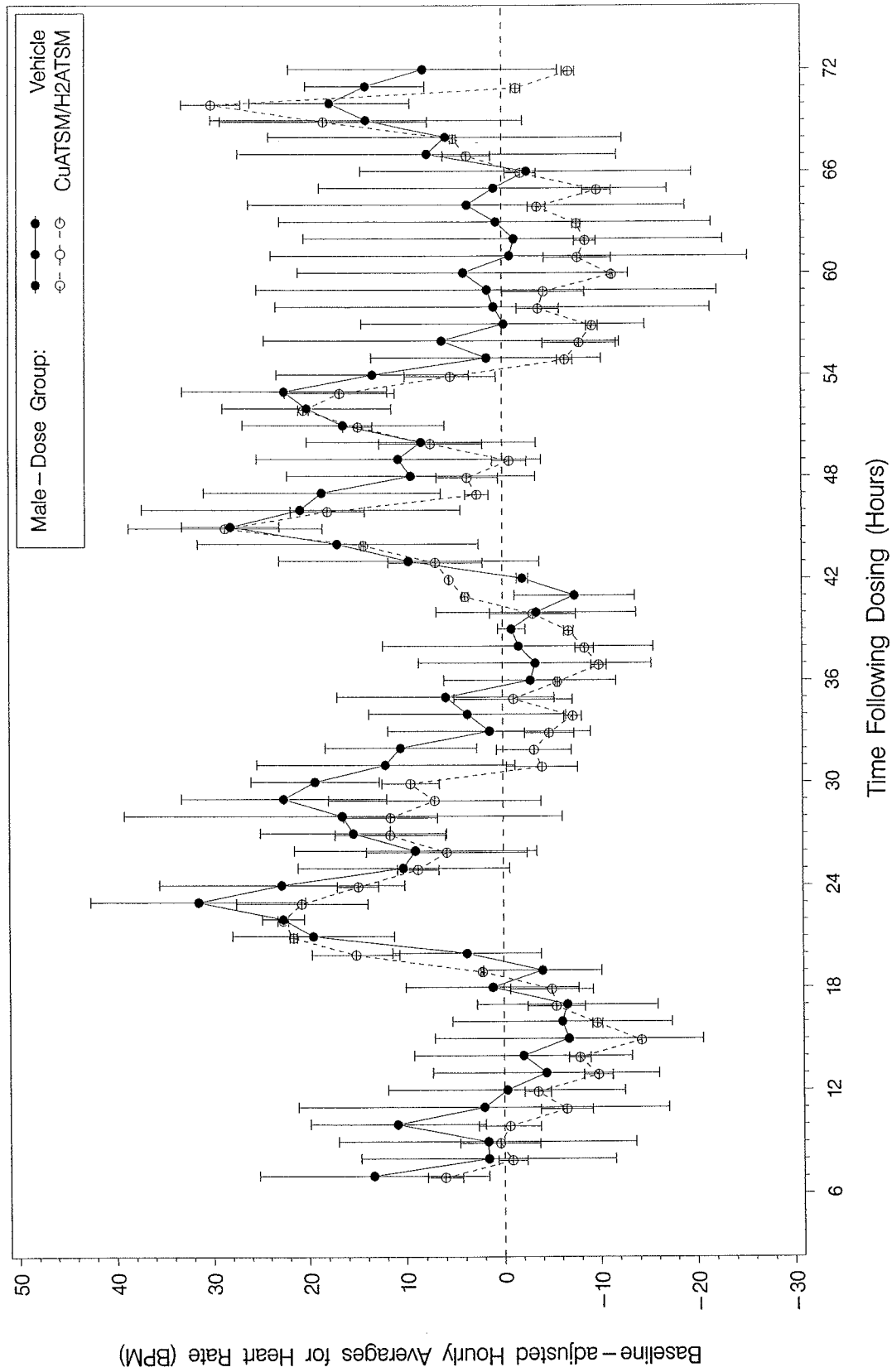


Figure 20. **Heart Rate (BPM), Male Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle**

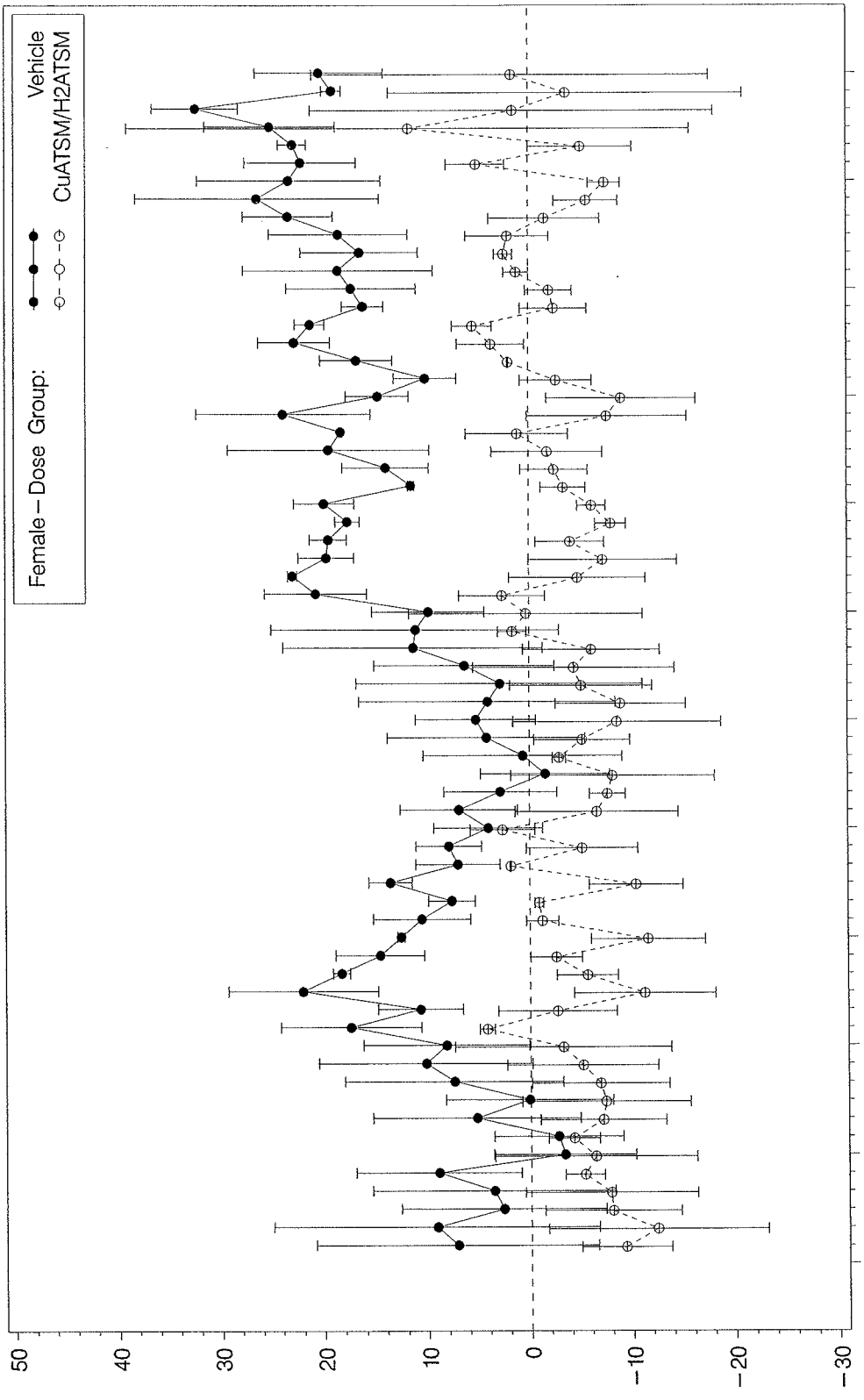


Figure 21. **Systolic Blood Pressure (mmHg), Female Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle**

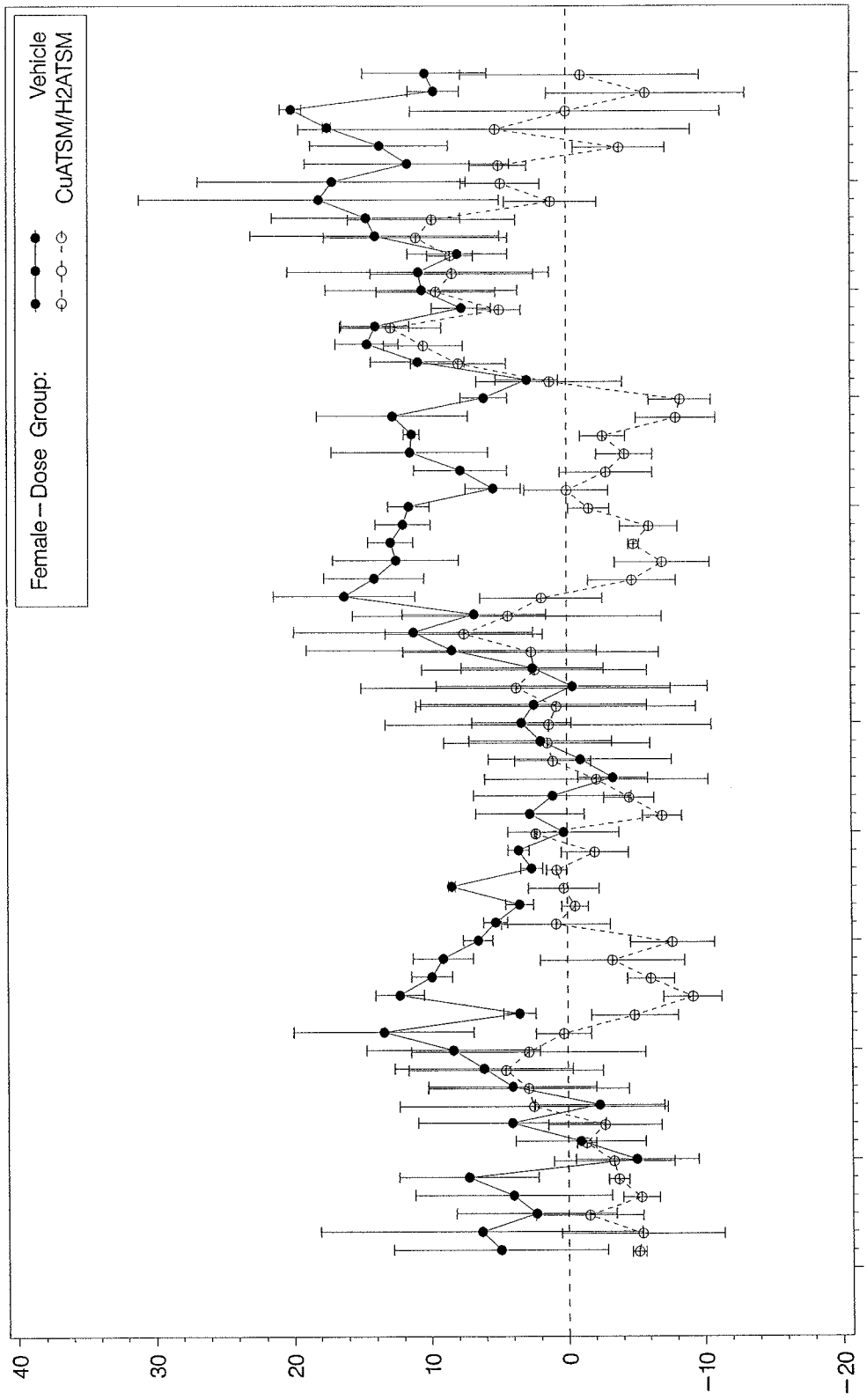


Figure 22. **Diastolic Blood Pressure (mmHg), Female Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle**

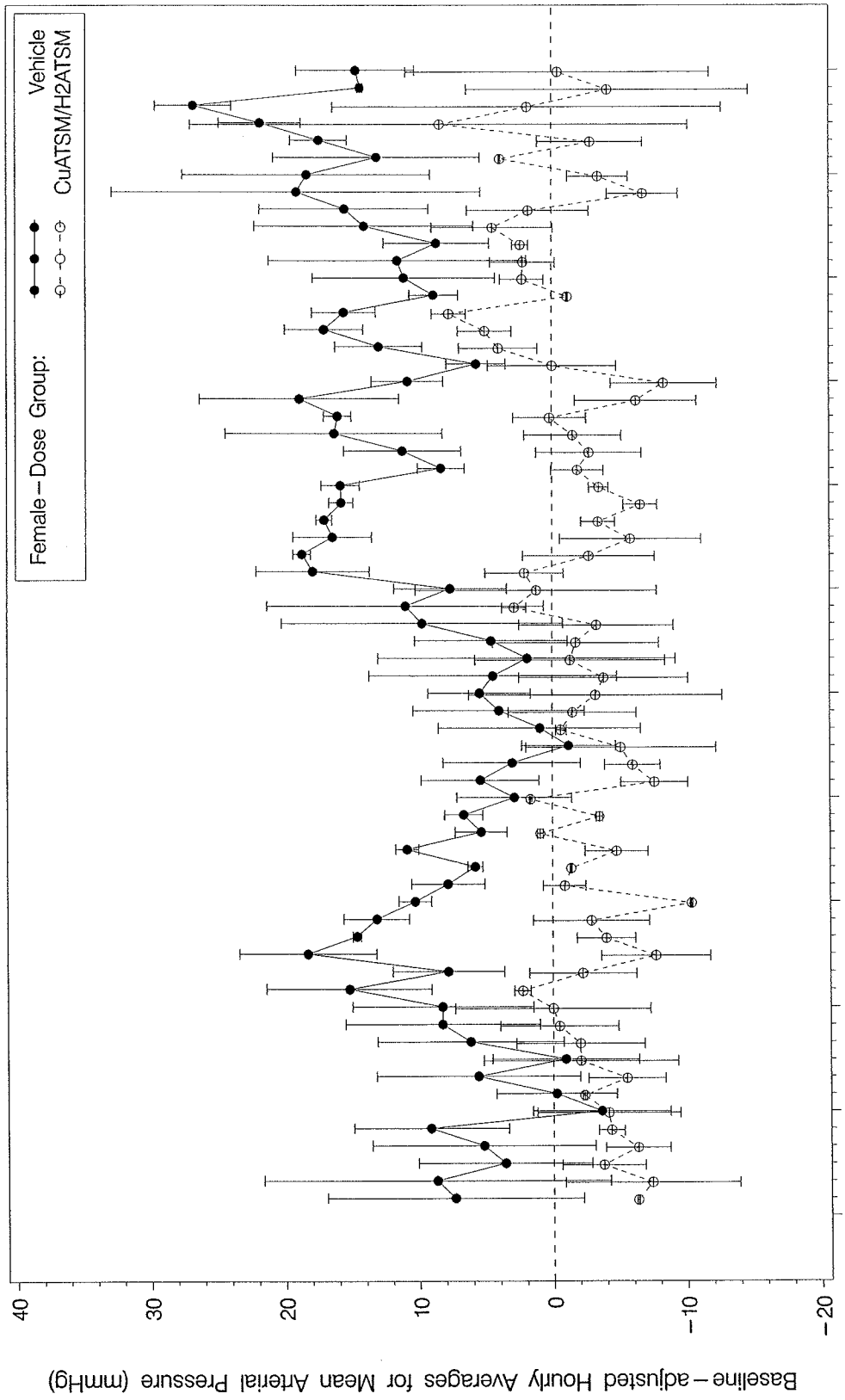


Figure 23. **Mean Arterial Pressure (mmHg), Female Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle**

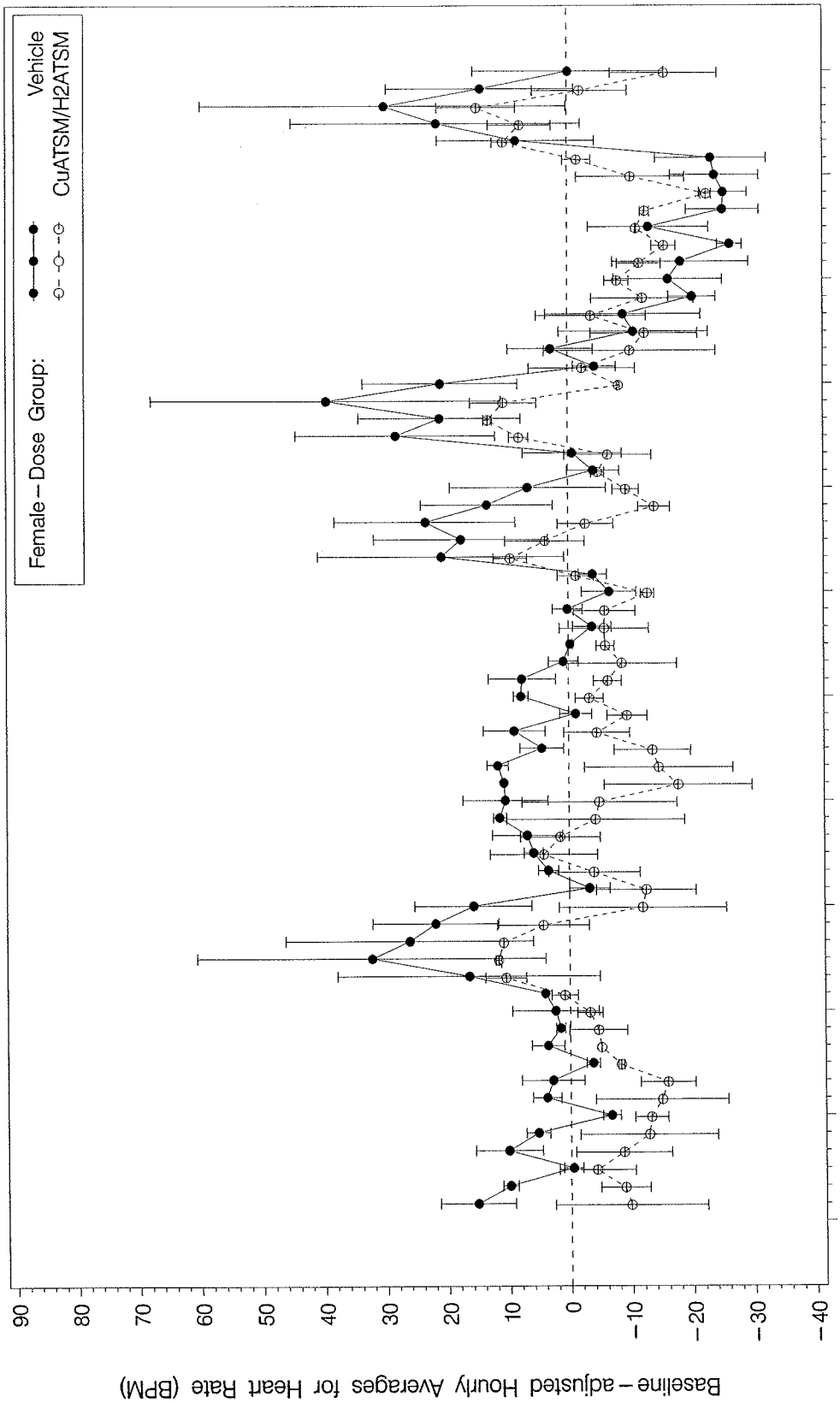


Figure 24. **Heart Rate (BPM), Female Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle**

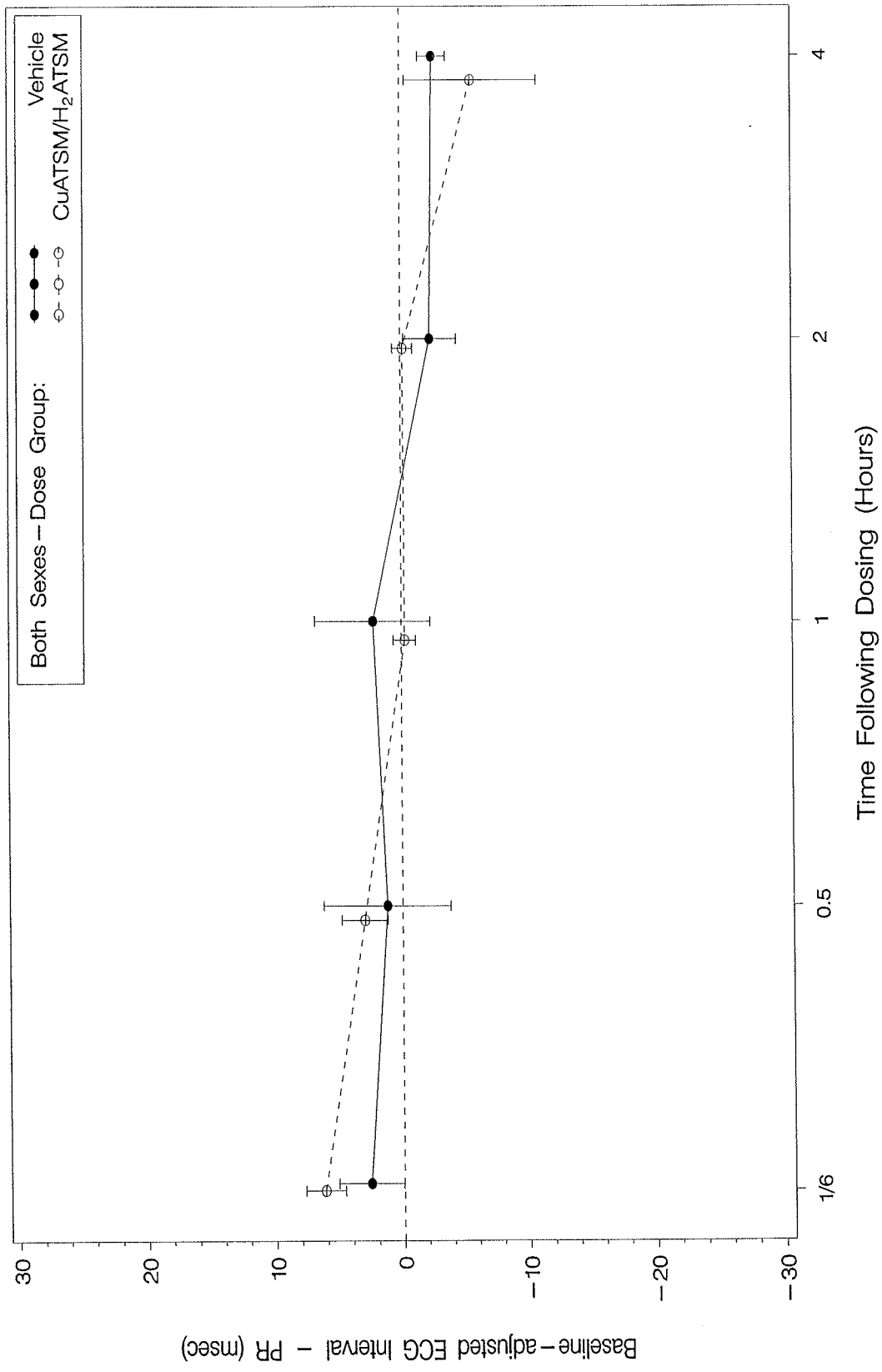


Figure 25. **PR Interval (msec), Both Sexes, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

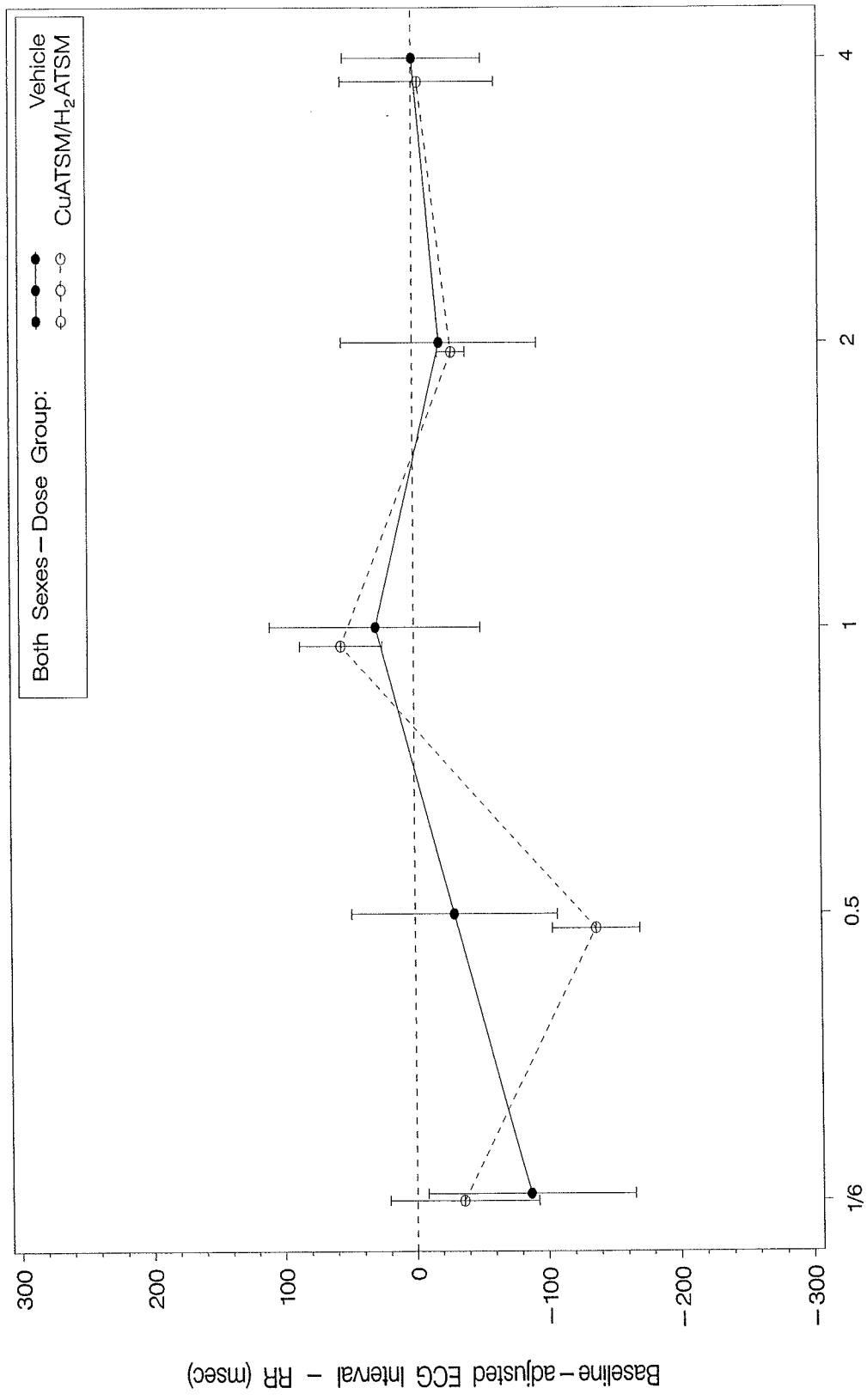


Figure 26. **RR Interval (msec), Both Sexes, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

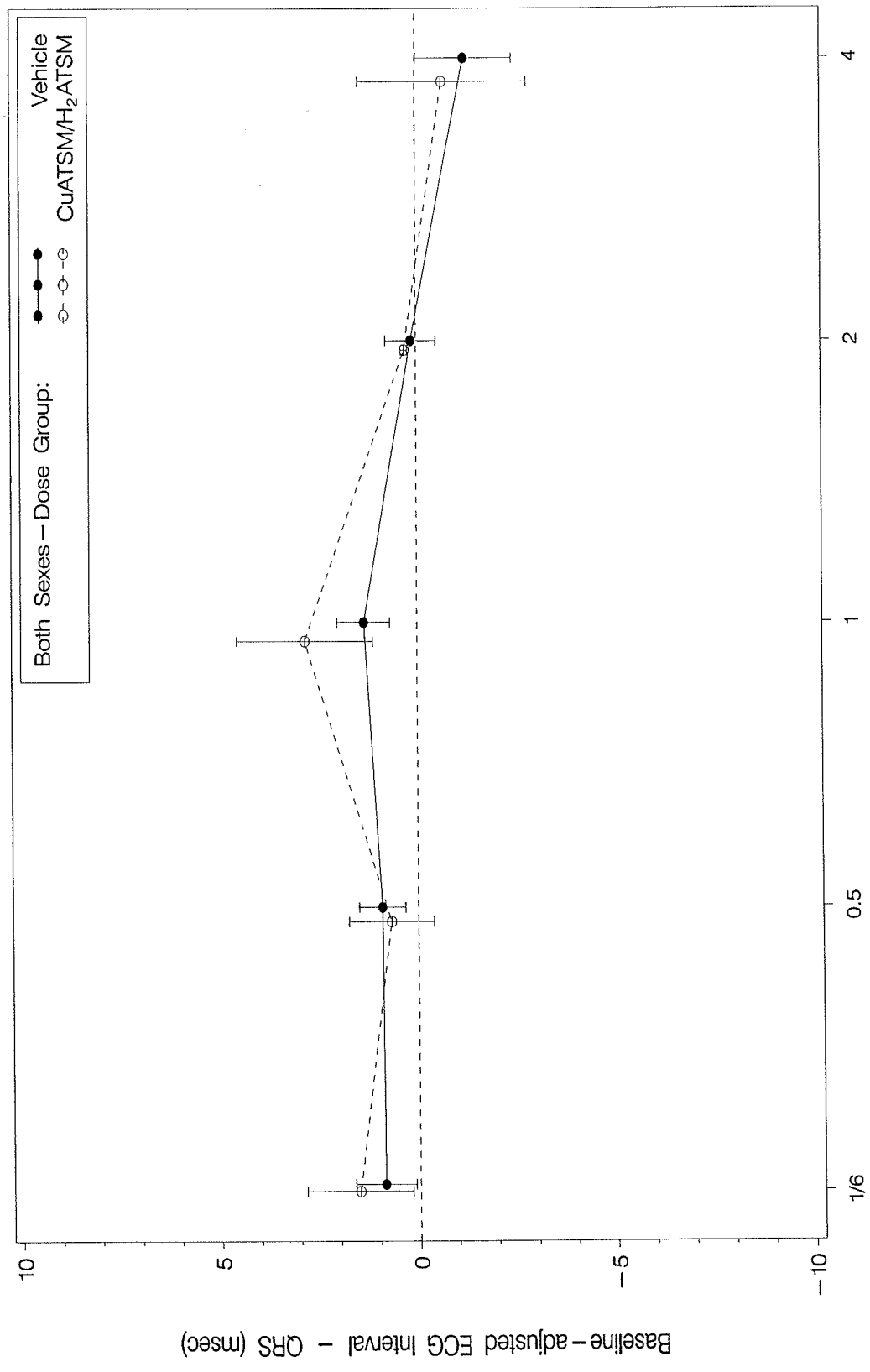


Figure 27. **QRS Interval (msec), Both Sexes, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

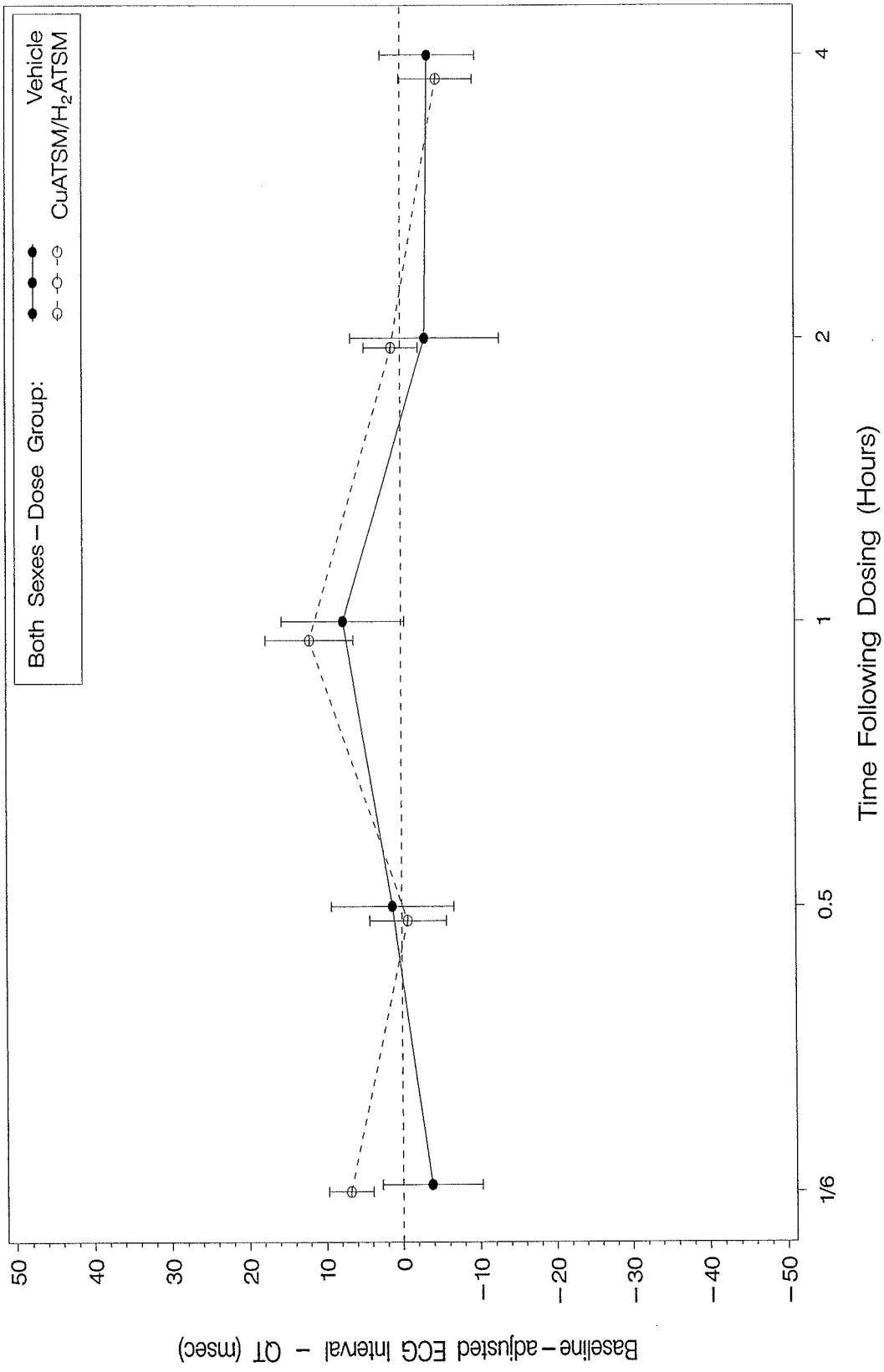


Figure 28. **QT Interval (msec), Both Sexes, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

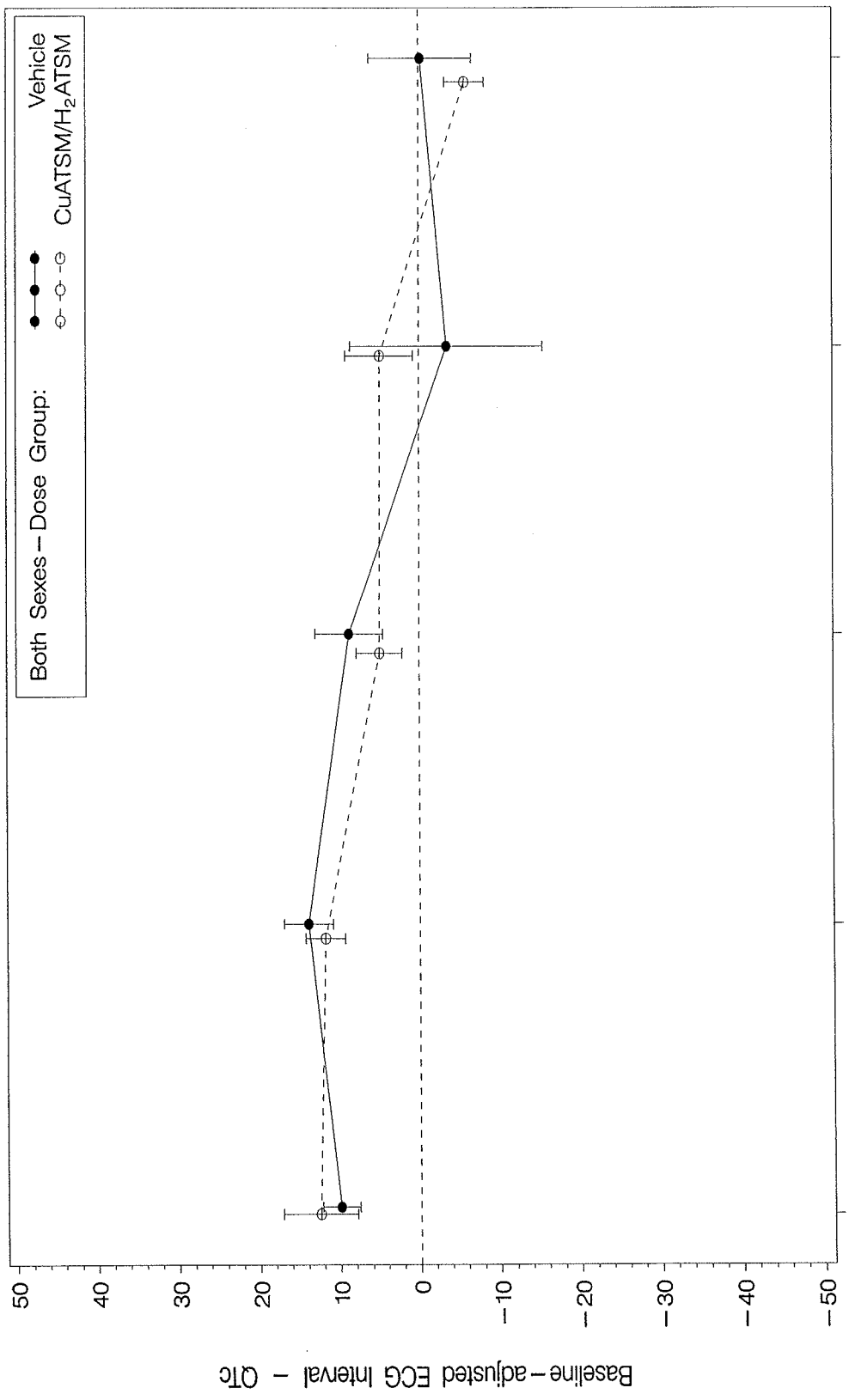


Figure 29. **Corrected QT Interval (QTc), Both Sexes, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

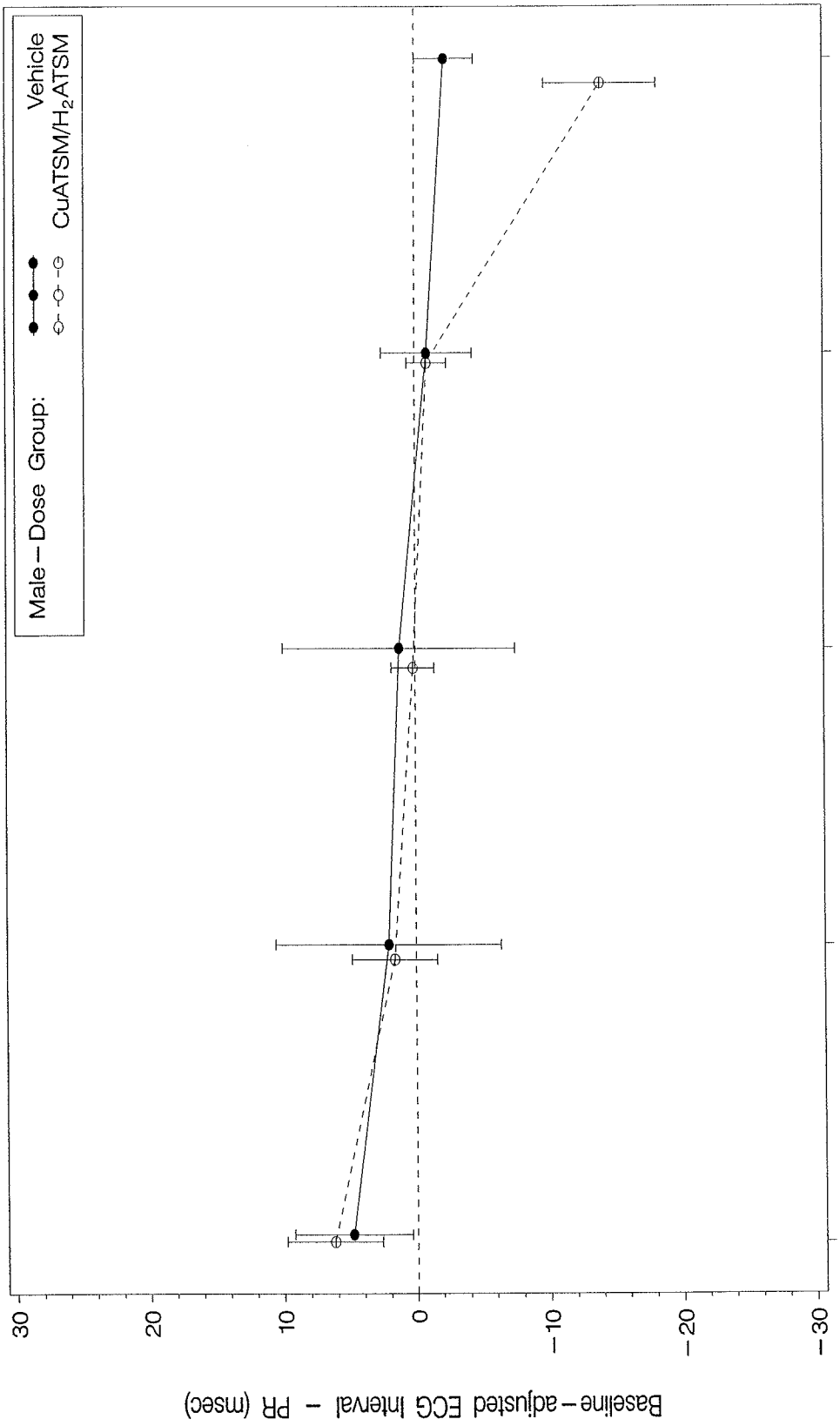


Figure 30. **PR Interval (msec), Male Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

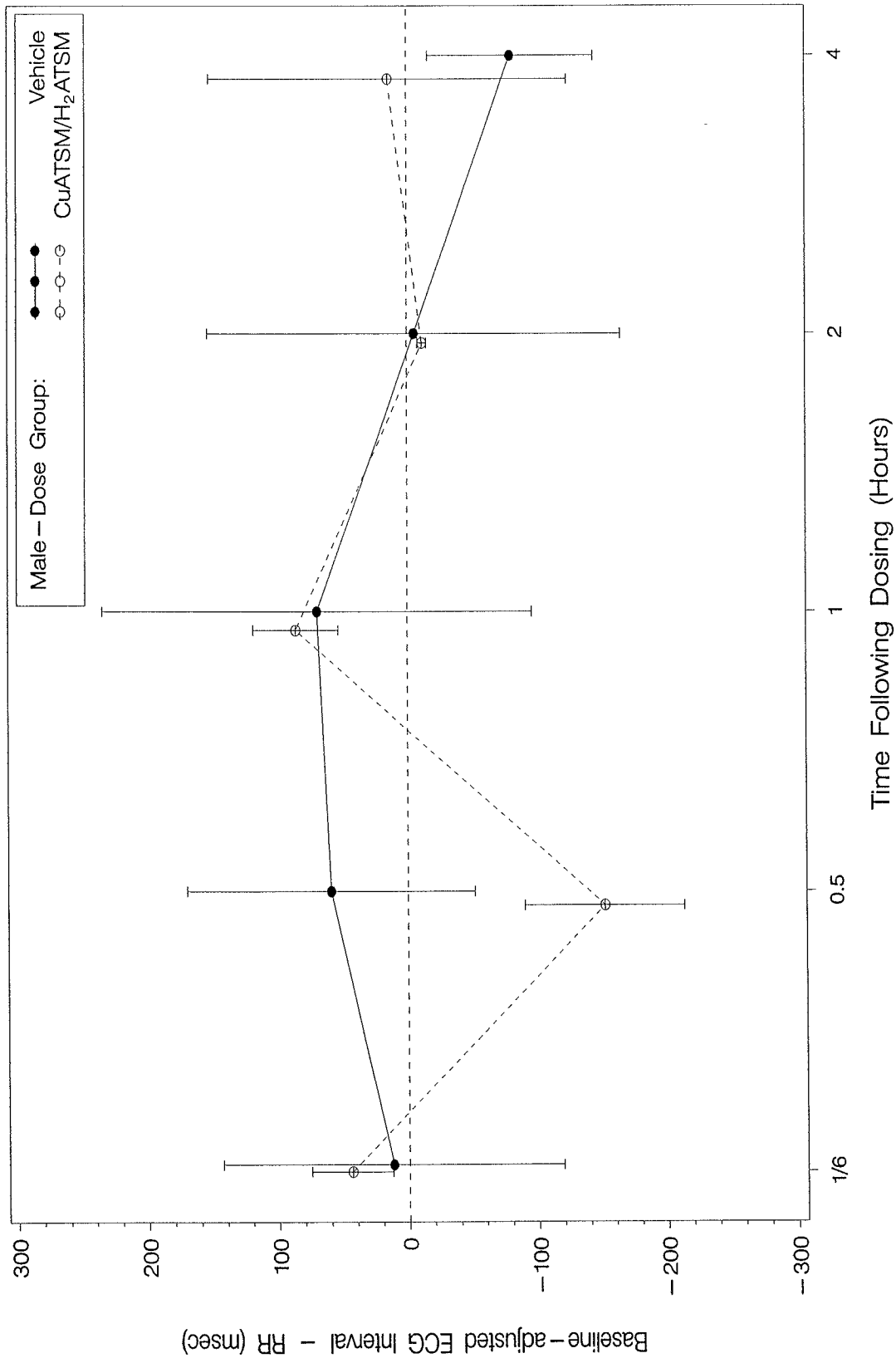


Figure 31. **RR Interval (msec), Male Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

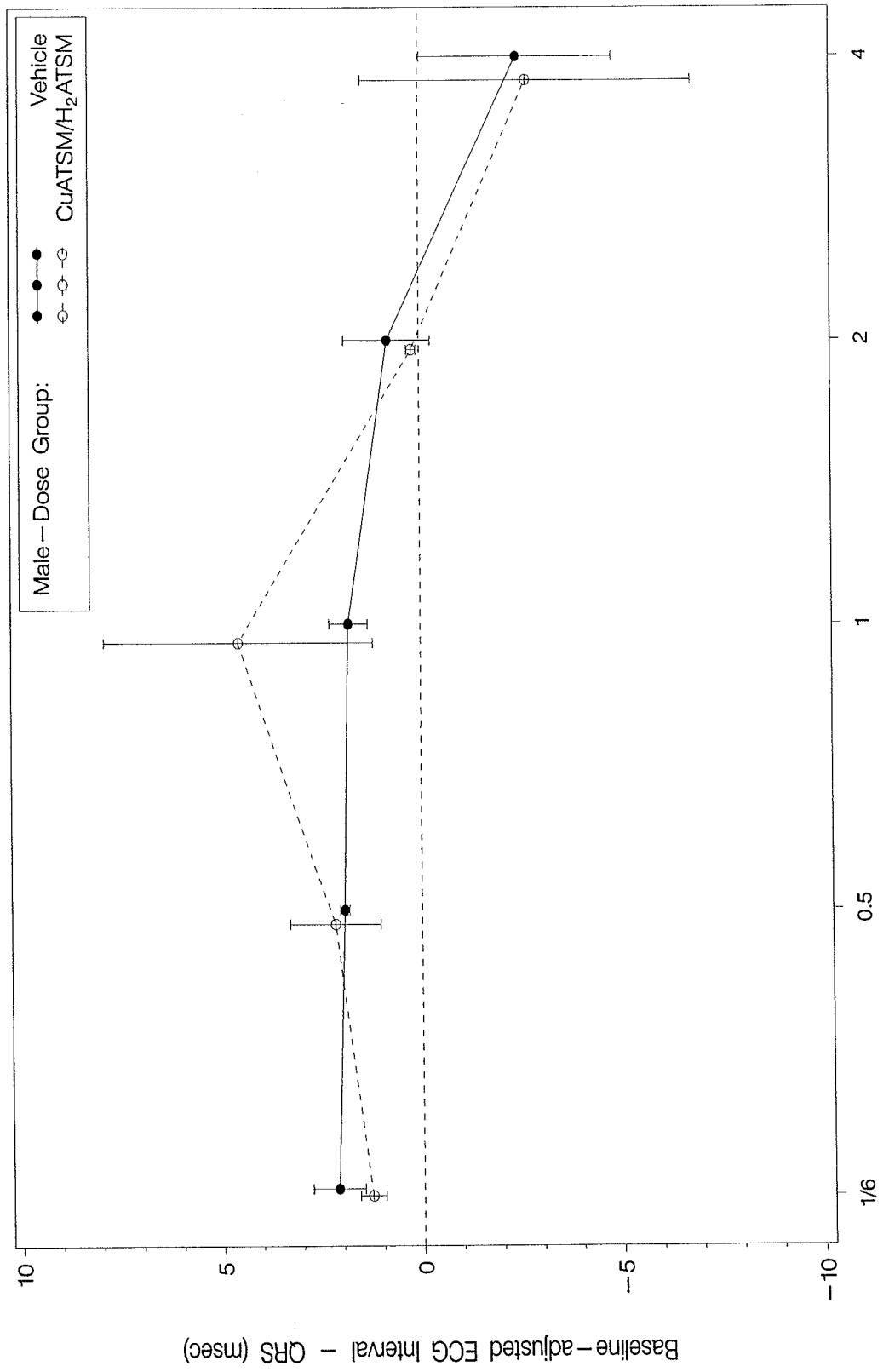


Figure 32. **QRS Interval (msec), Male Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

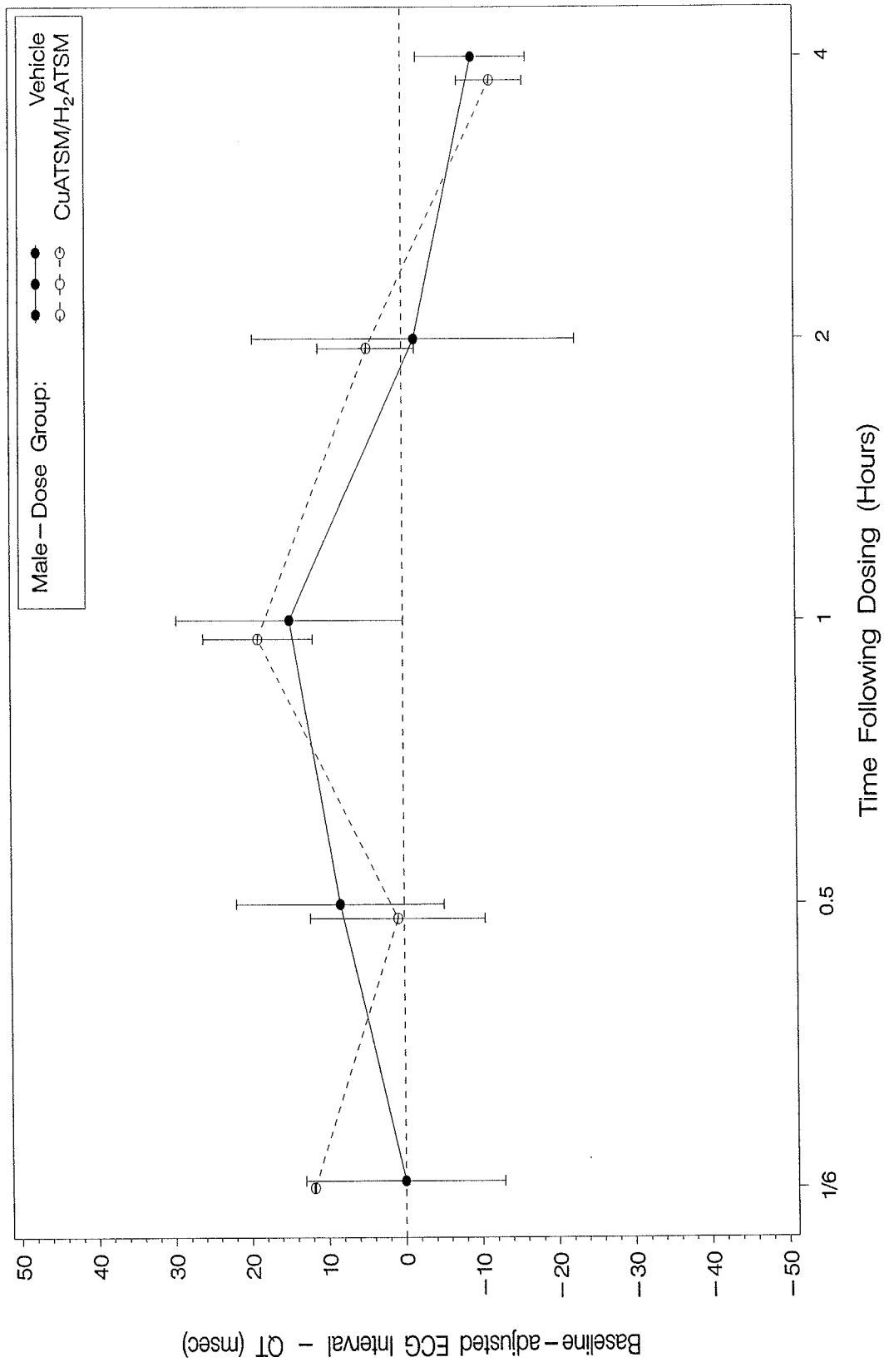


Figure 33. QT Interval (msec), Male Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

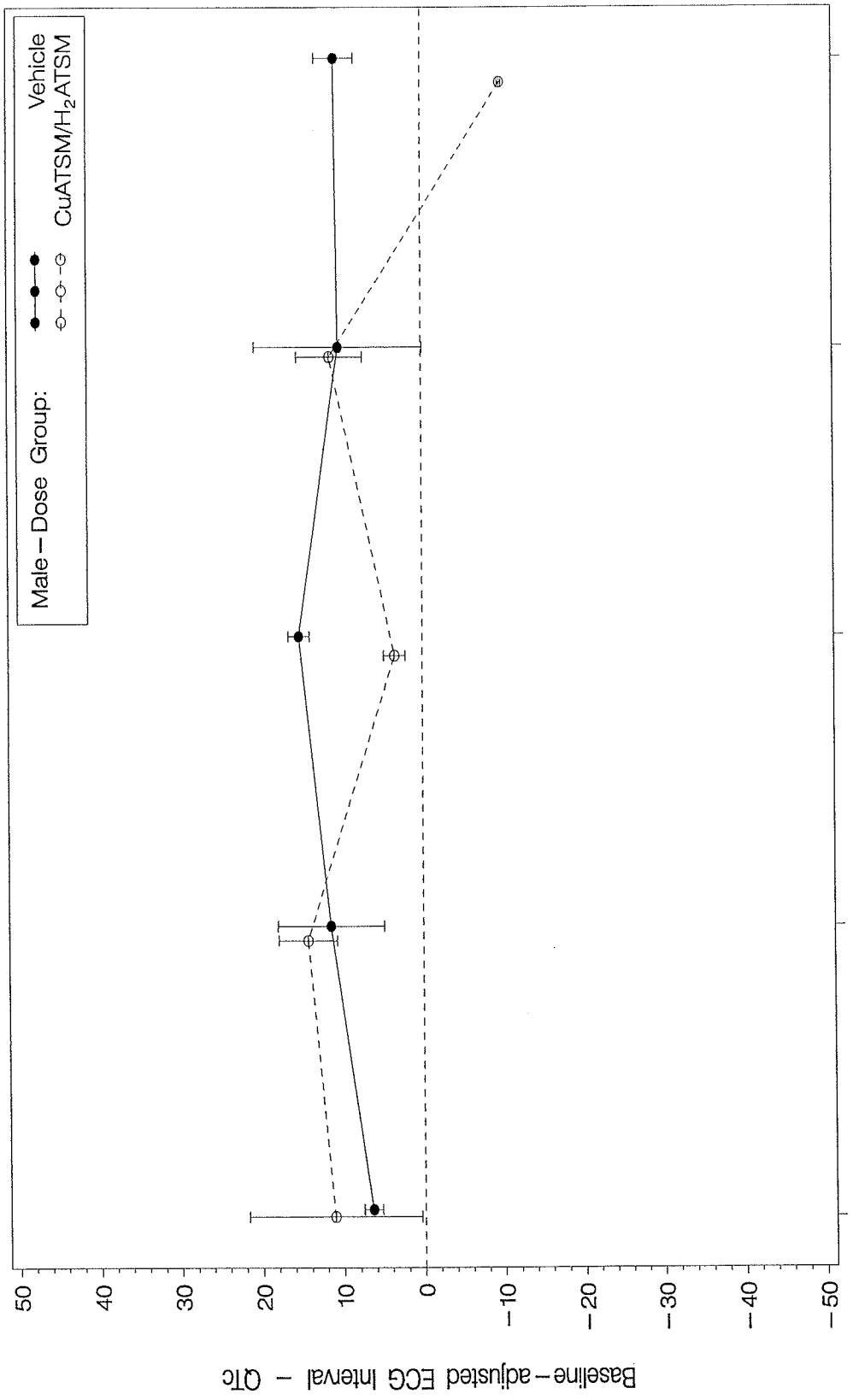


Figure 34. **Corrected QT Interval (QTc), Male Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the 4-Hour Period Immediately Following Dosing with $CuATSM/H_2ATSM$ or Vehicle**

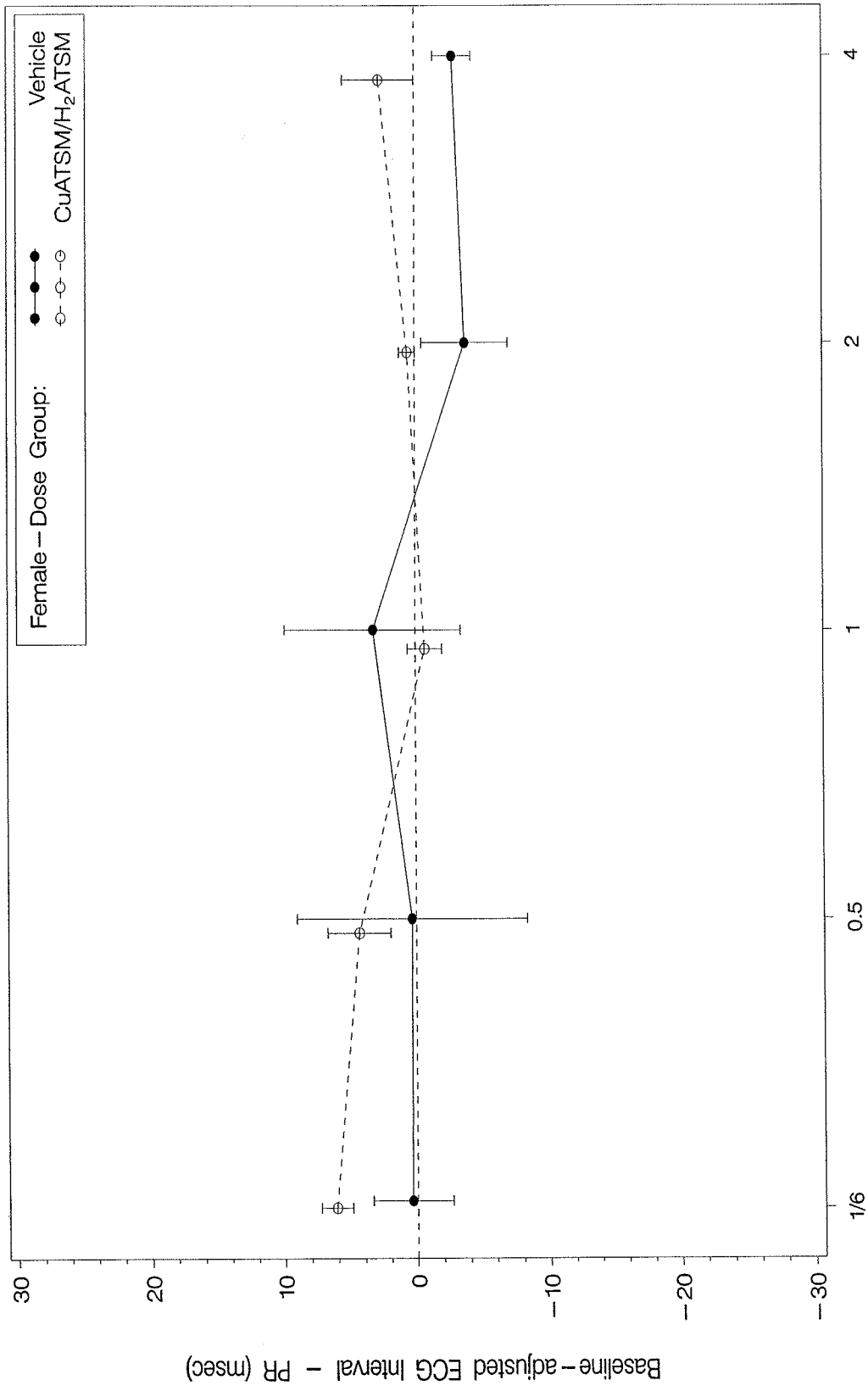


Figure 35. PR Interval (msec), Female Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

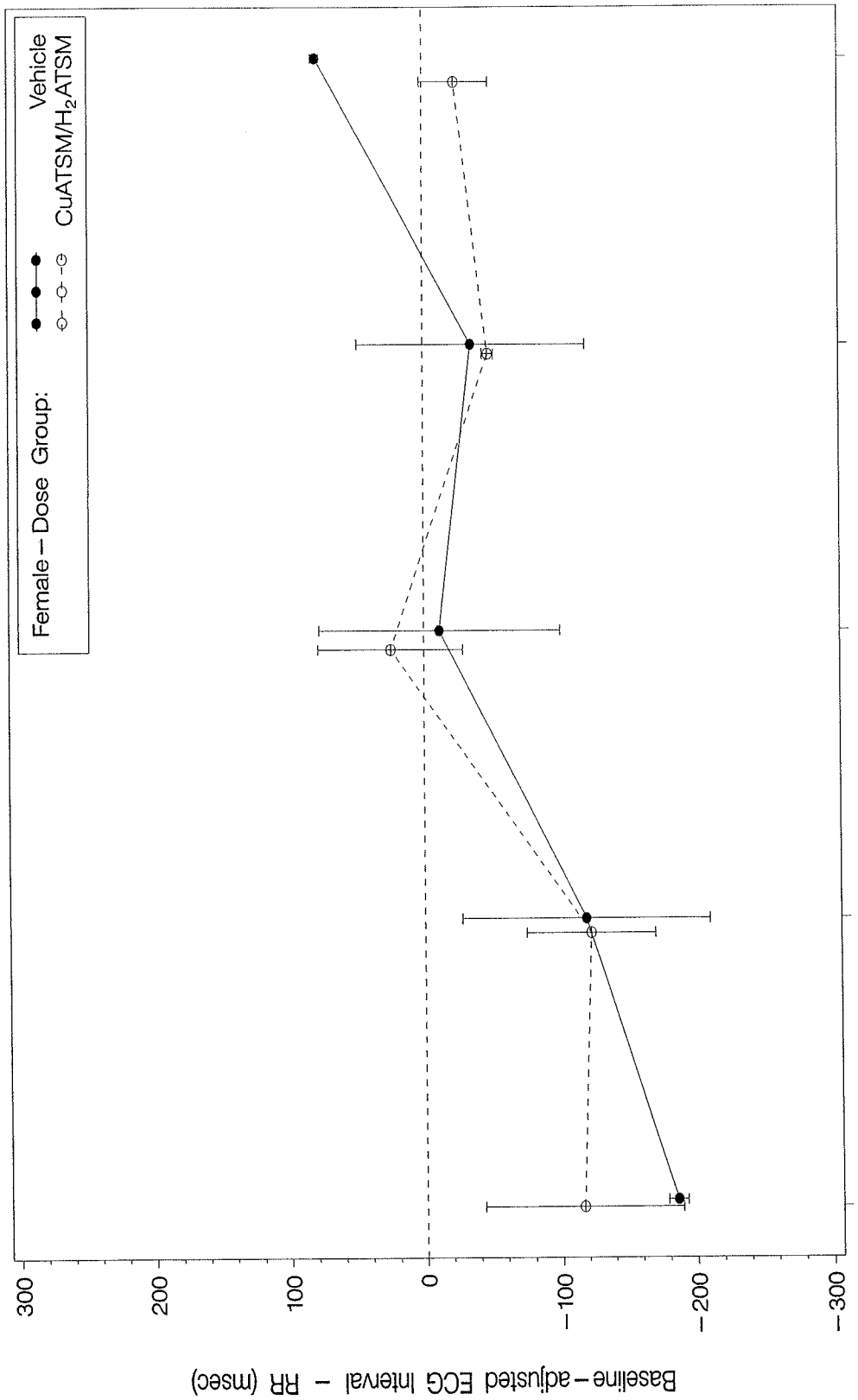


Figure 36. RR Interval (msec), Female Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

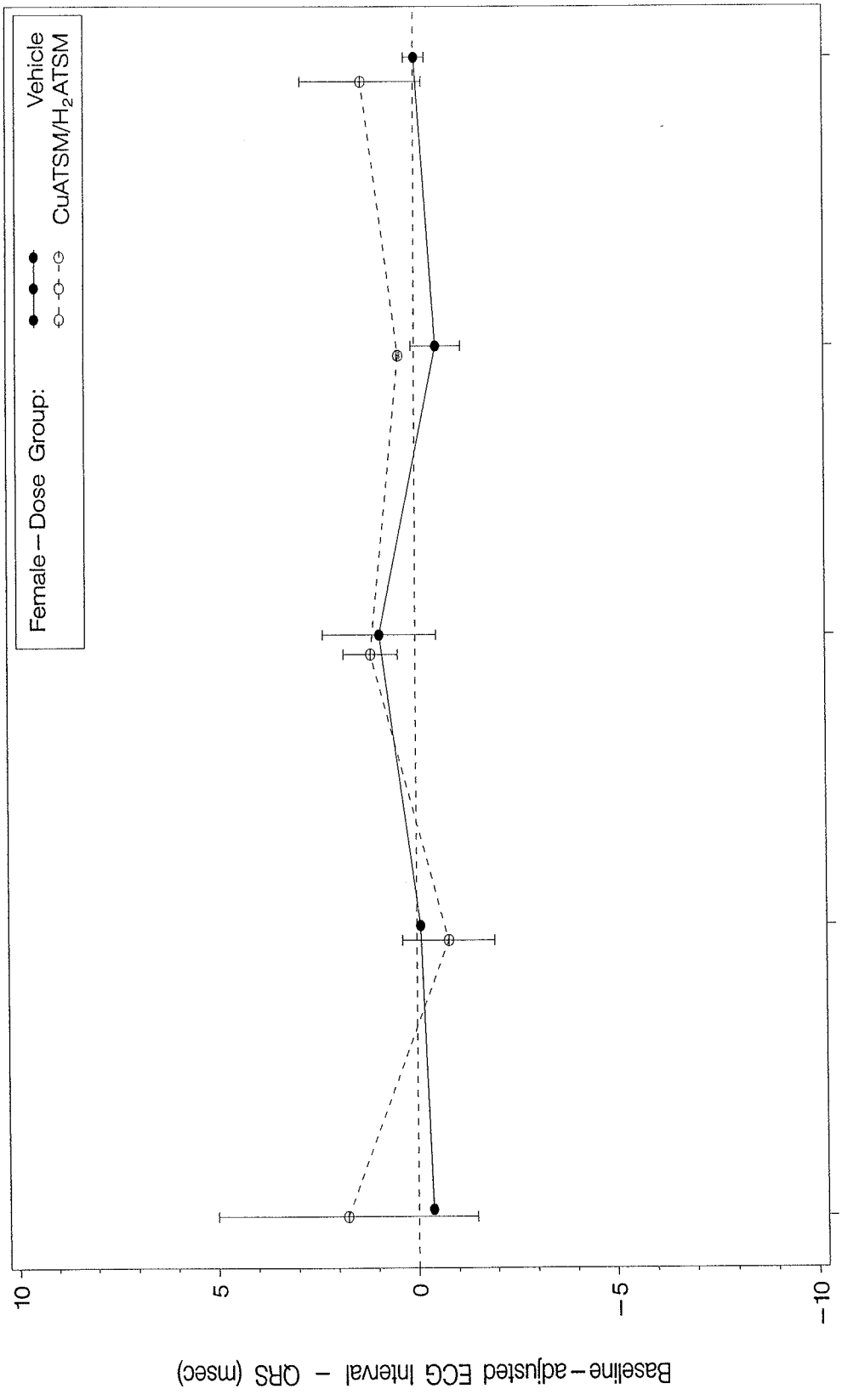


Figure 37. QRS Interval (msec), Female Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

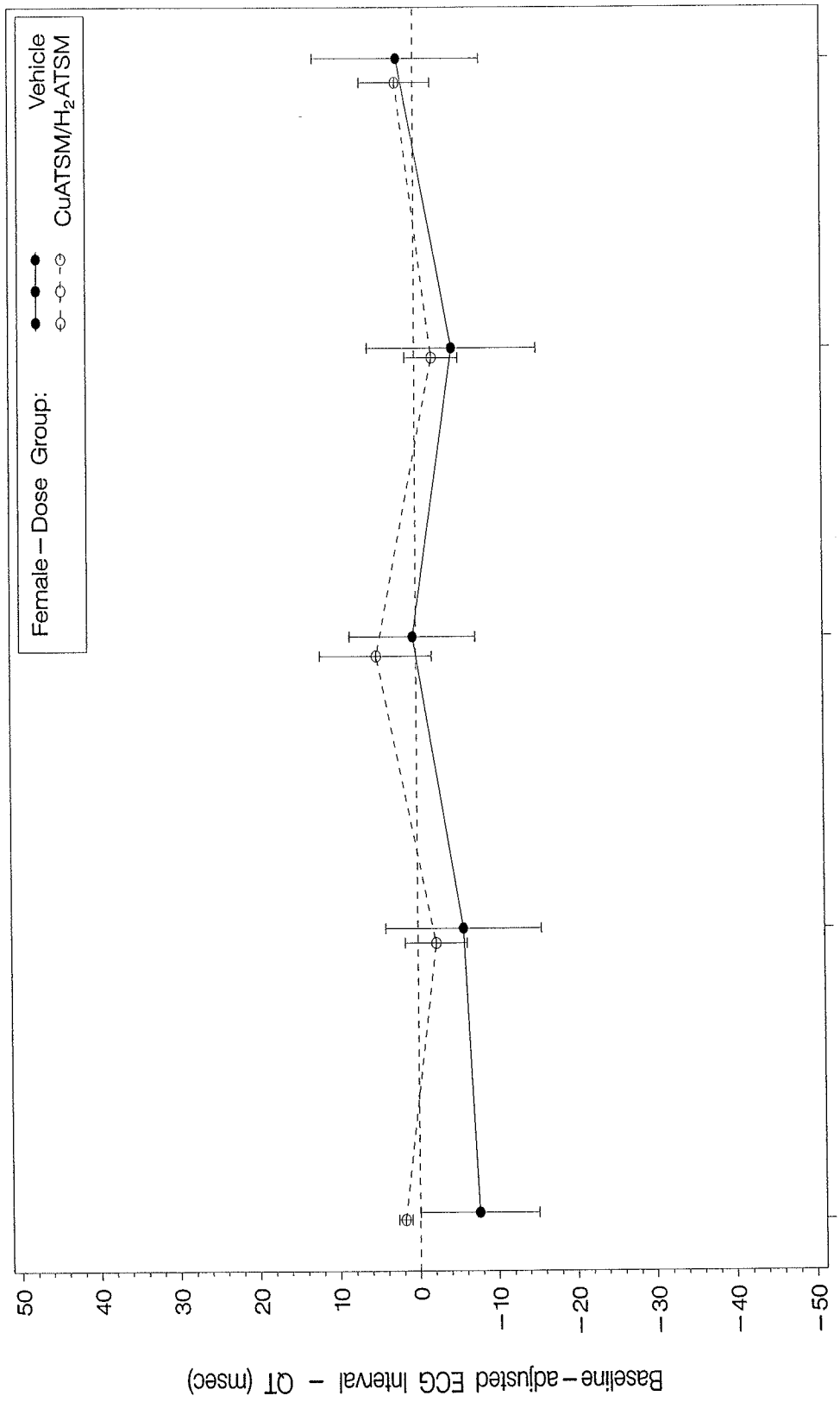


Figure 38. **QT Interval (msec), Female Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

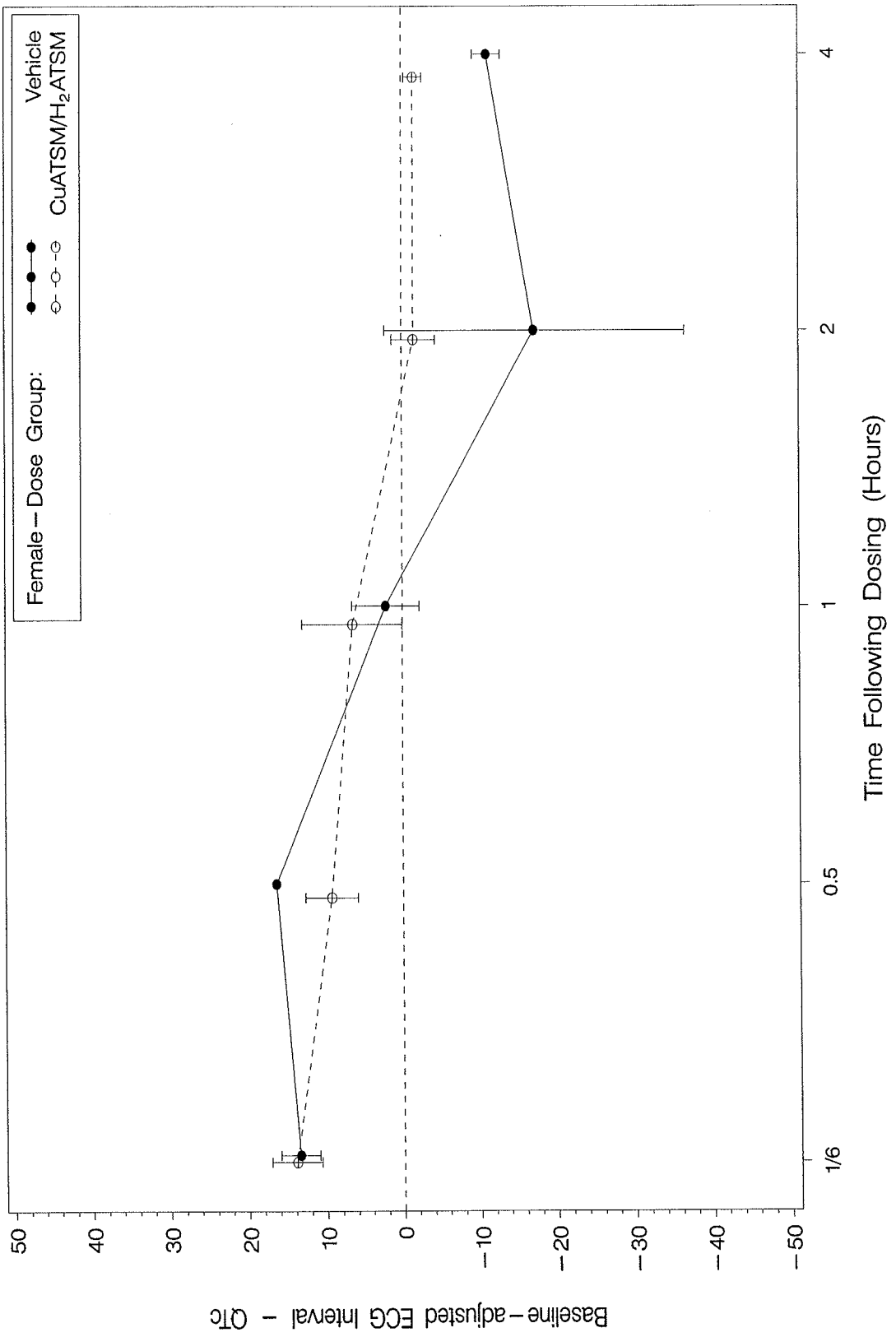


Figure 39. **Corrected QT Interval (QTc), Female Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

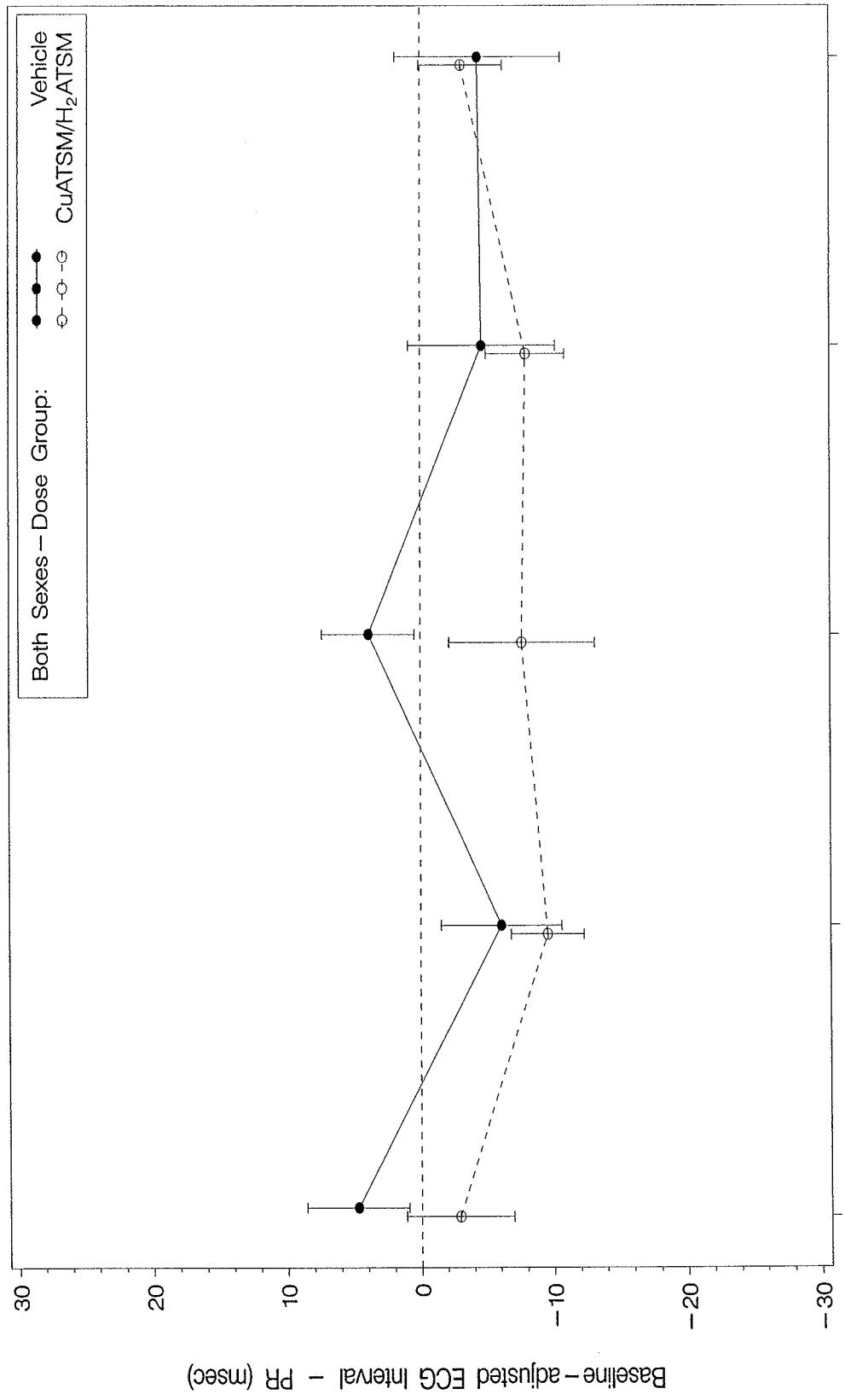


Figure 40. **PR Interval (msec), Both Sexes, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

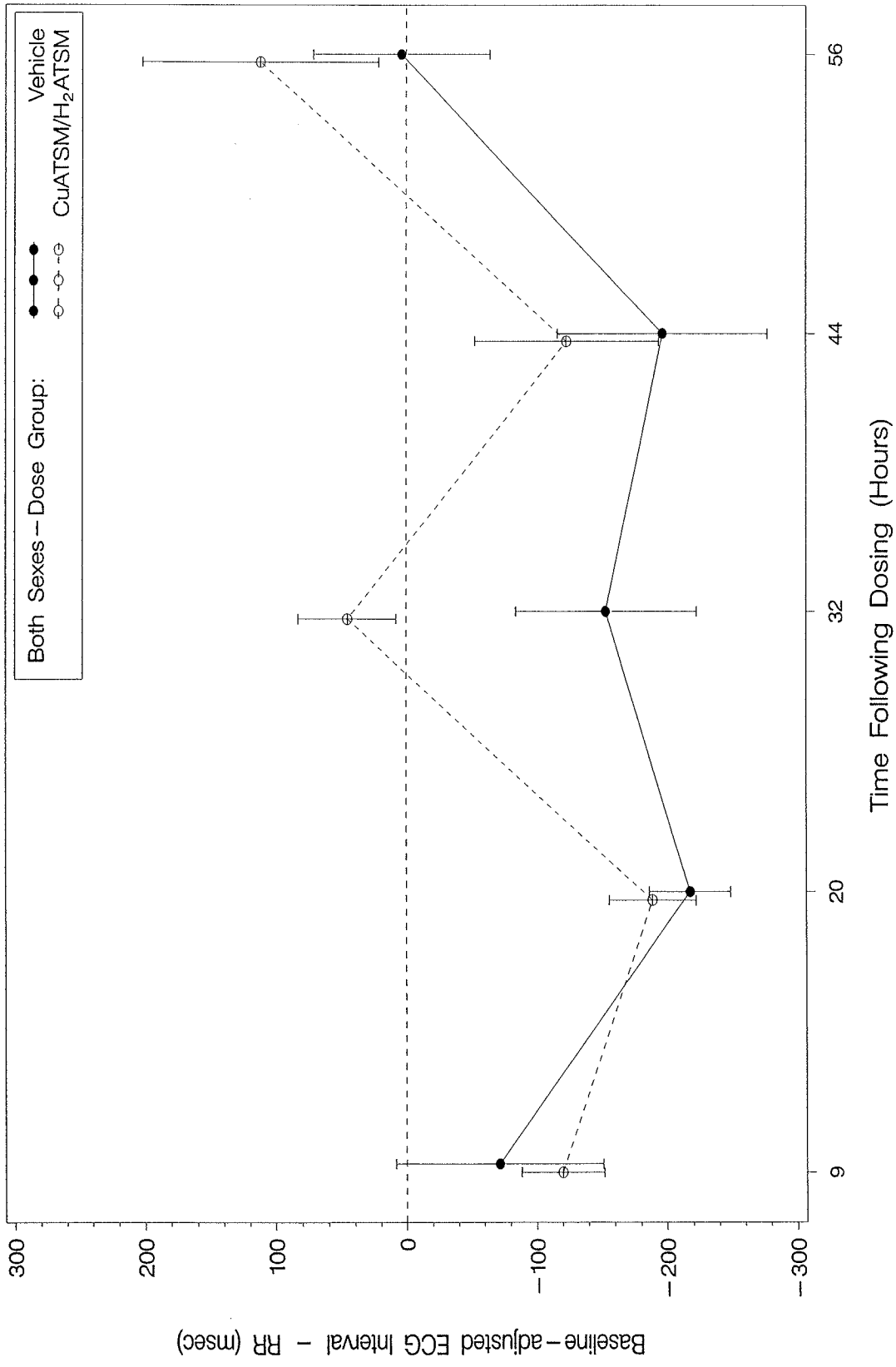


Figure 41. **RR Interval (msec), Both Sexes, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

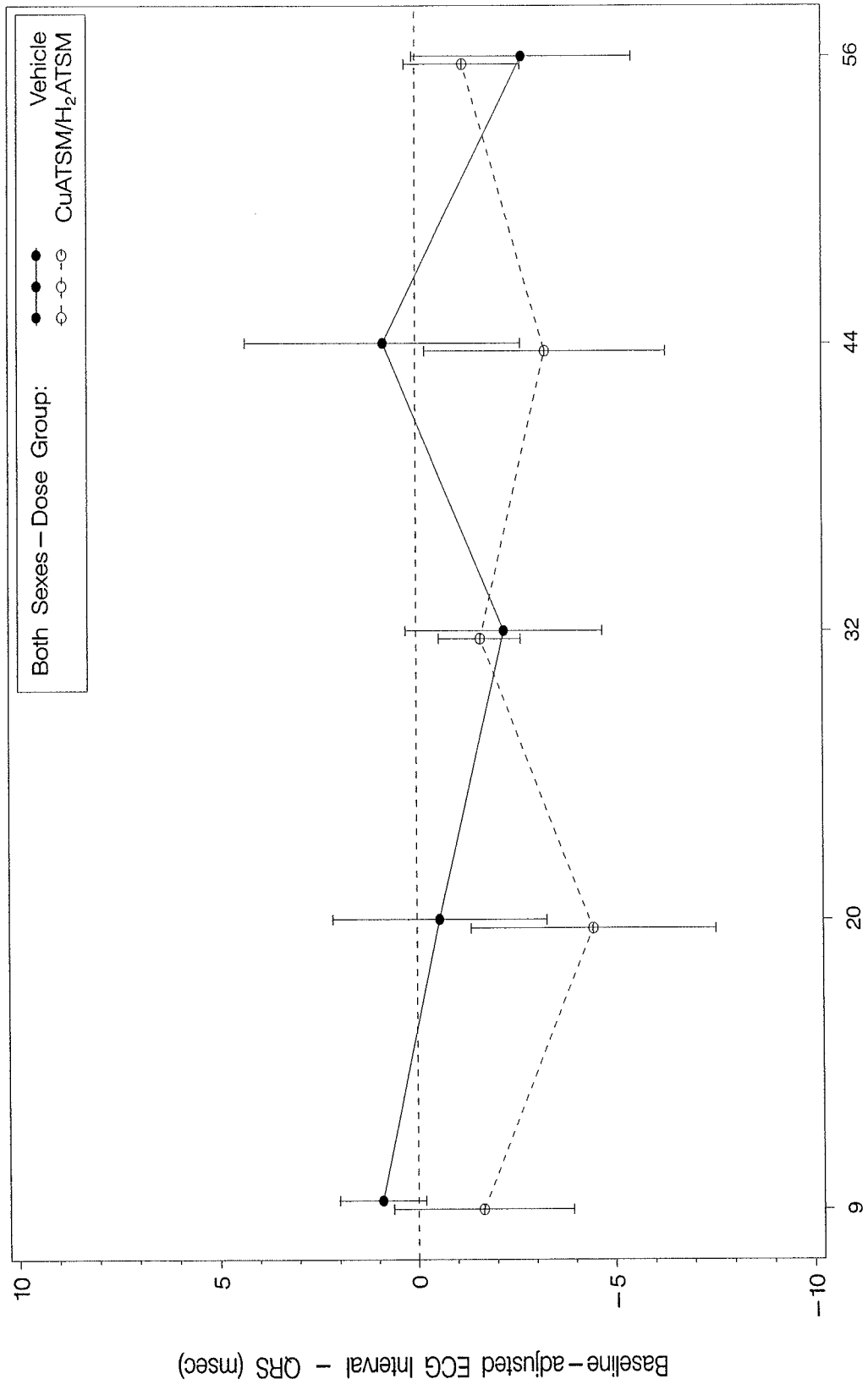


Figure 42. **QRS Interval (msec), Both Sexes, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

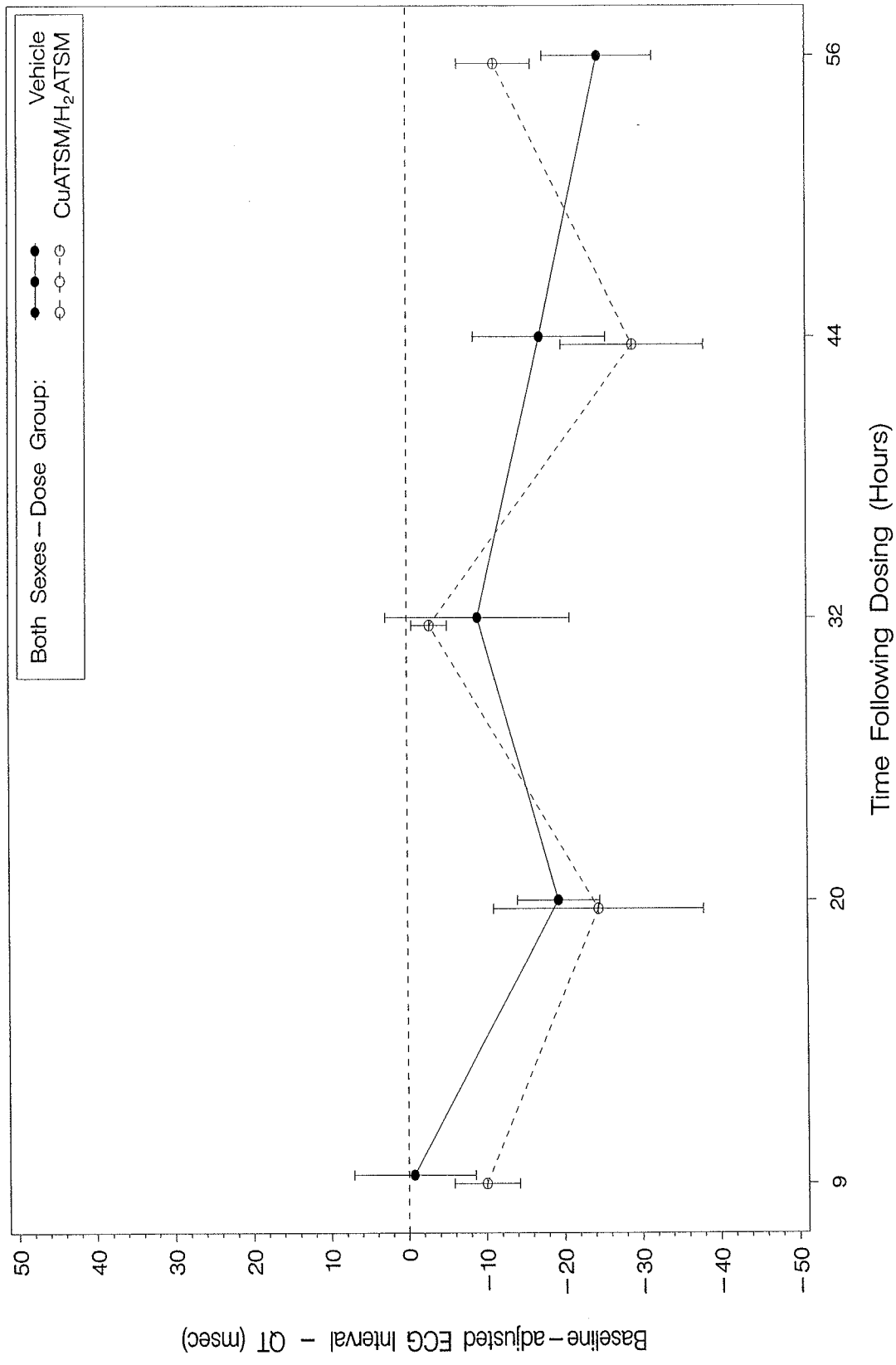


Figure 43. **QT Interval (msec), Both Sexes, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

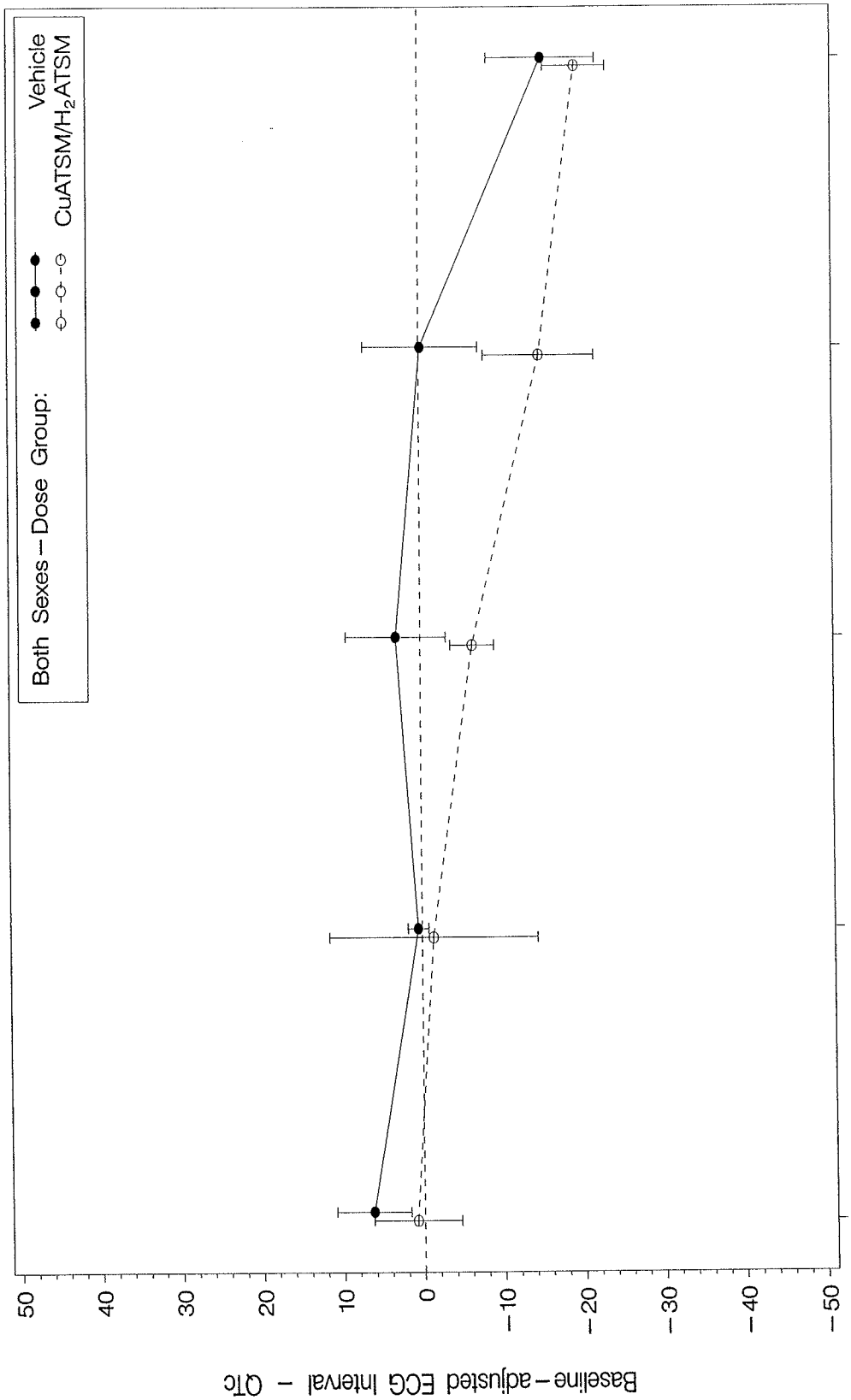


Figure 44. **Corrected QT Interval (QTc), Both Sexes, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

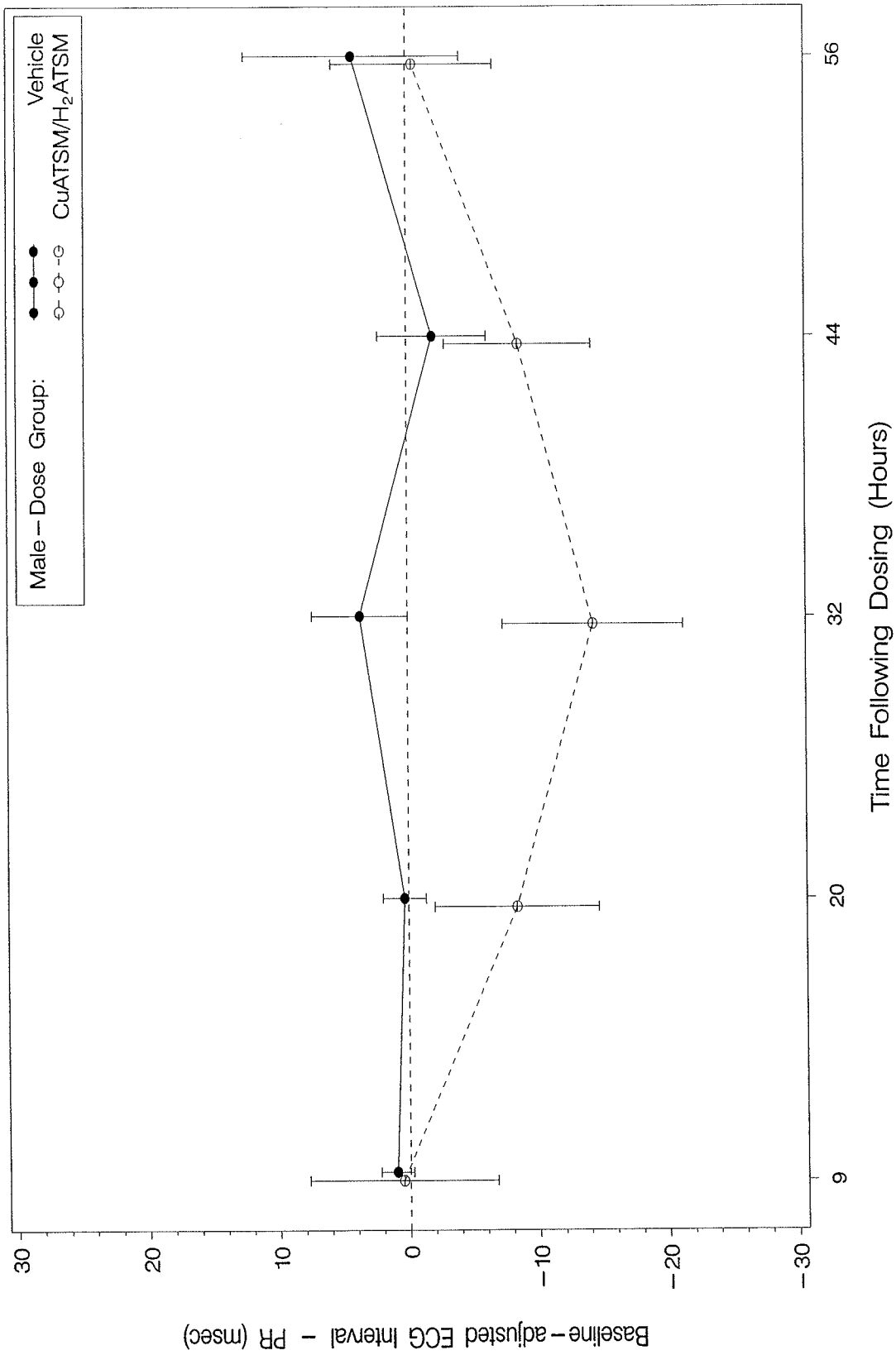


Figure 45. **PR Interval (msec), Male Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

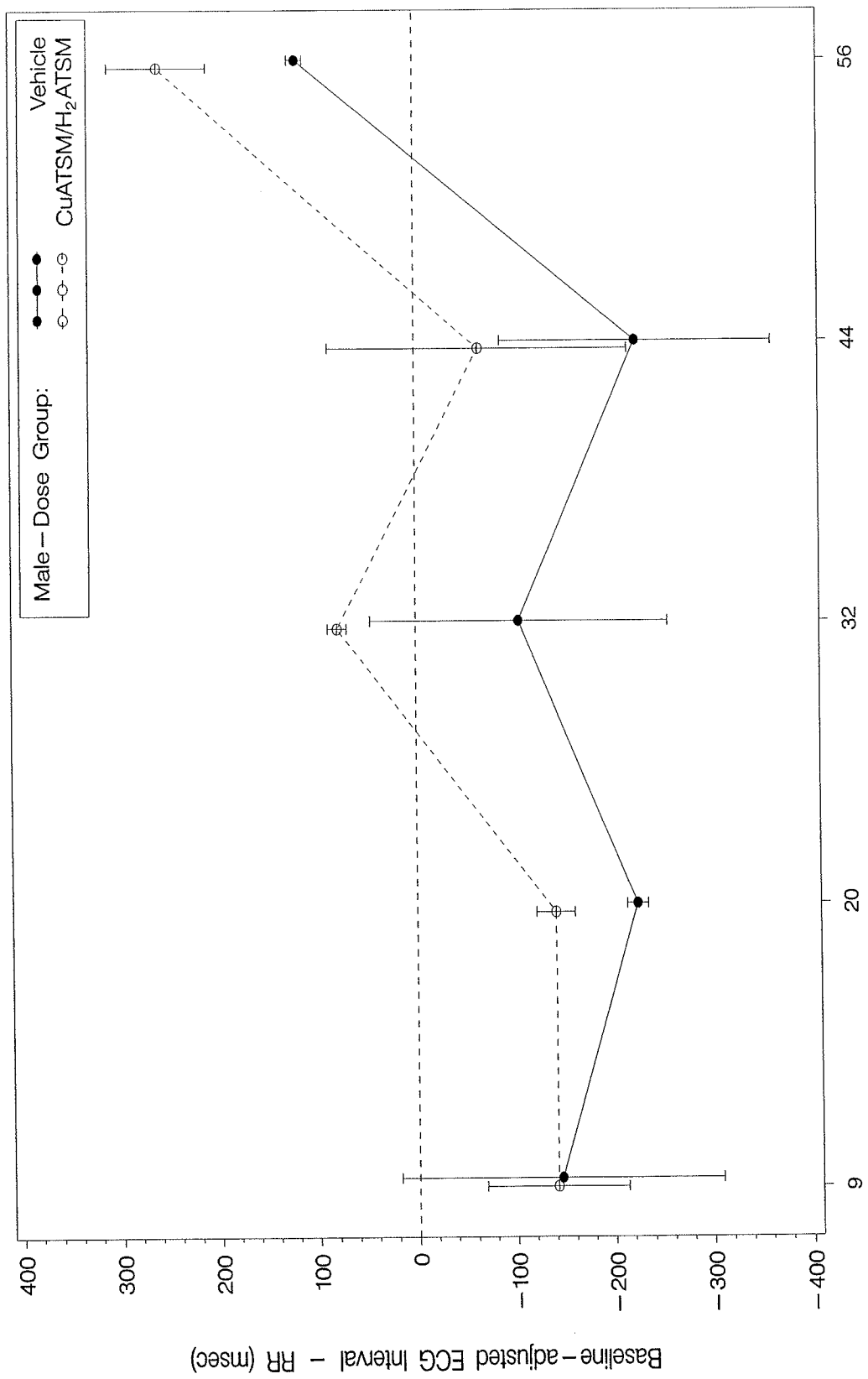


Figure 46. **RR Interval (msec), Male Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

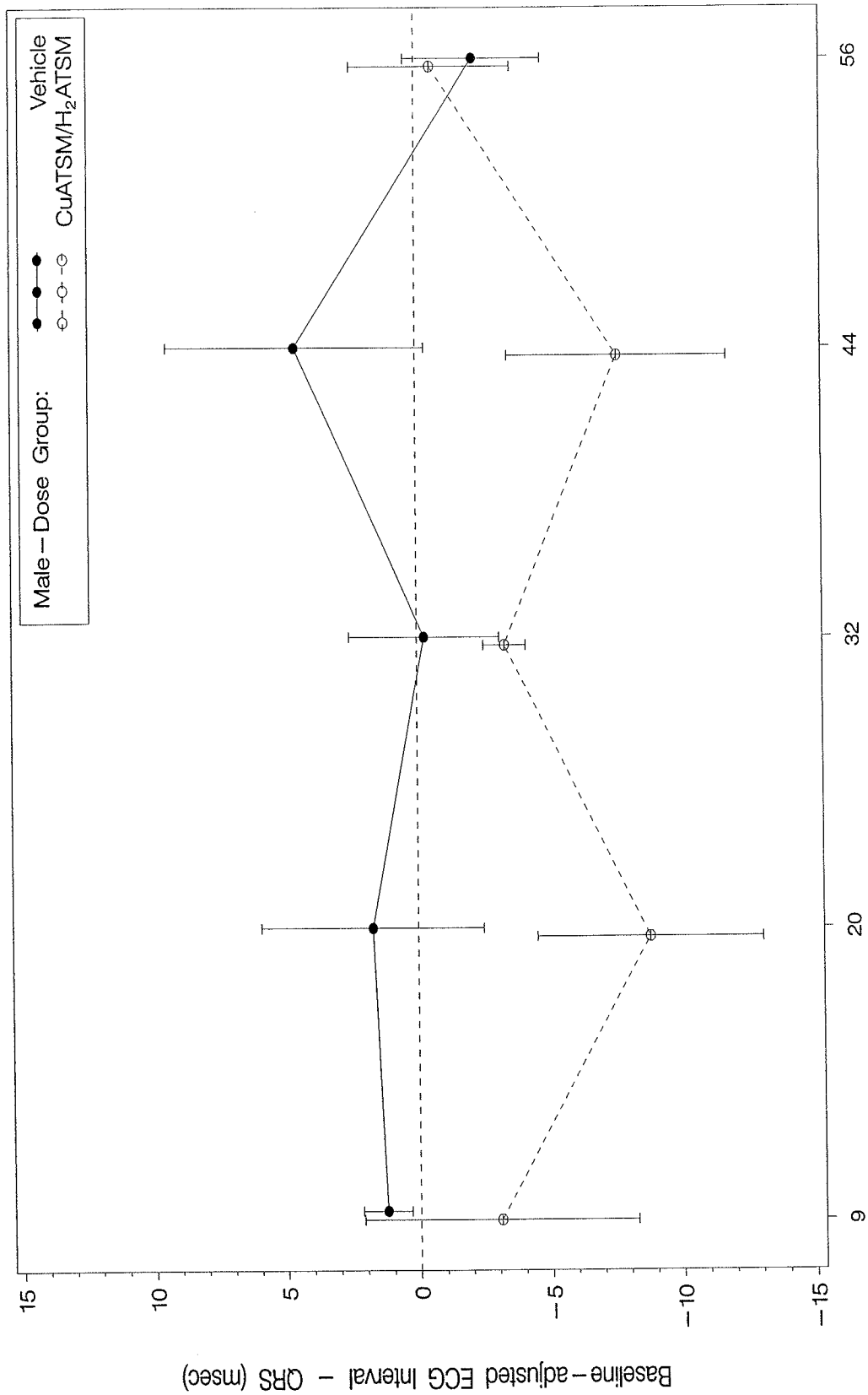


Figure 47. **QRS Interval (msec), Male Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

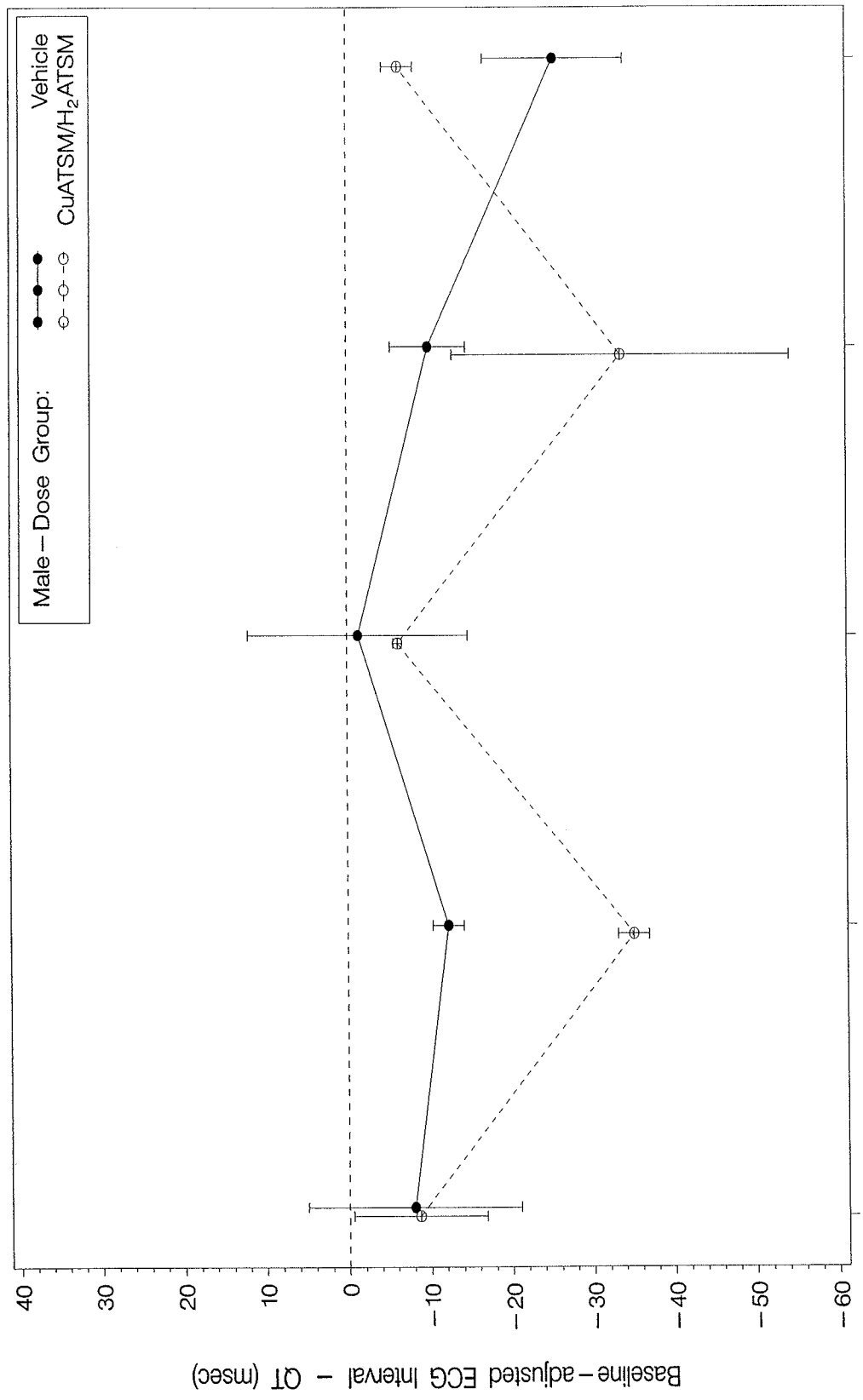


Figure 48. **QT Interval (msec), Male Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

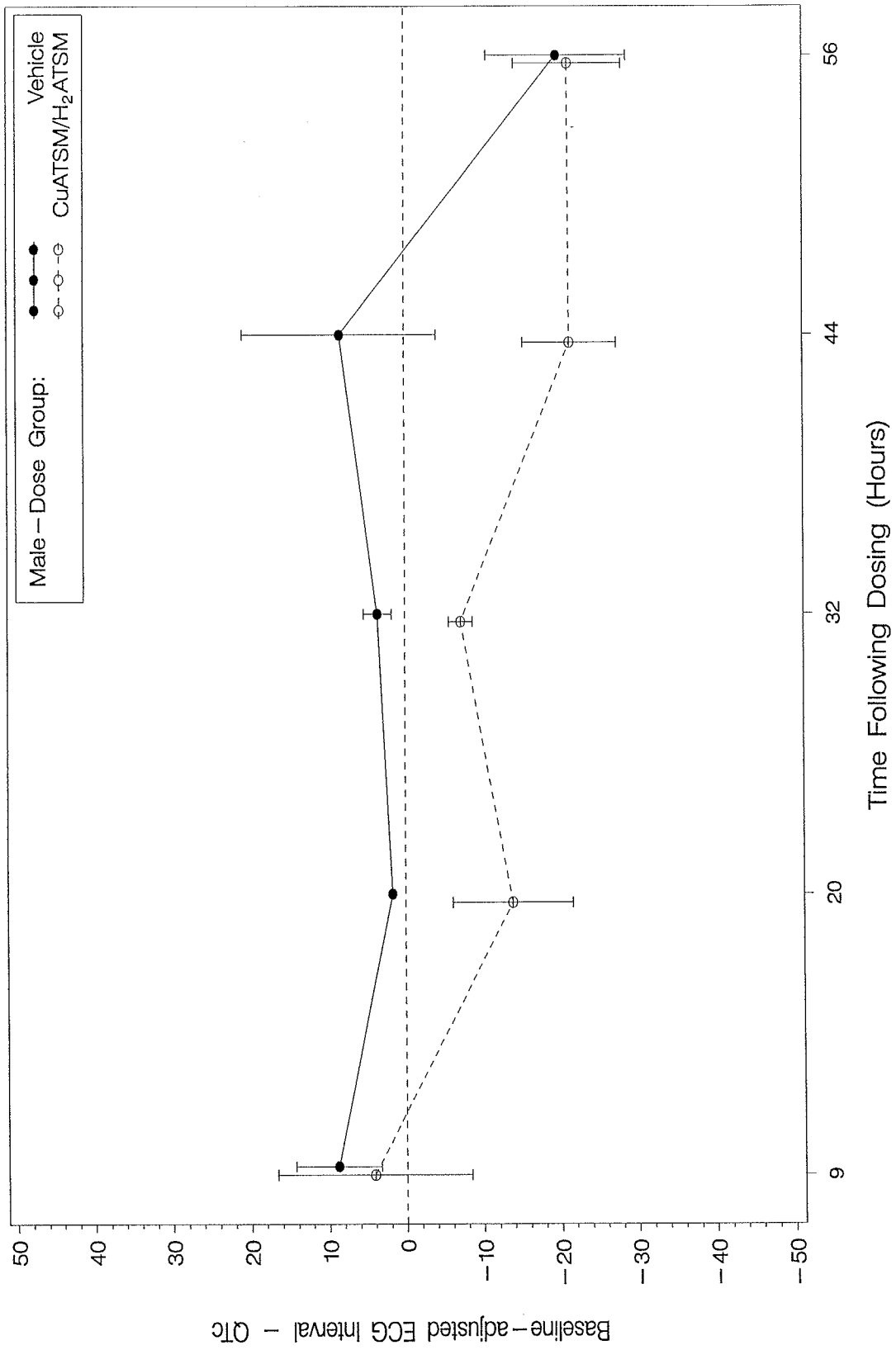


Figure 49. **Corrected QT Interval (QTc), Male Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

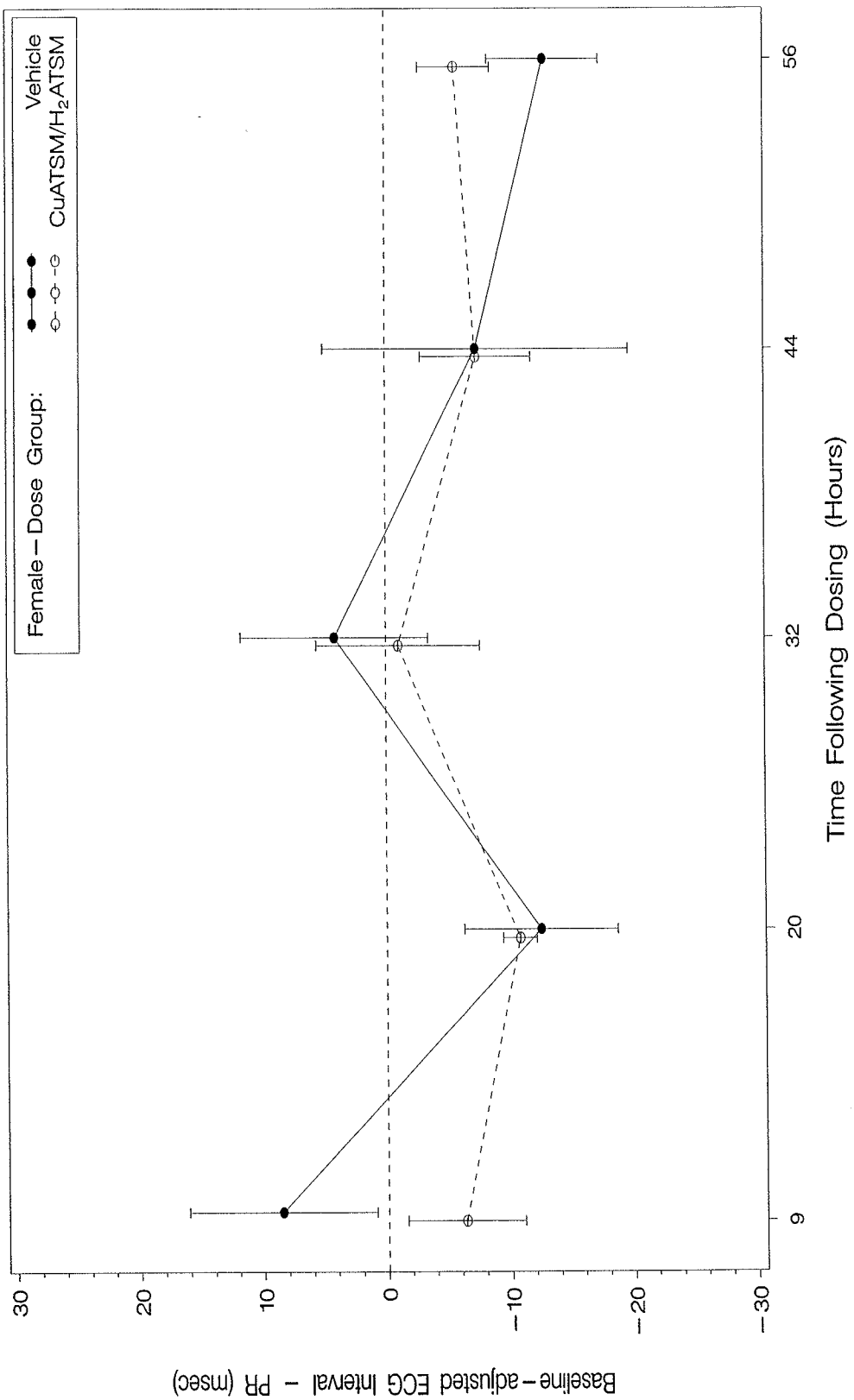


Figure 50. **PR Interval (msec), Female Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

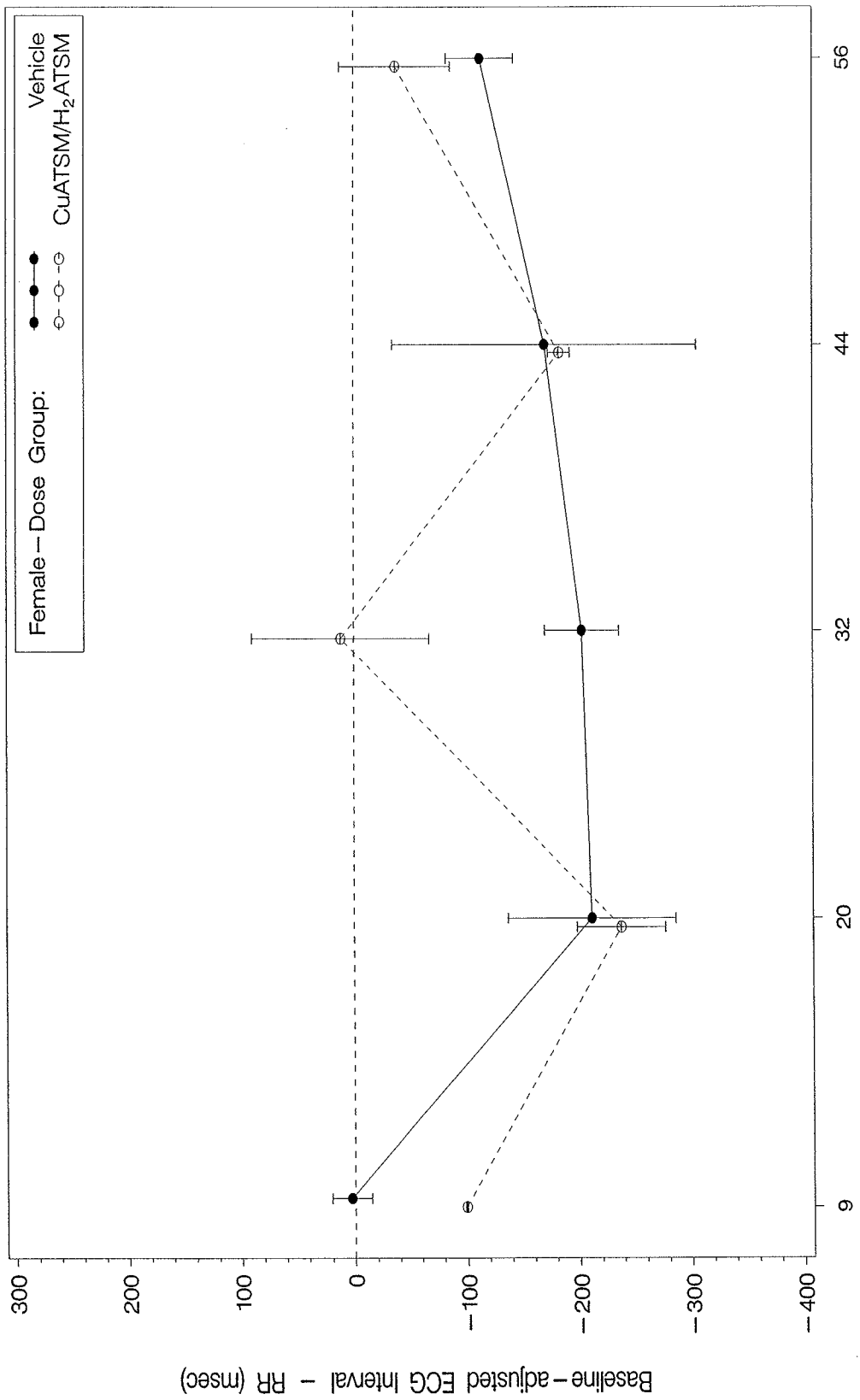


Figure 51. **RR Interval (msec), Female Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

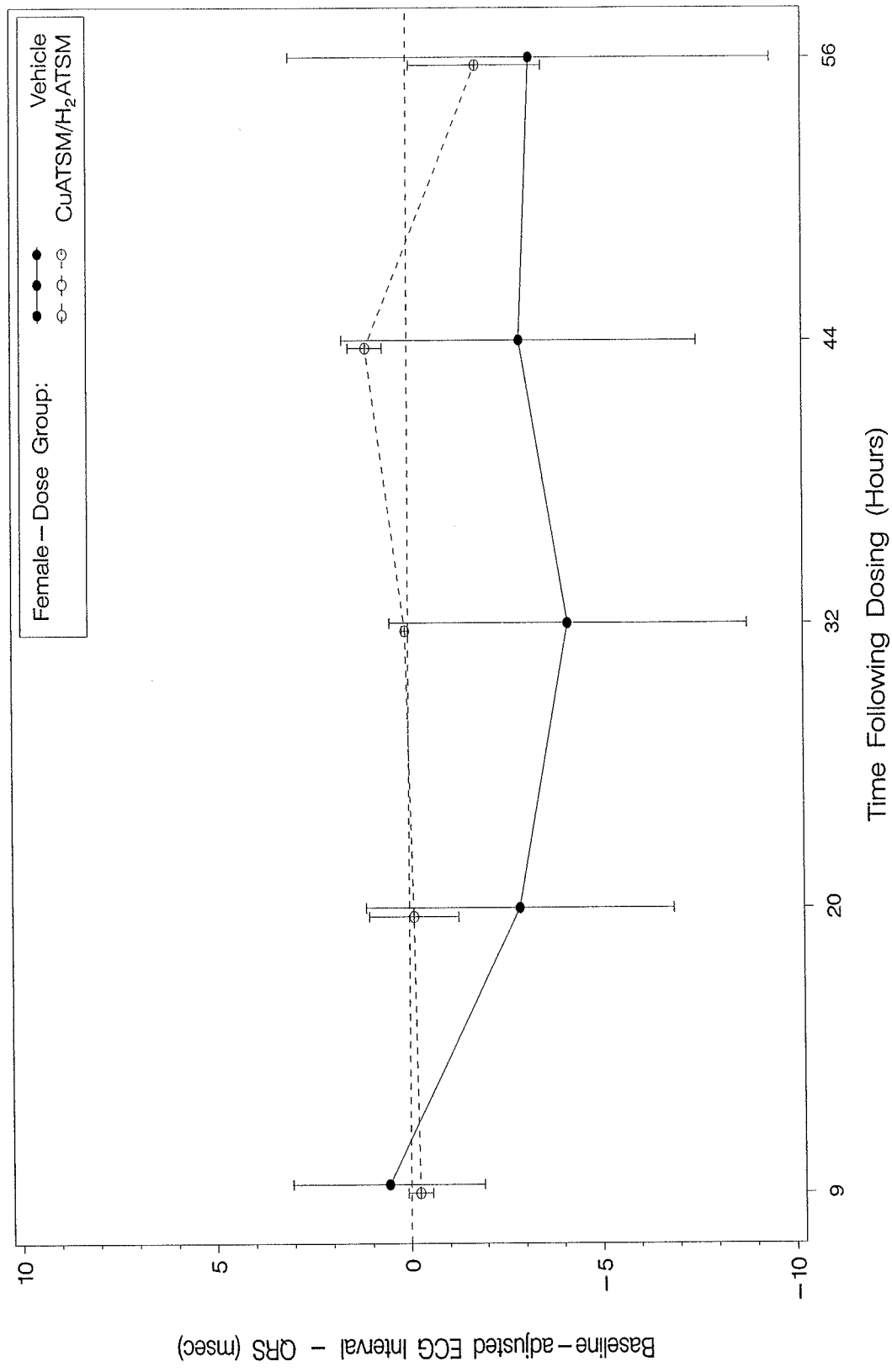


Figure 52. **QRS Interval (msec), Female Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

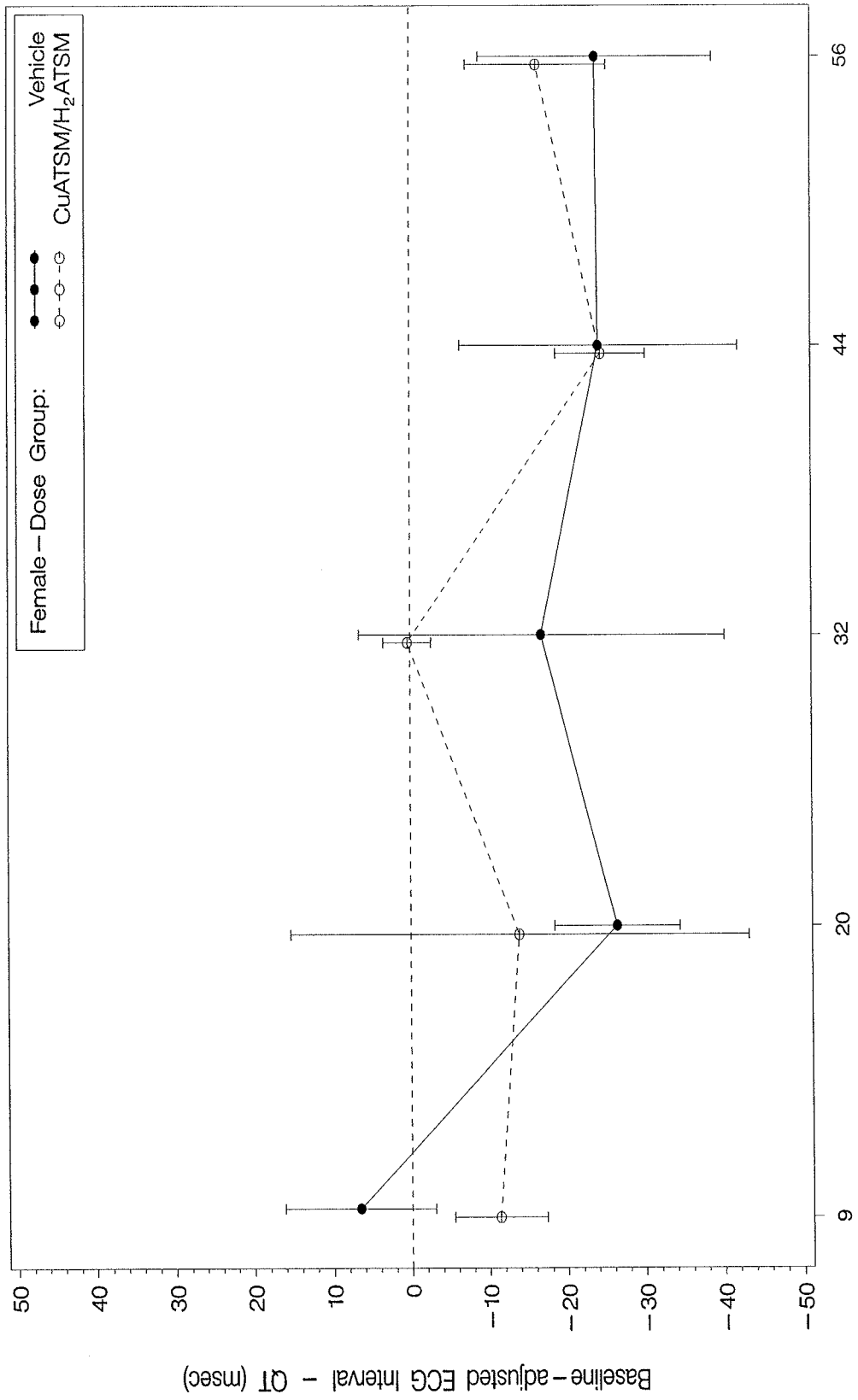


Figure 53. **QT Interval (msec), Female Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

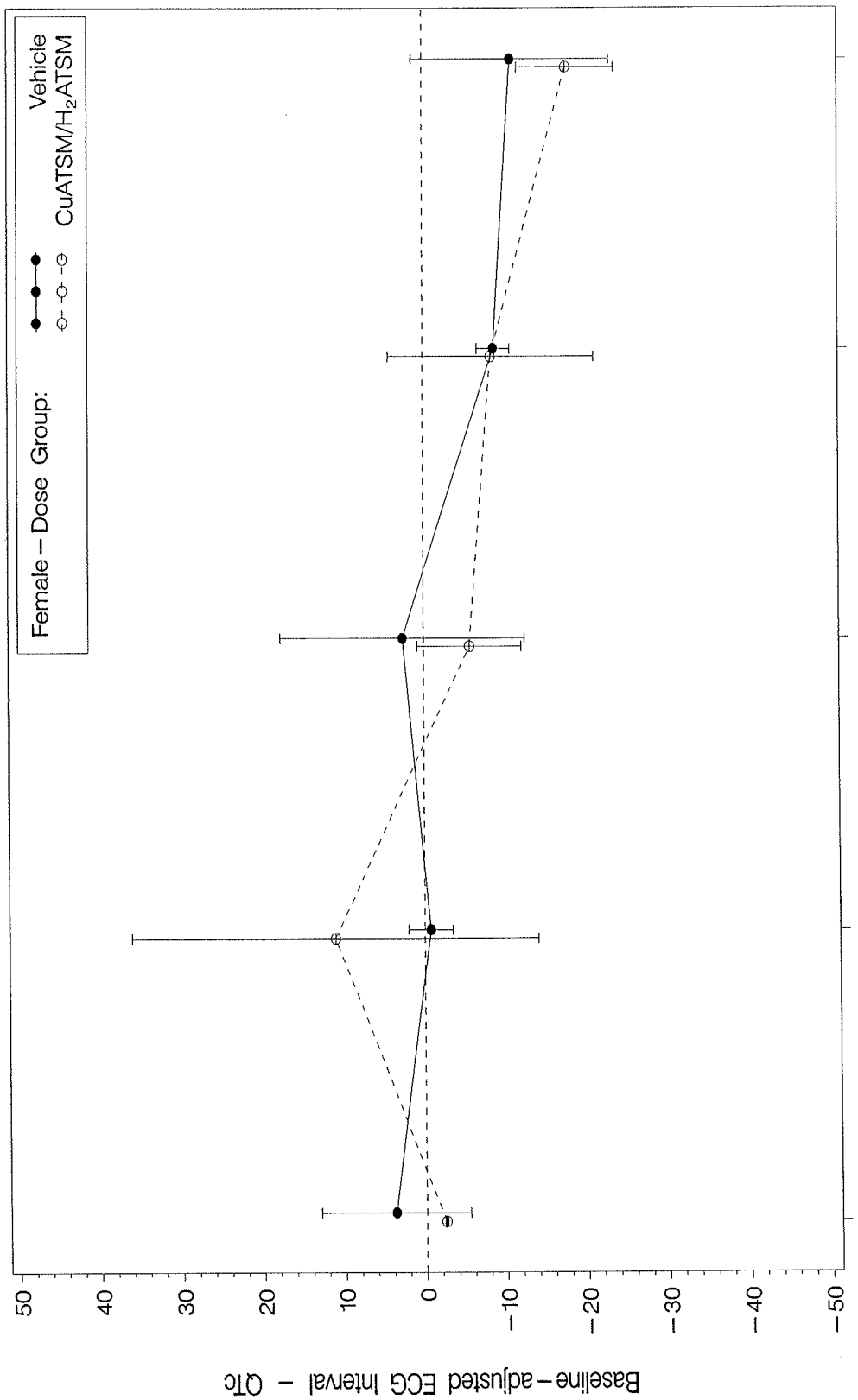


Figure 54. **Corrected QT Interval (QTc), Female Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline-Adjusted Averages Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

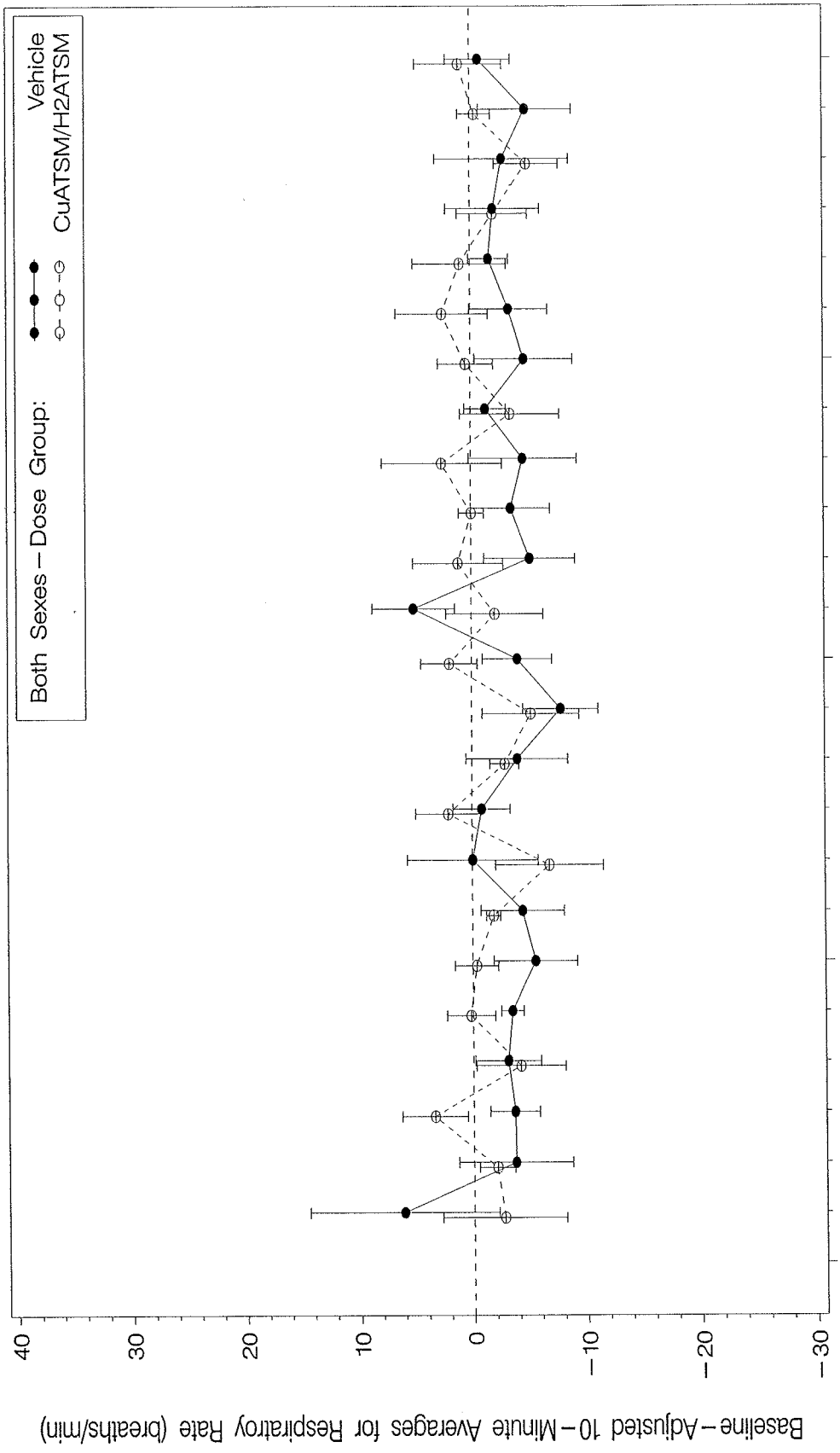


Figure 55. **Respiratory Rate (breaths/min), Both Sexes, Dose Group Means (and Standard Errors) of Baseline-Adjusted 10-Minute Averages during the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

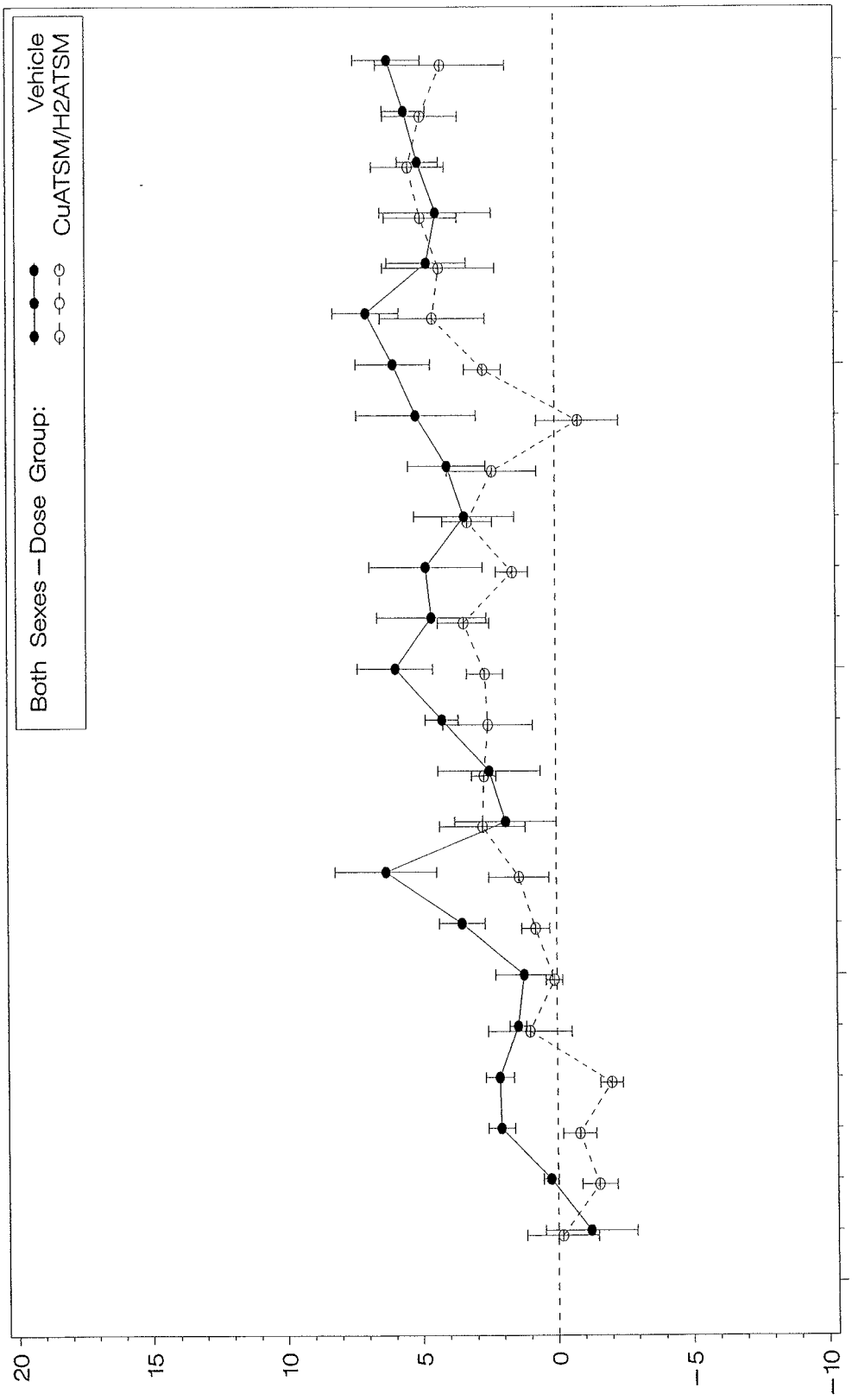


Figure 56. **Body Weight-Adjusted Tidal Volume (mL/breath/kg), Both Sexes, Dose Group Means (and Standard Errors) of Baseline-Adjusted 10-Minute Averages during the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

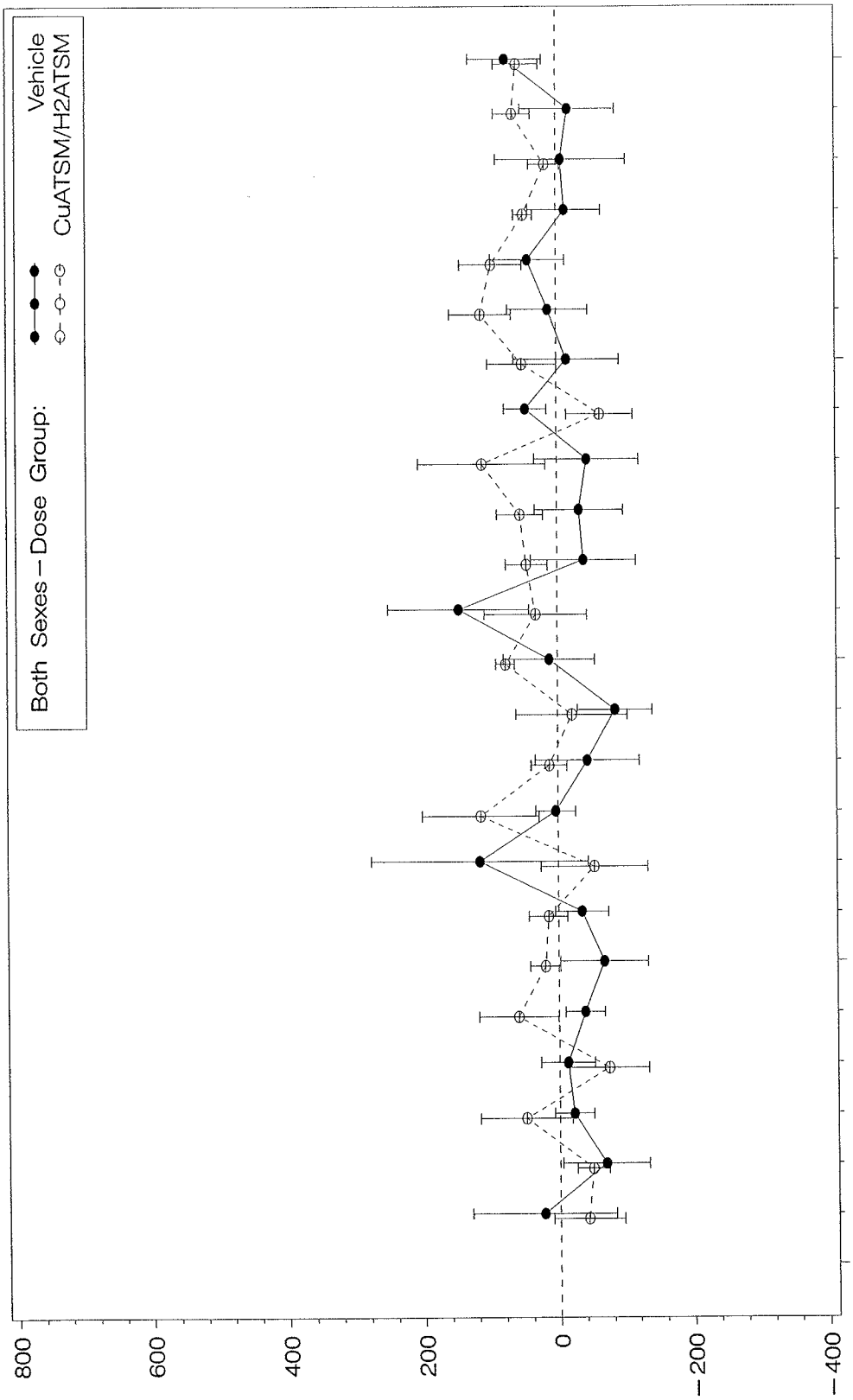


Figure 57. **Body Weight-Adjusted Minute Volume (mL/min/kg), Both Sexes, Dose Group Means (and Standard Errors) of Baseline-Adjusted 10-Minute Averages during the 4-Hour Period Immediately Following Dosing with $CuATSM/H_2ATSM$ or Vehicle**

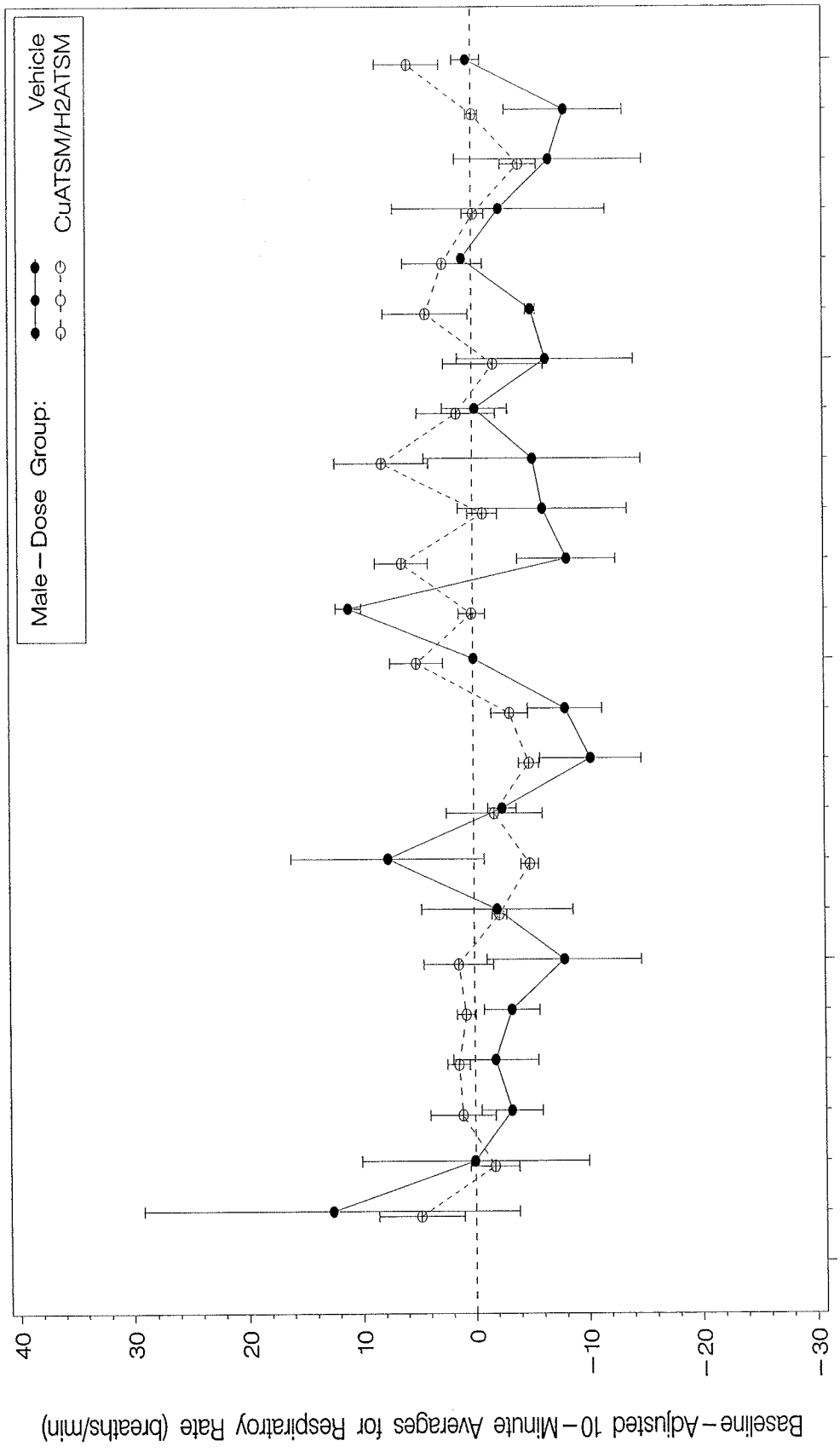


Figure 58. **Respiratory Rate (breaths/min), Male Animals, Dose Group Means (and Standard Errors) of Baseline-Adjusted 10-Minute Averages during the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

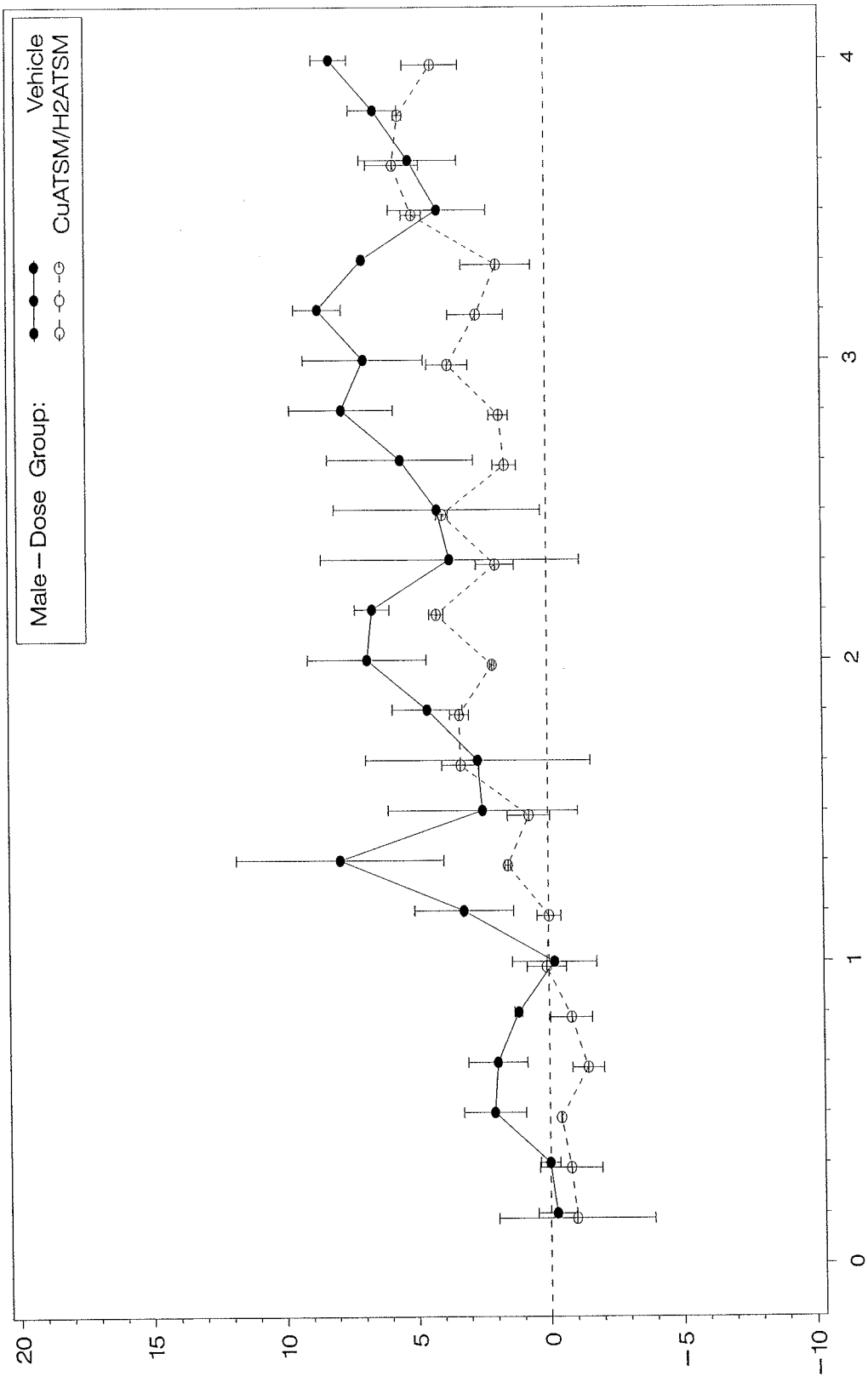


Figure 59. **Body Weight-Adjusted Tidal Volume (mL/breath/kg), Male Animals, Dose Group Means (and Standard Errors) of Baseline-Adjusted 10-Minute Averages during the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

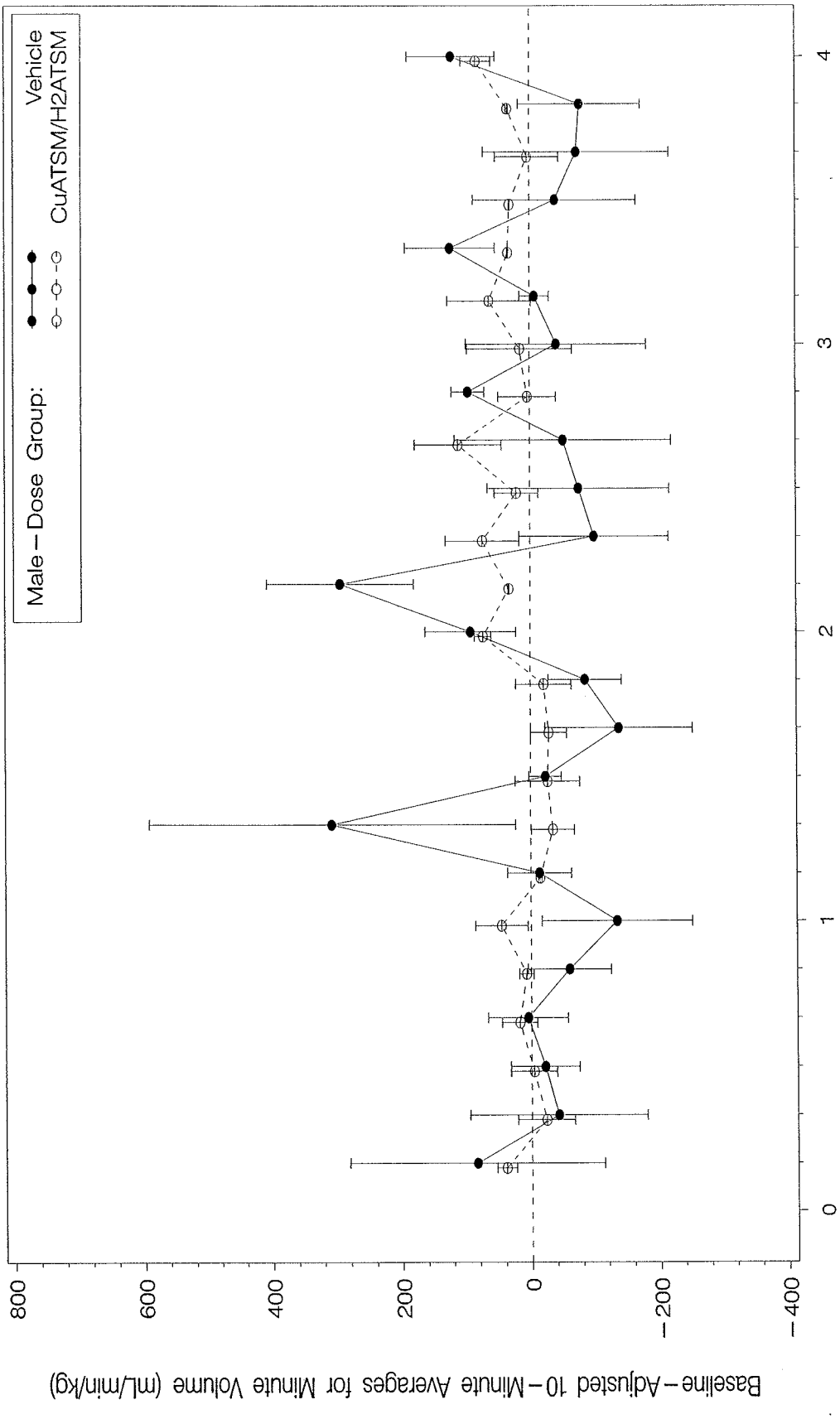


Figure 60. **Body Weight-Adjusted Minute Volume (mL/min/kg), Male Animals, Dose Group Means (and Standard Errors) of Baseline-Adjusted 10-Minute Averages during the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

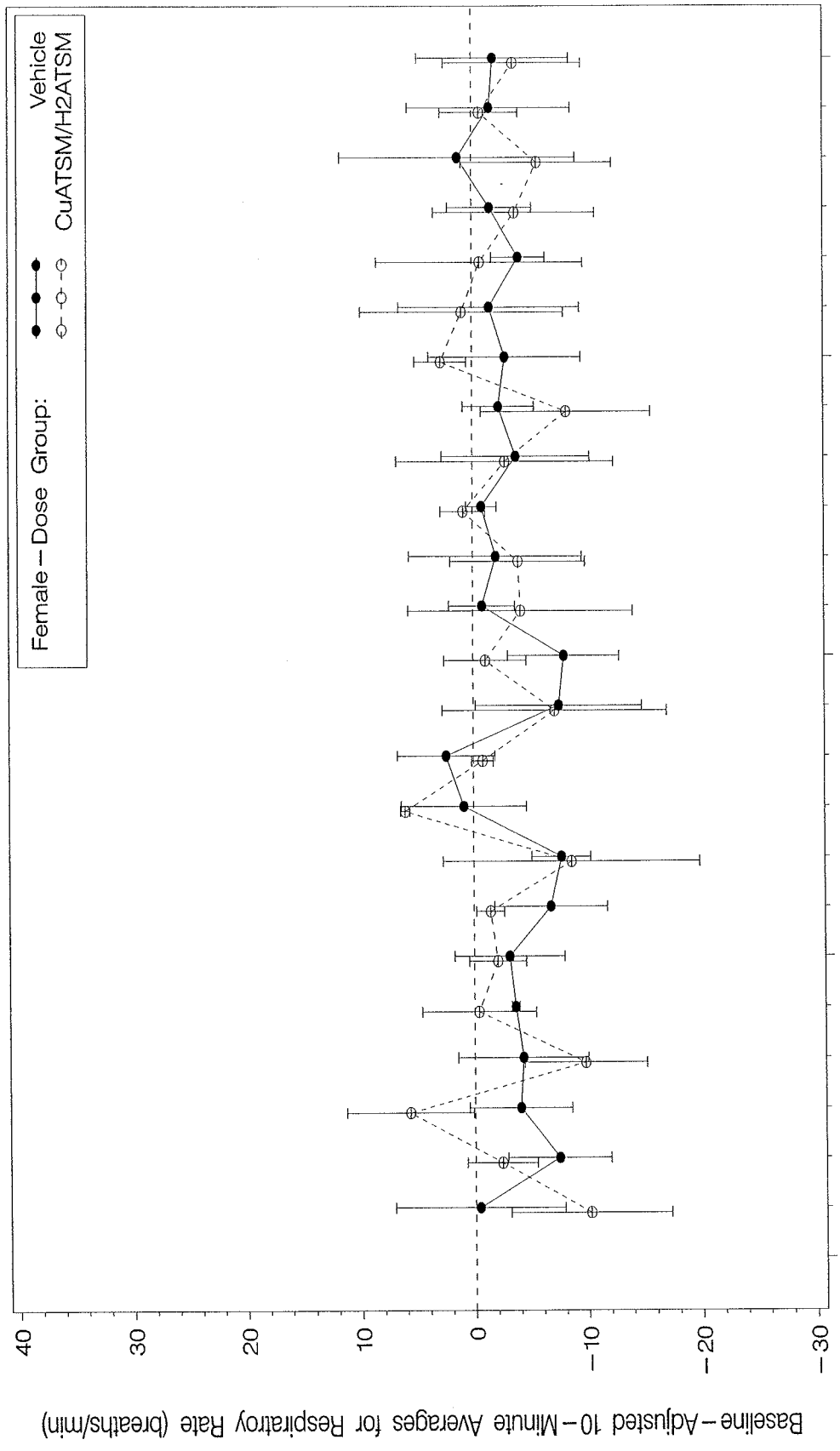


Figure 61. **Respiratory Rate (breaths/min), Female Animals, Dose Group Means (and Standard Errors) of Baseline-Adjusted 10-Minute Averages during the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

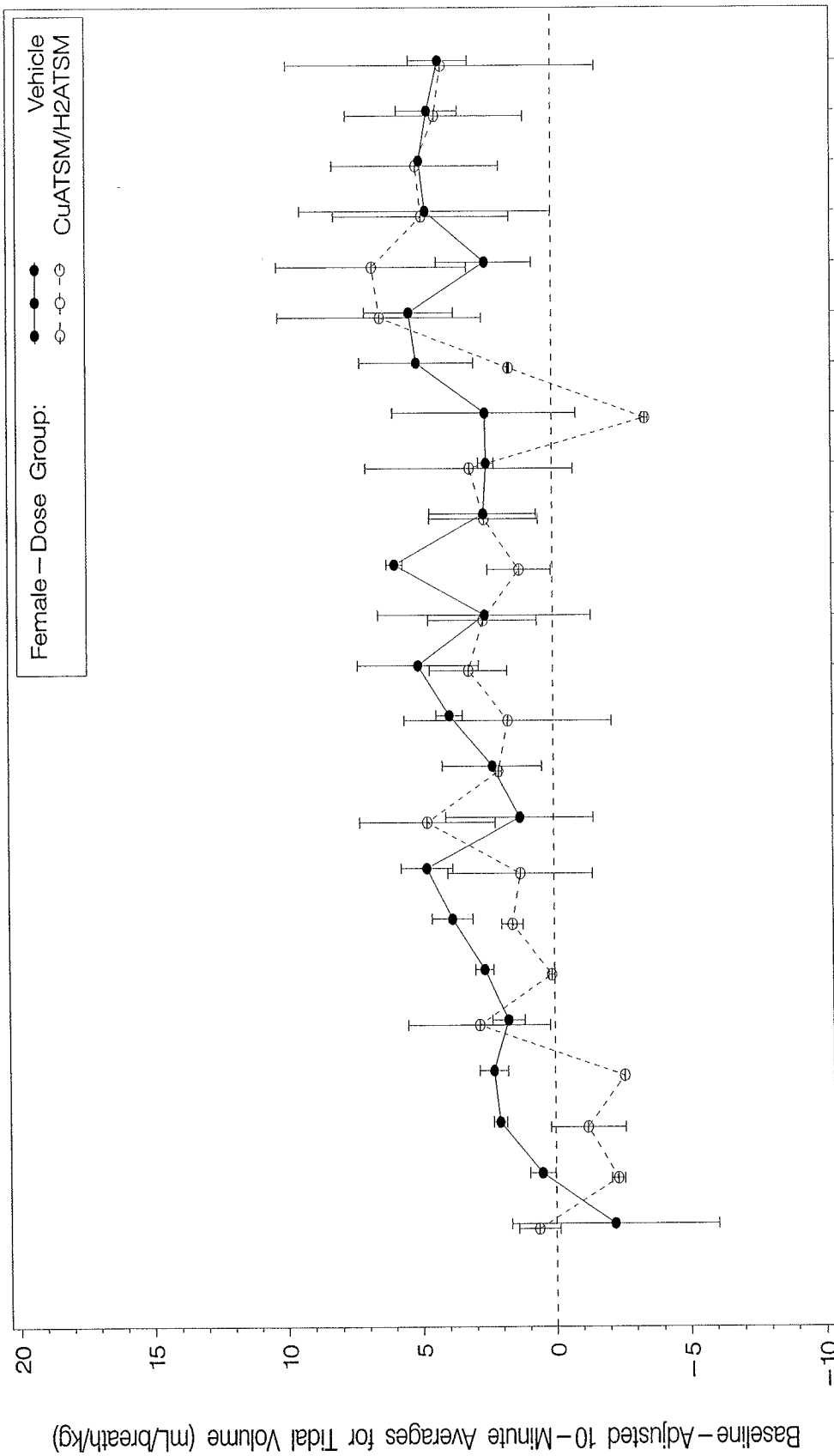


Figure 62. **Body Weight-Adjusted Tidal Volume (mL/breath/kg), Female Animals, Dose Group Means (and Standard Errors) of Baseline-Adjusted 10-Minute Averages during the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

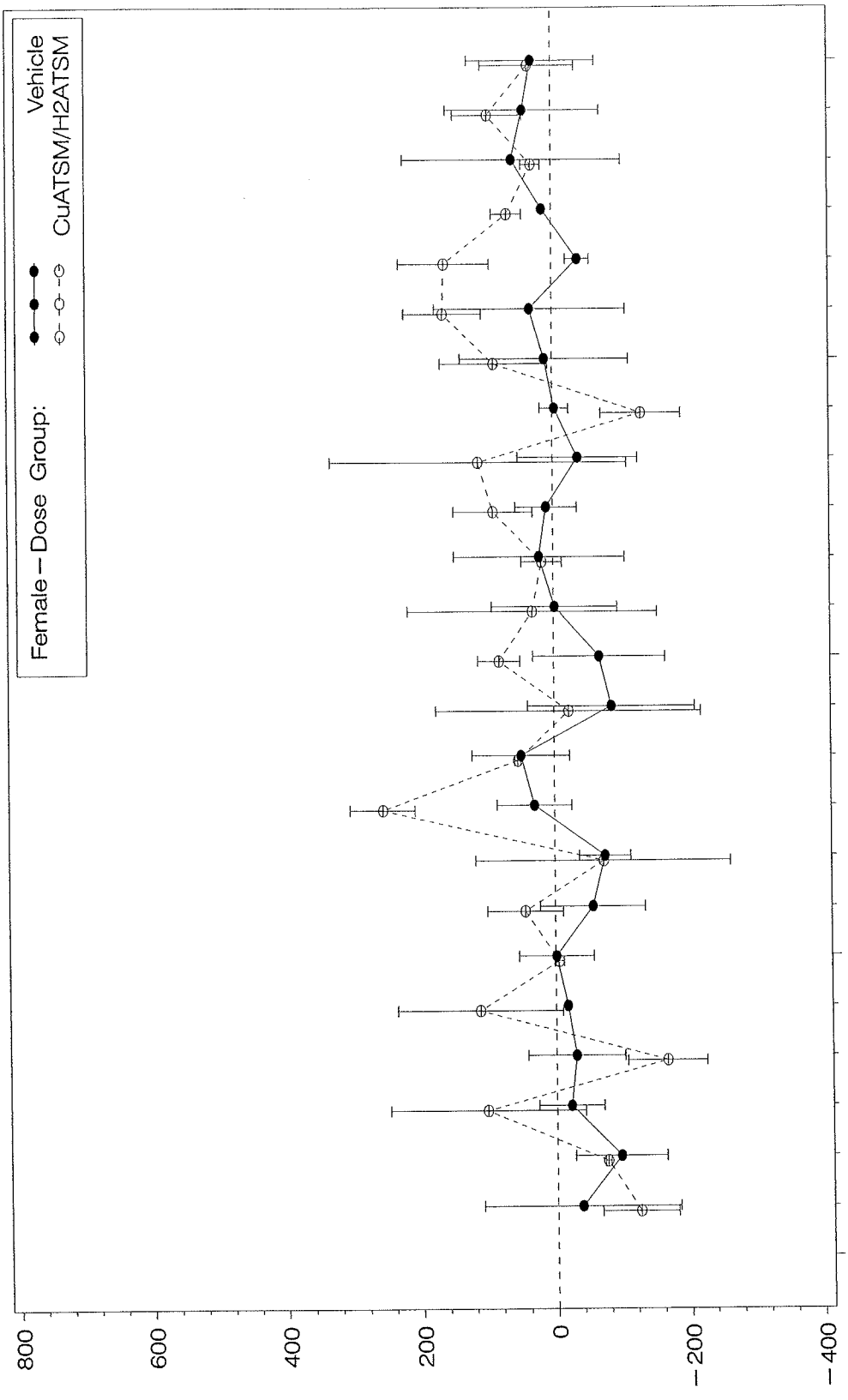


Figure 63. **Body Weight-Adjusted Minute Volume (mL/min/kg), Female Animals, Dose Group Means (and Standard Errors) of Baseline-Adjusted 10-Minute Averages during the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

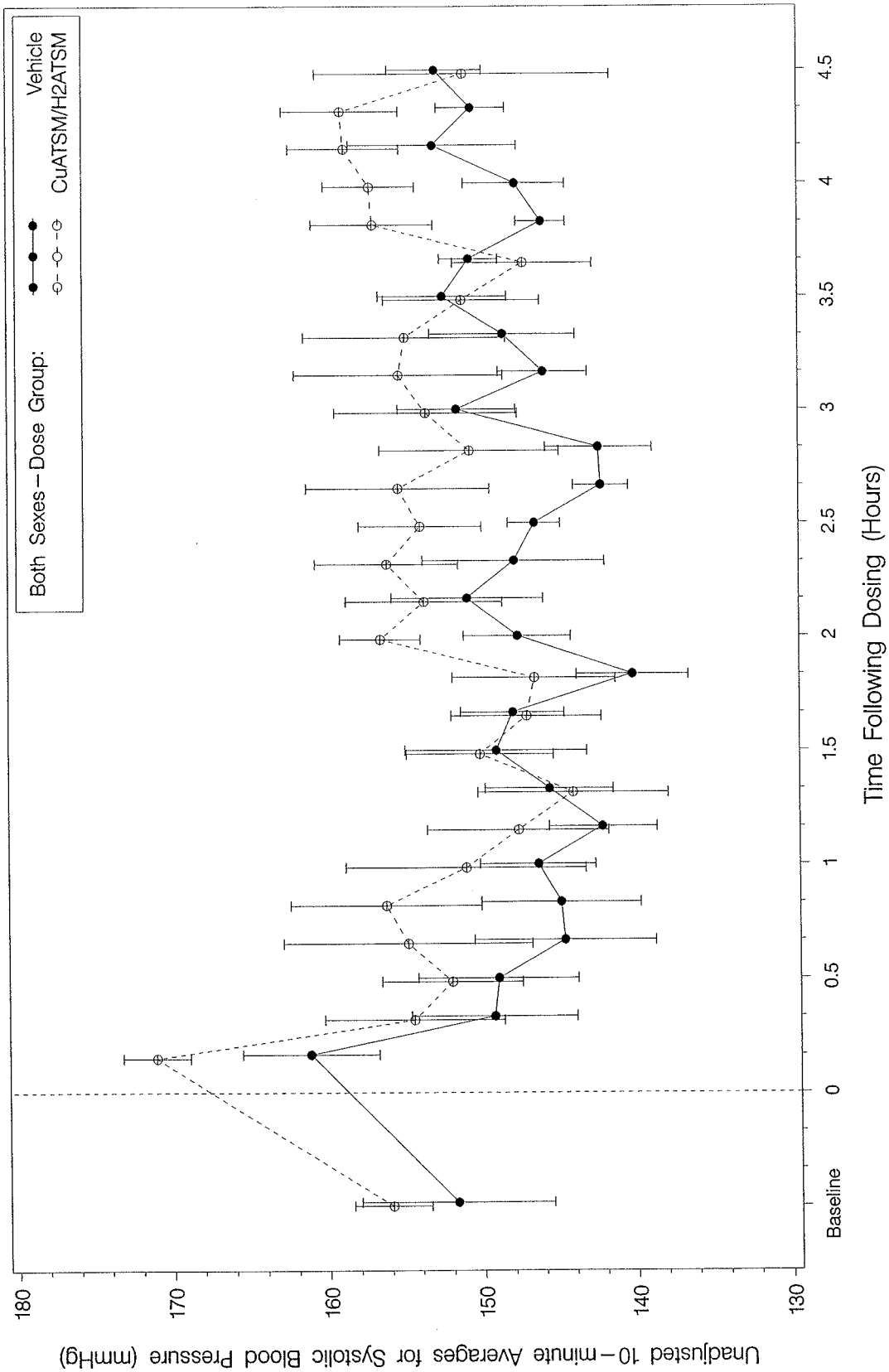


Figure U-1. **Systolic Blood Pressure (mmHg), Both Sexes, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

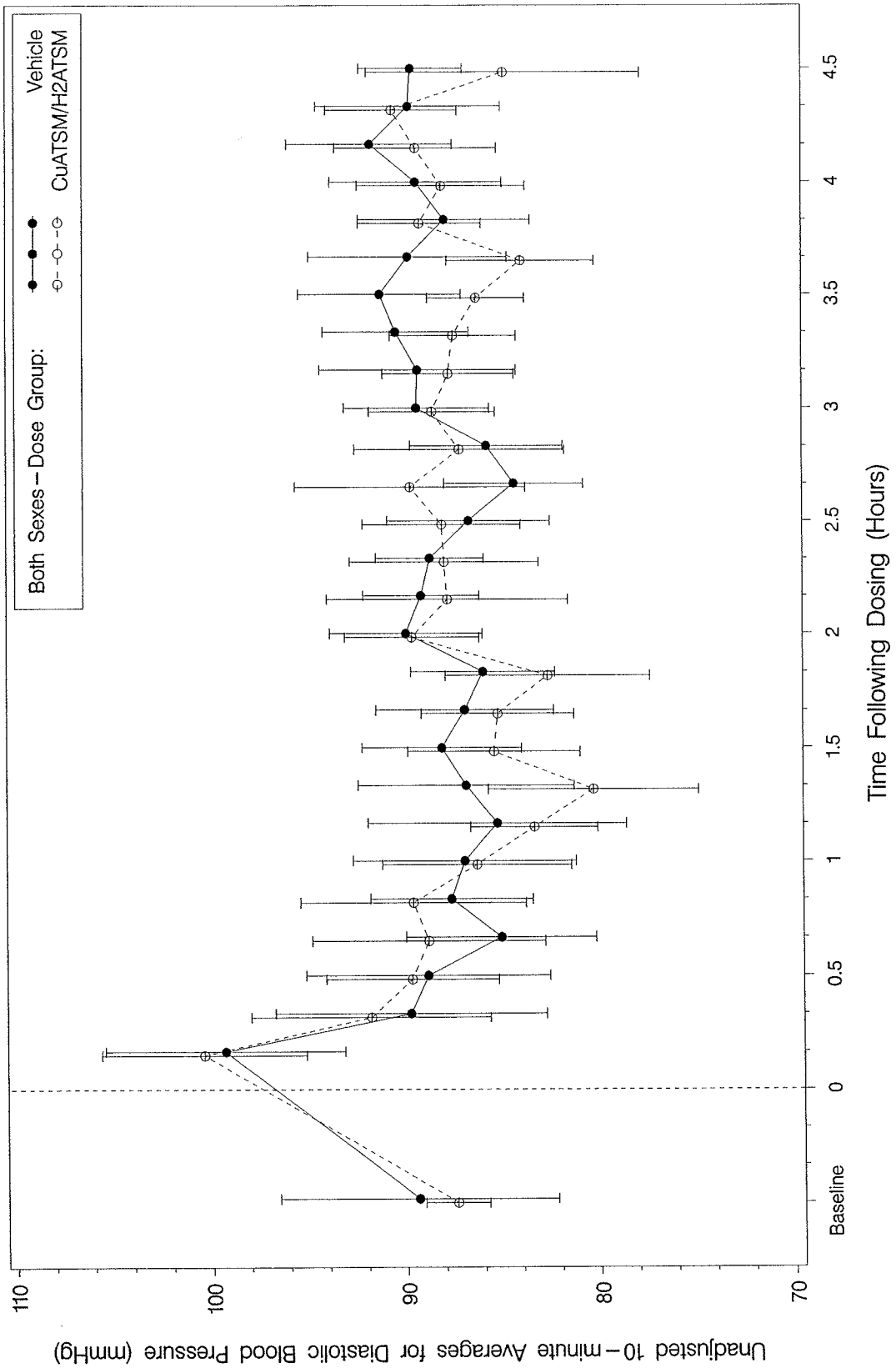


Figure U-2. **Diastolic Blood Pressure (mmHg), Both Sexes, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

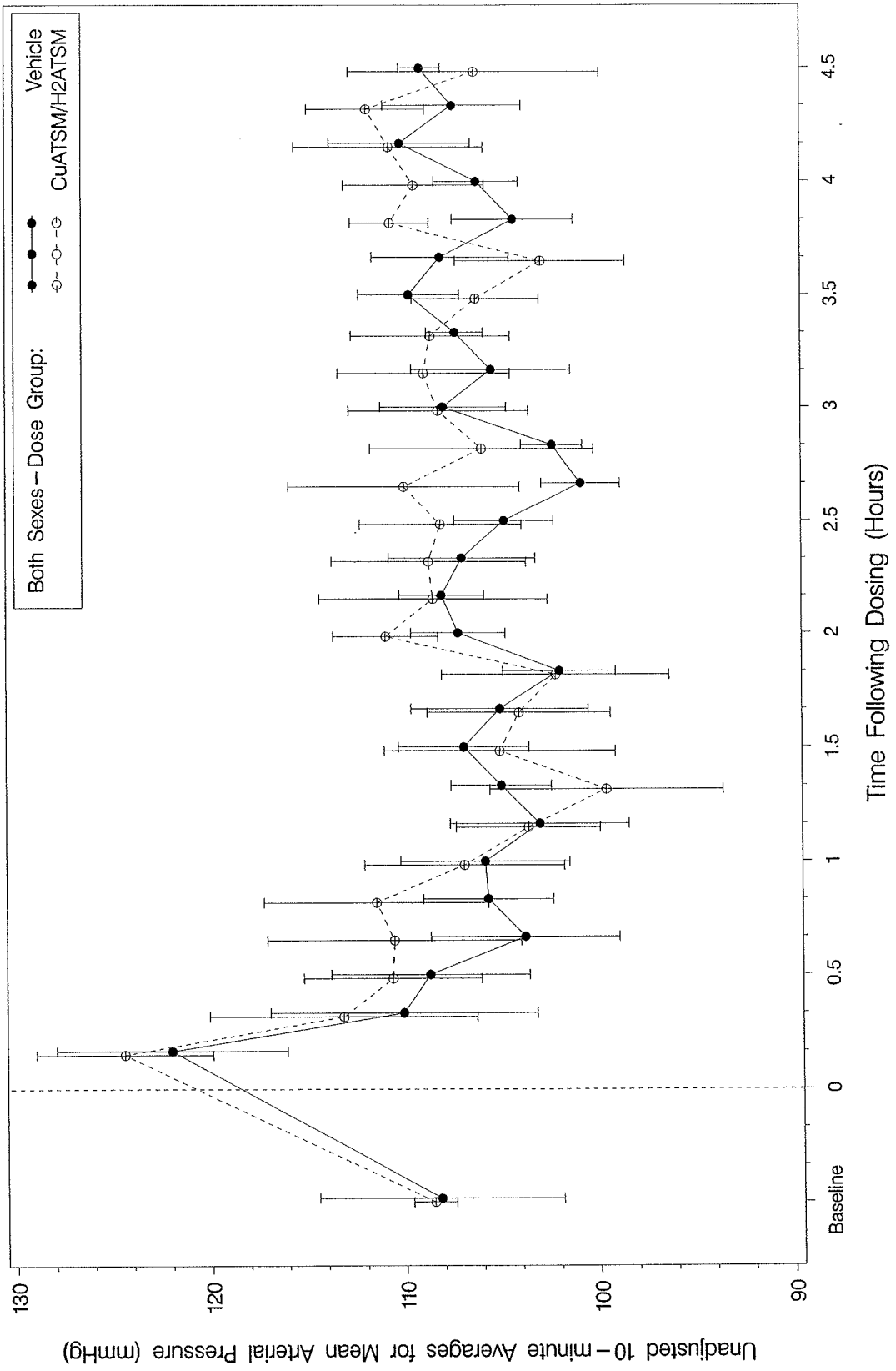


Figure U-3. **Mean Arterial Pressure (mmHg), Both Sexes, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

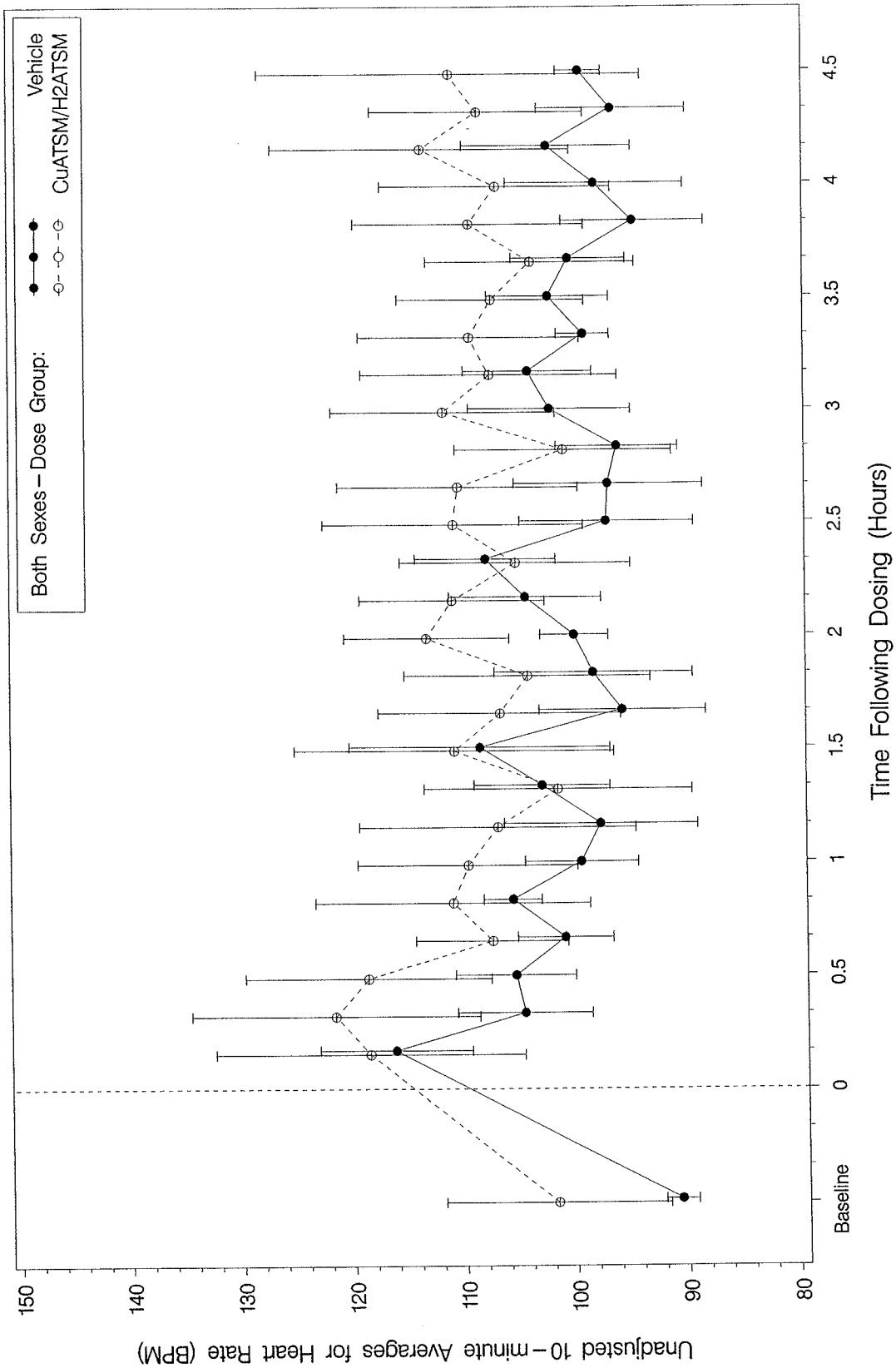


Figure U-4. **Heart Rate (BPM), Both Sexes, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with $CuATSM/H_2ATSM$ or Vehicle**

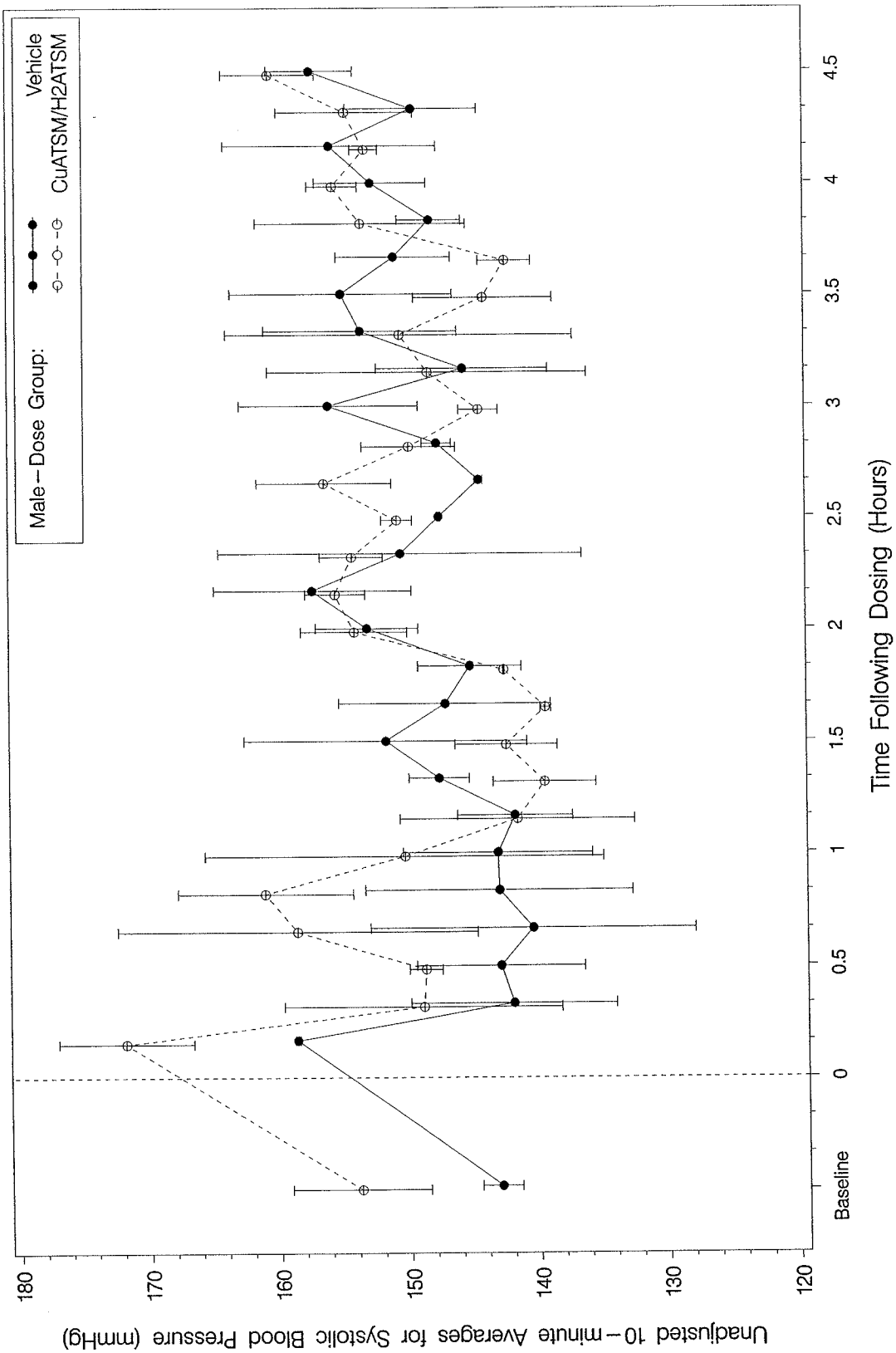


Figure U-5. **Systolic Blood Pressure (mmHg), Male Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

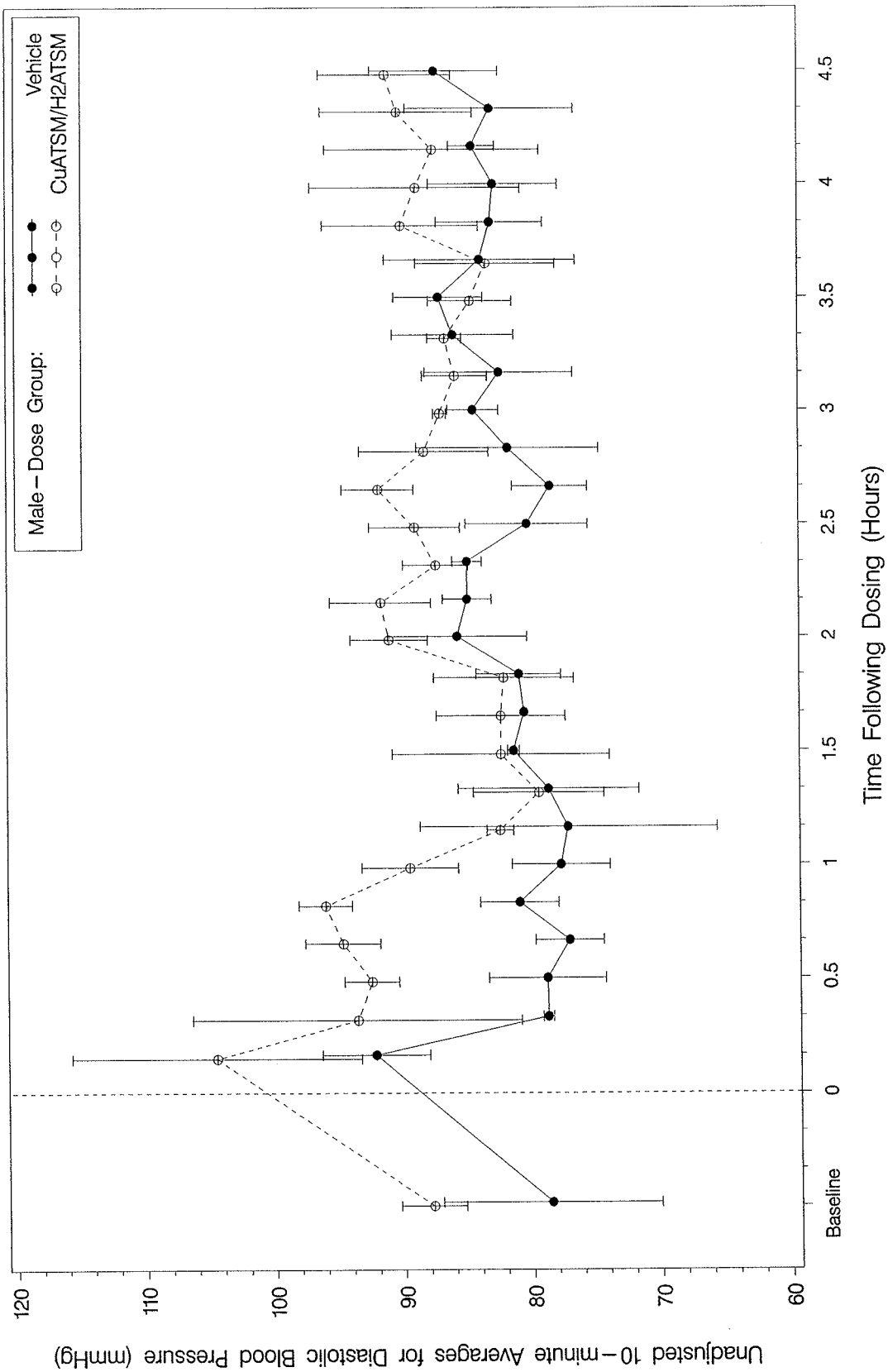


Figure U-6. **Diastolic Blood Pressure (mmHg), Male Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

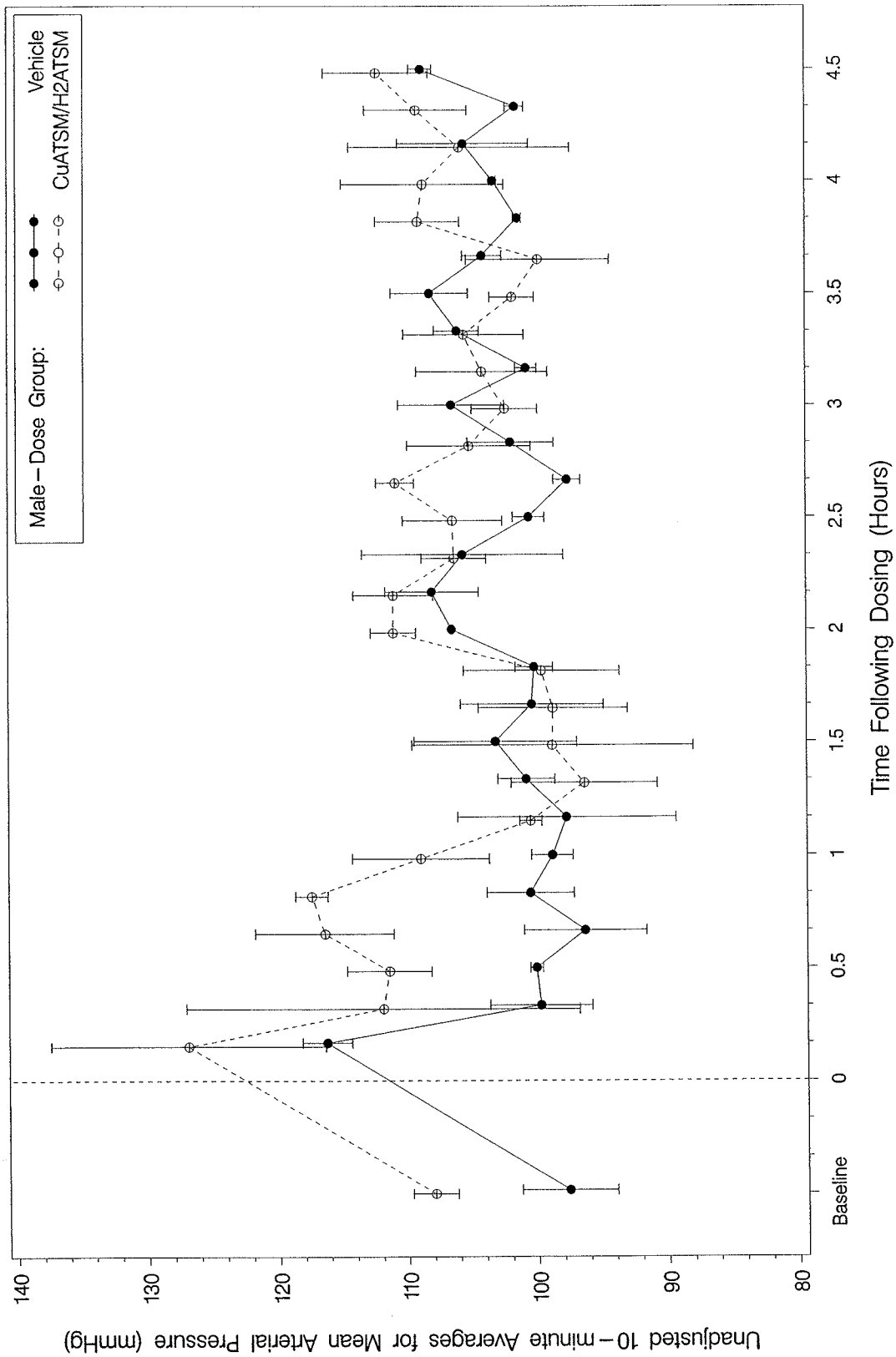


Figure U-7. **Mean Arterial Pressure (mmHg), Male Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

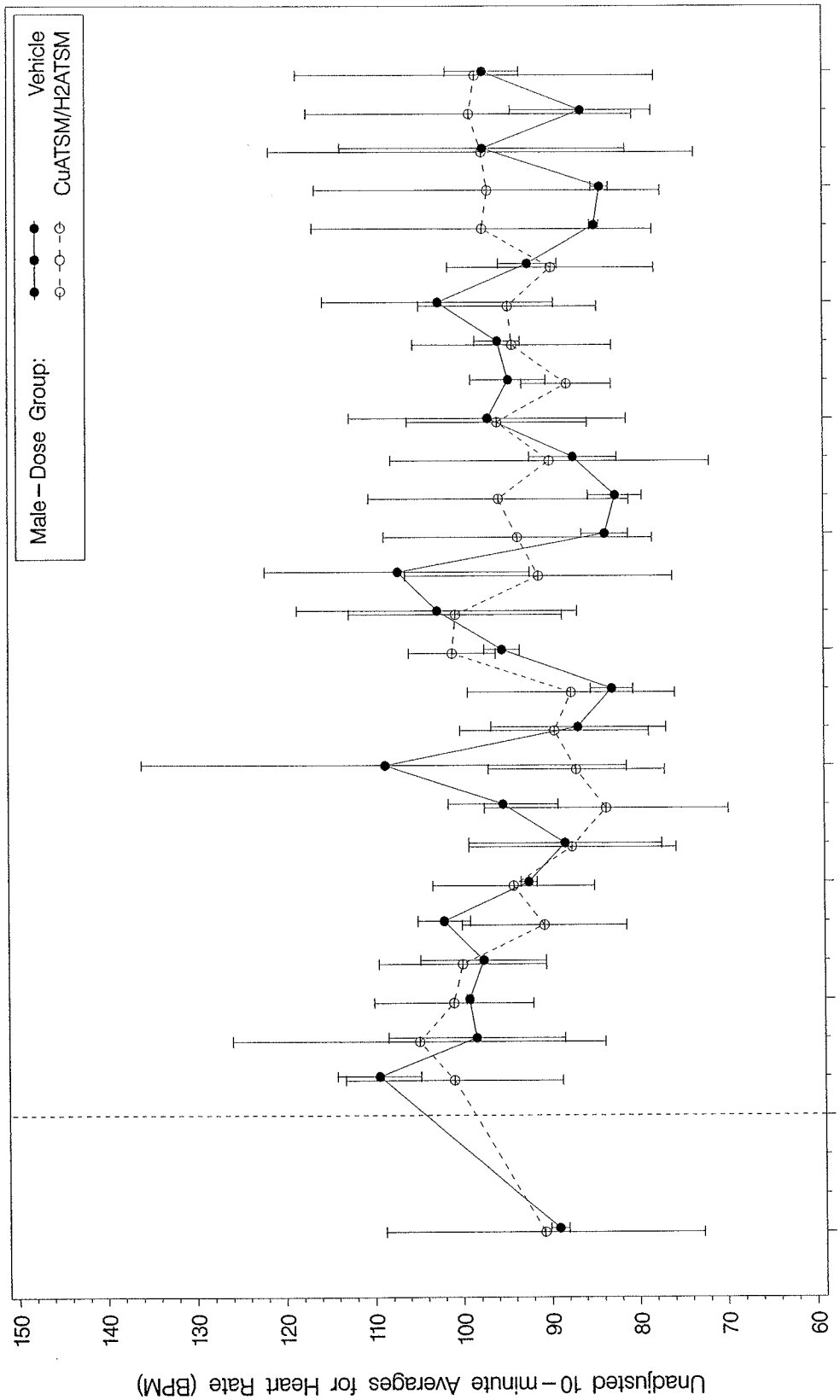


Figure U-8. **Heart Rate (BPM), Male Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with $CuATSM/H_2ATSM$ or Vehicle**

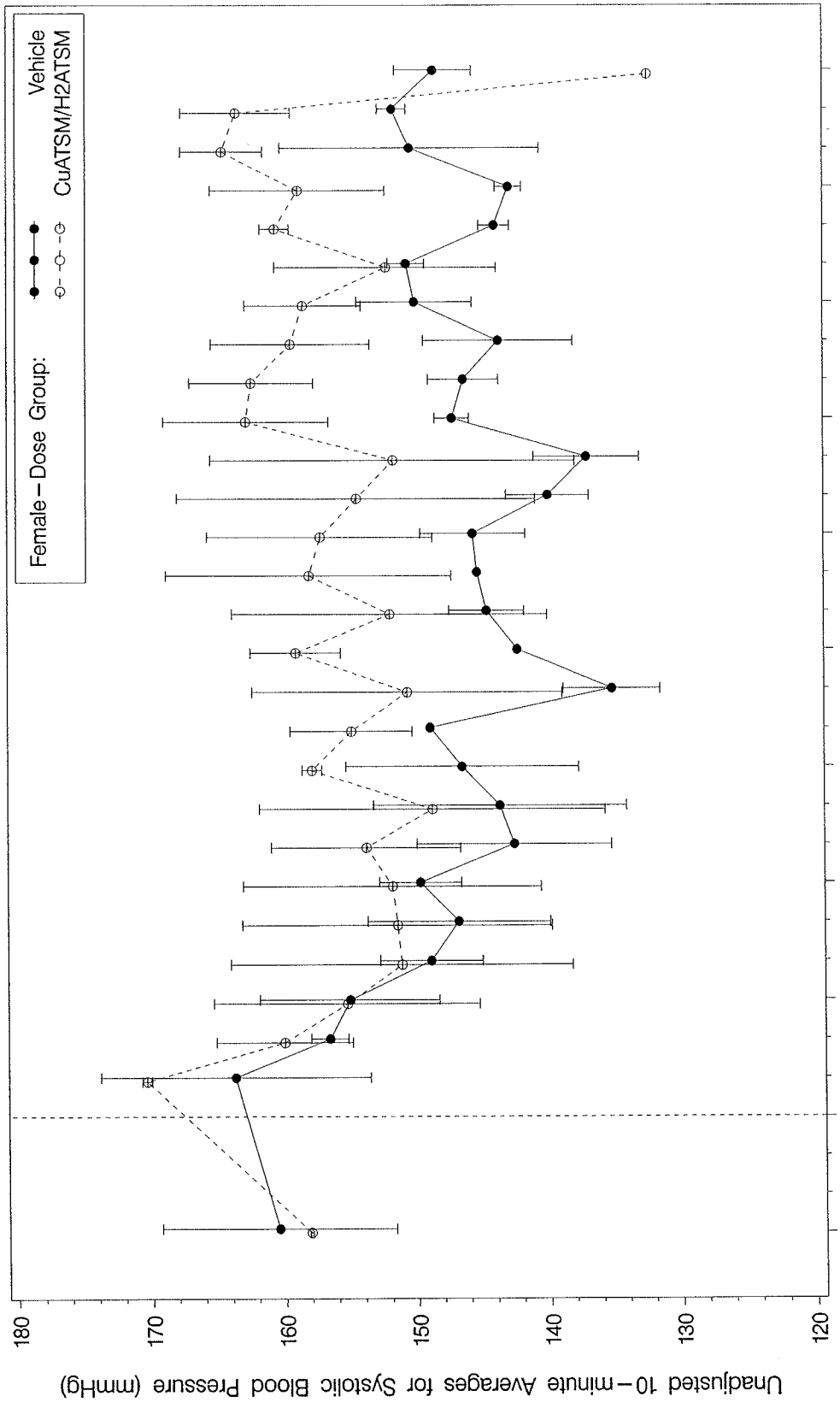


Figure U-9. **Systolic Blood Pressure (mmHg), Female Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

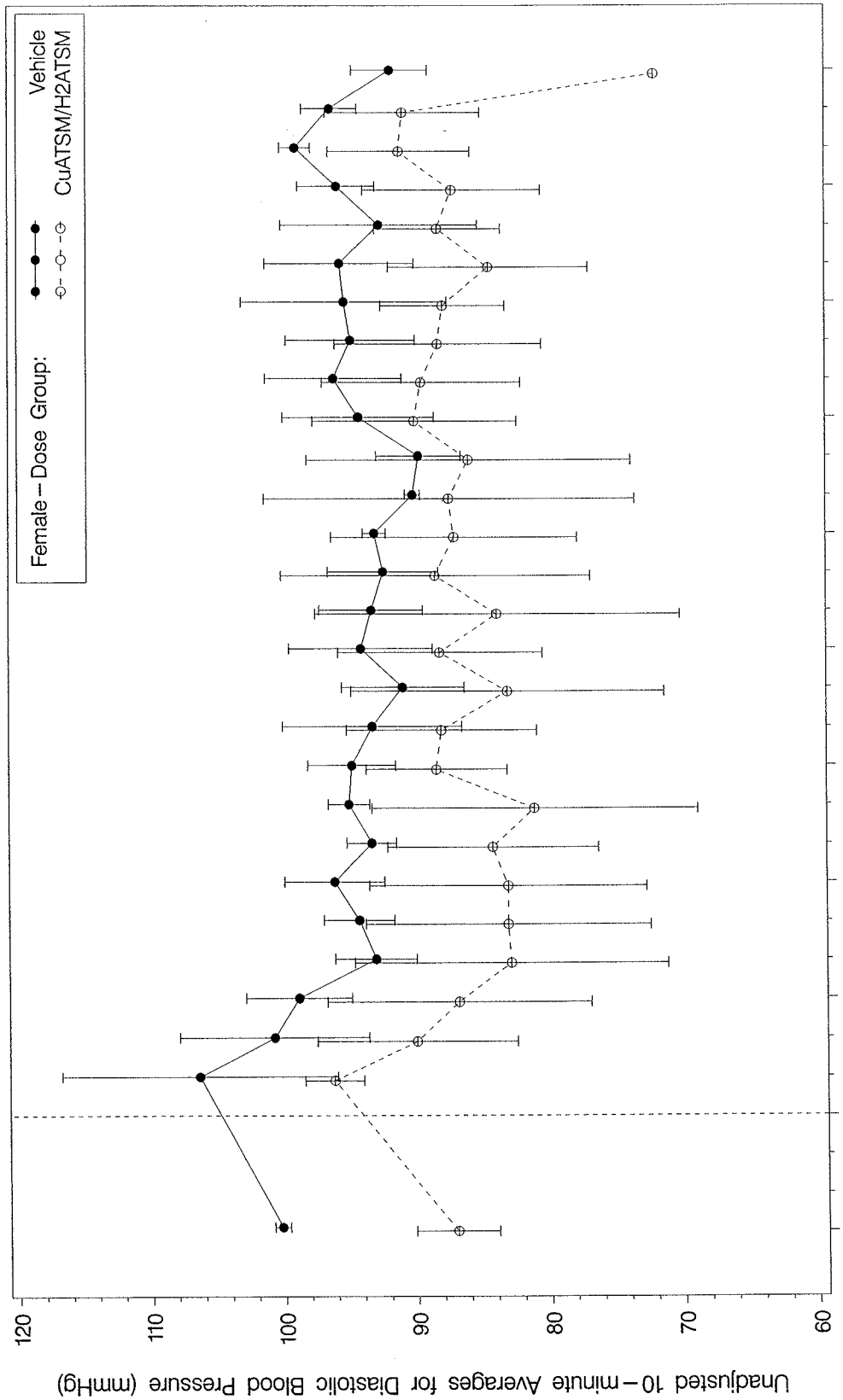


Figure U-10. **Diastolic Blood Pressure (mmHg), Female Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

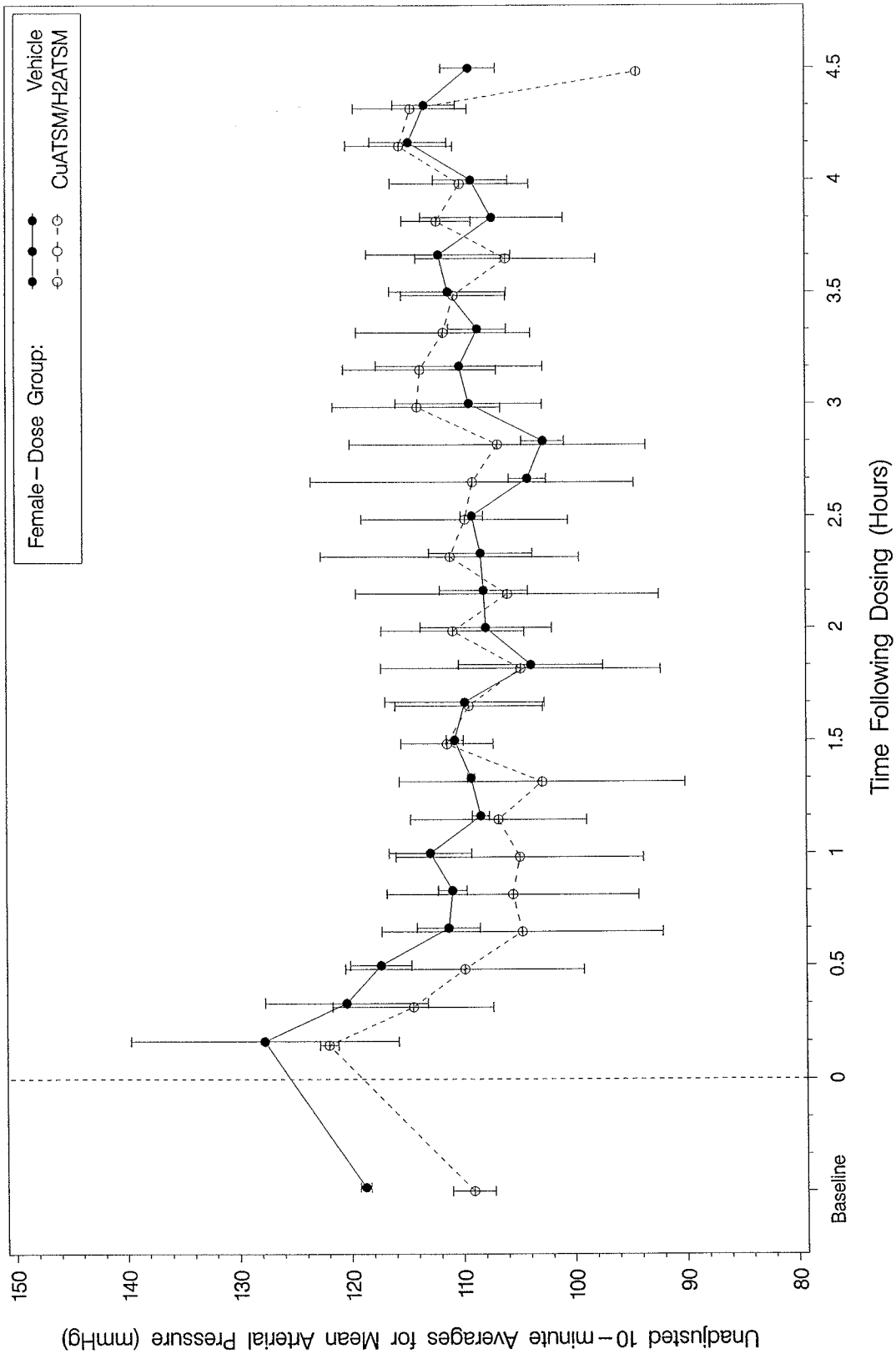


Figure U-11. Mean Arterial Pressure (mmHg), Female Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

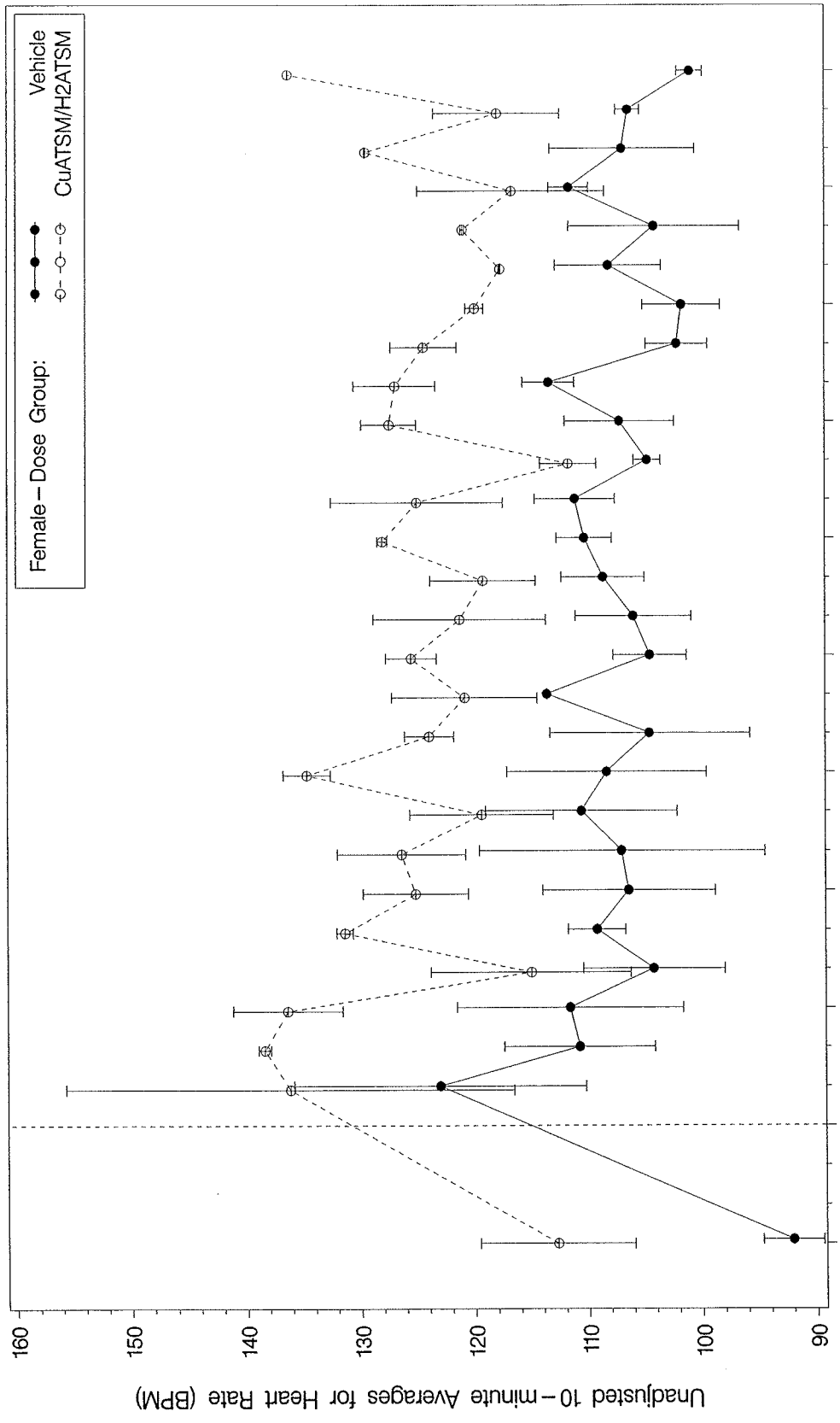


Figure U-12. **Heart Rate (BPM), Female Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted 10-Minute Averages Within the 4.5-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

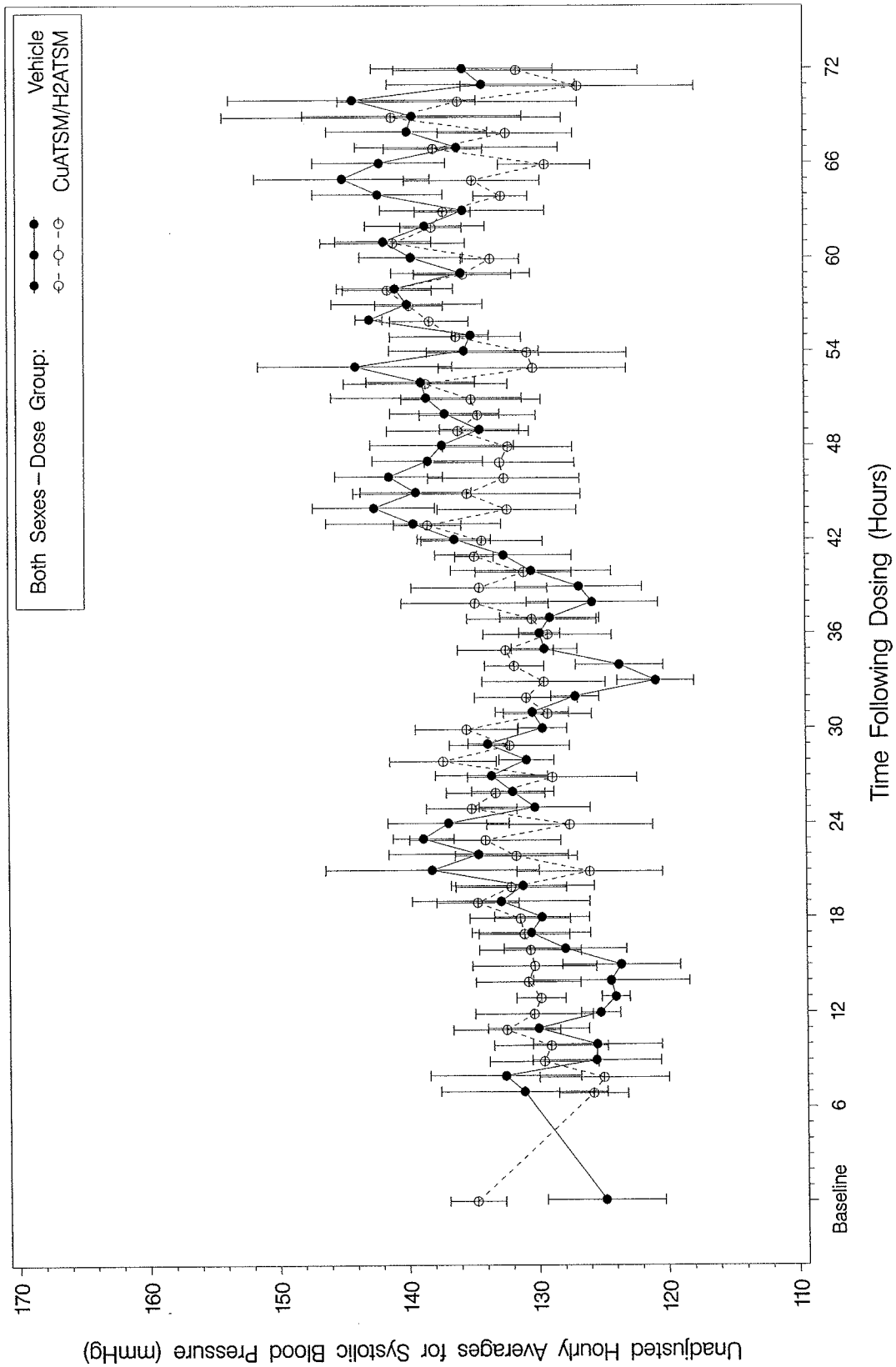


Figure U-13. **Systolic Blood Pressure (mmHg), Both Sexes, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted Hourly Averages Within a 66-Hour Period Following Dosing with $CuATSM/H_2ATSM$ or Vehicle**

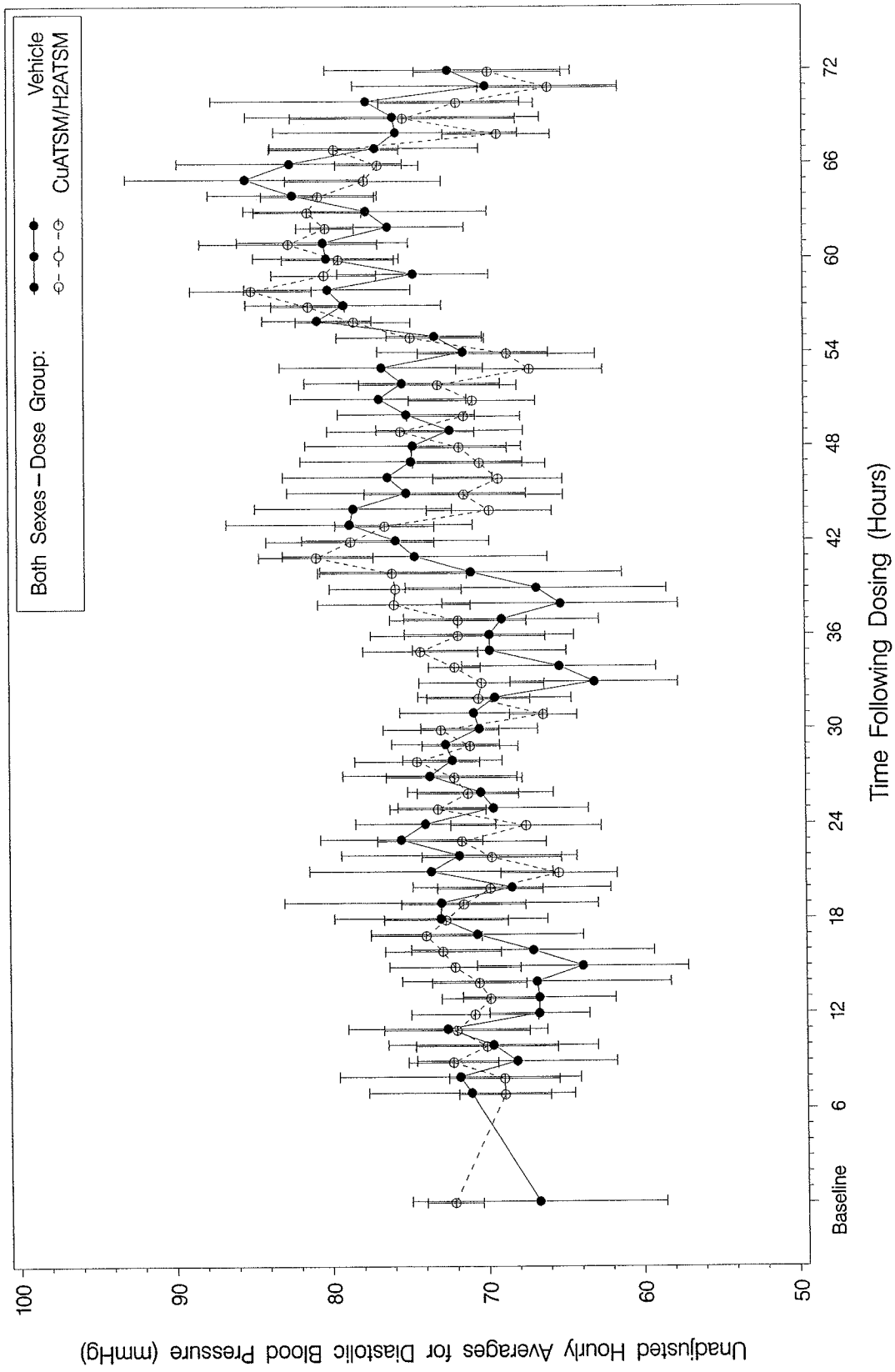


Figure U-14. **Diastolic Blood Pressure (mmHg), Both Sexes, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle**

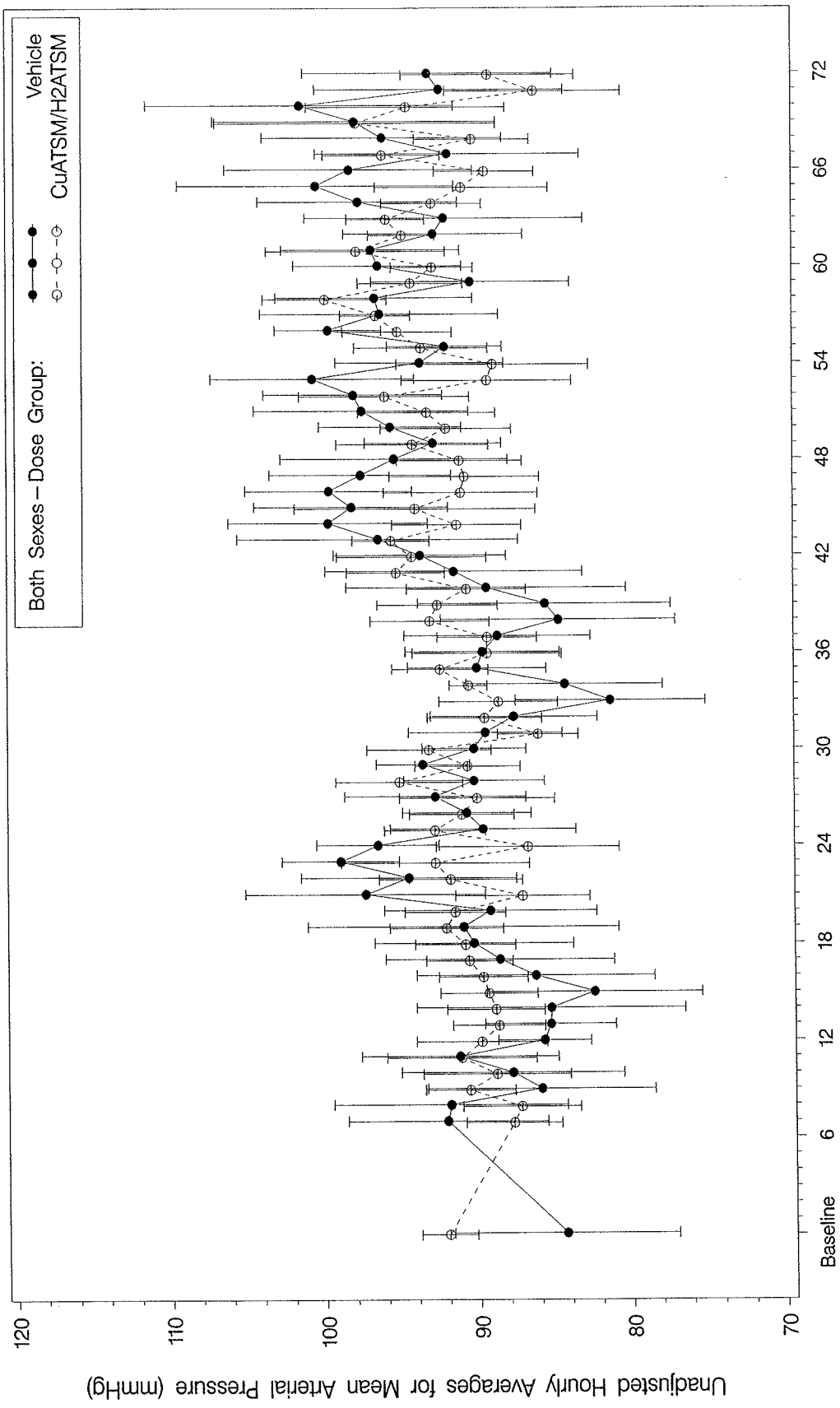


Figure U-15. **Mean Arterial Pressure (mmHg), Both Sexes, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle**

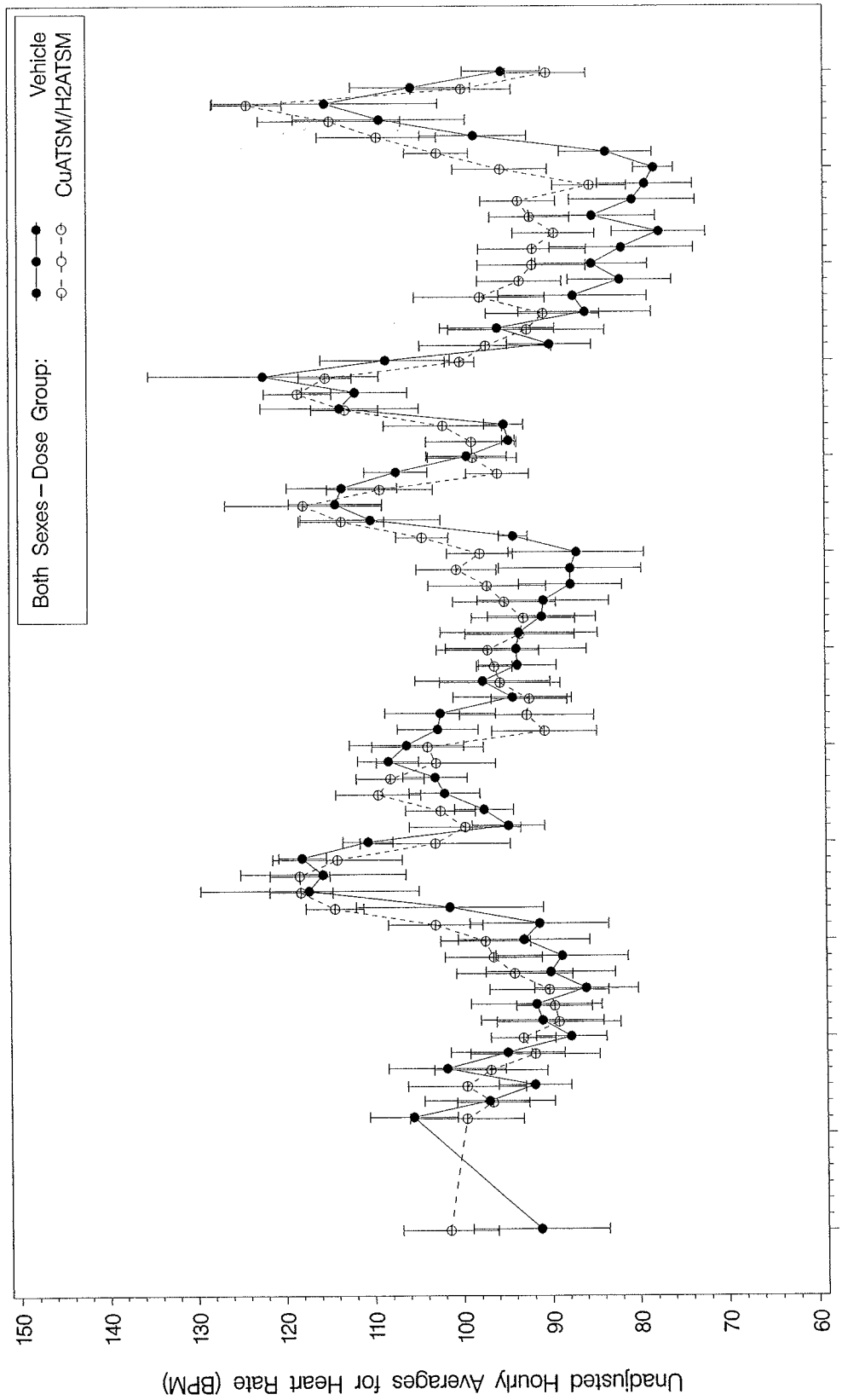


Figure U-16. Heart Rate (BPM), Both Sexes, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle

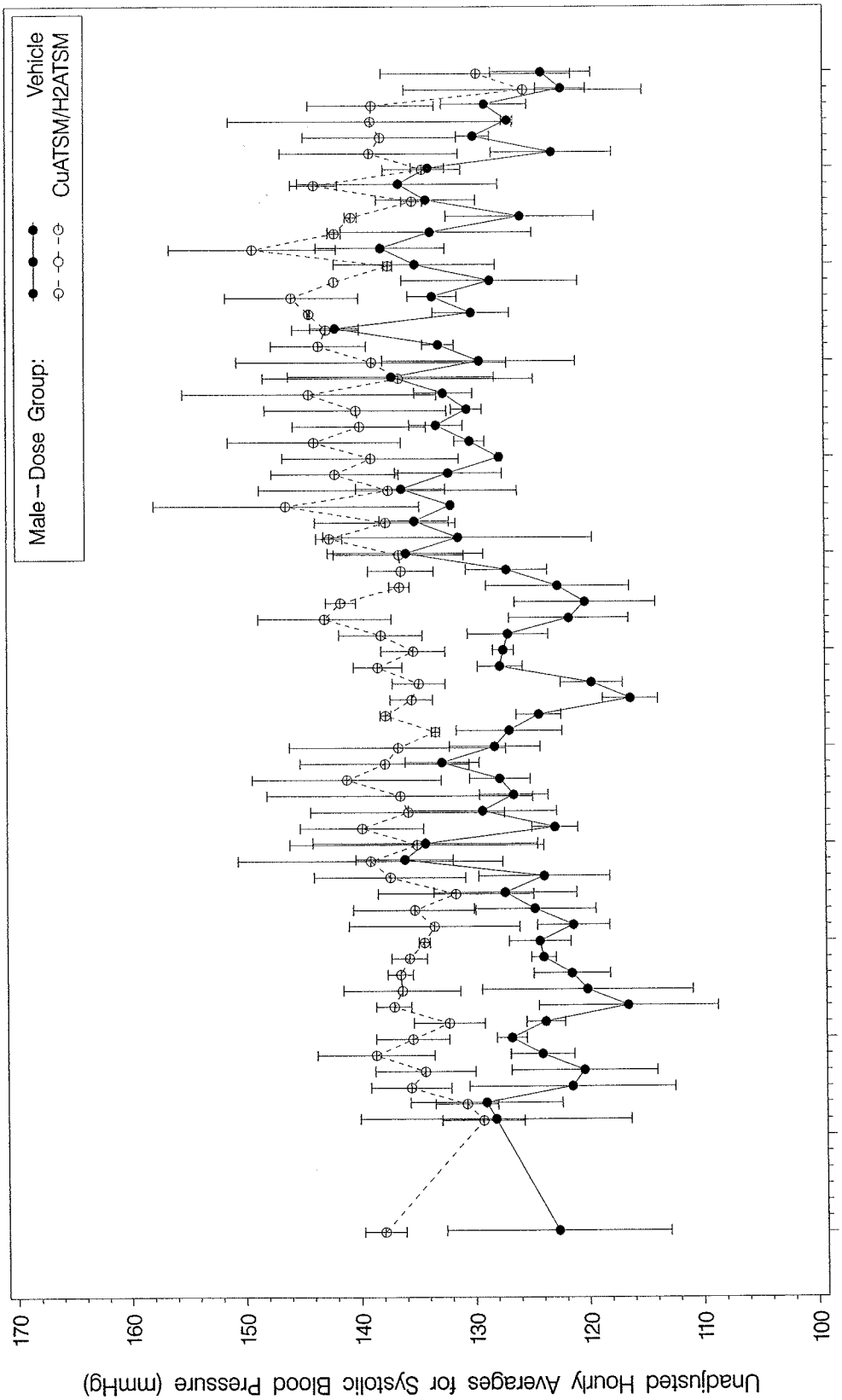


Figure U-17. **Systolic Blood Pressure (mmHg), Male Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle**

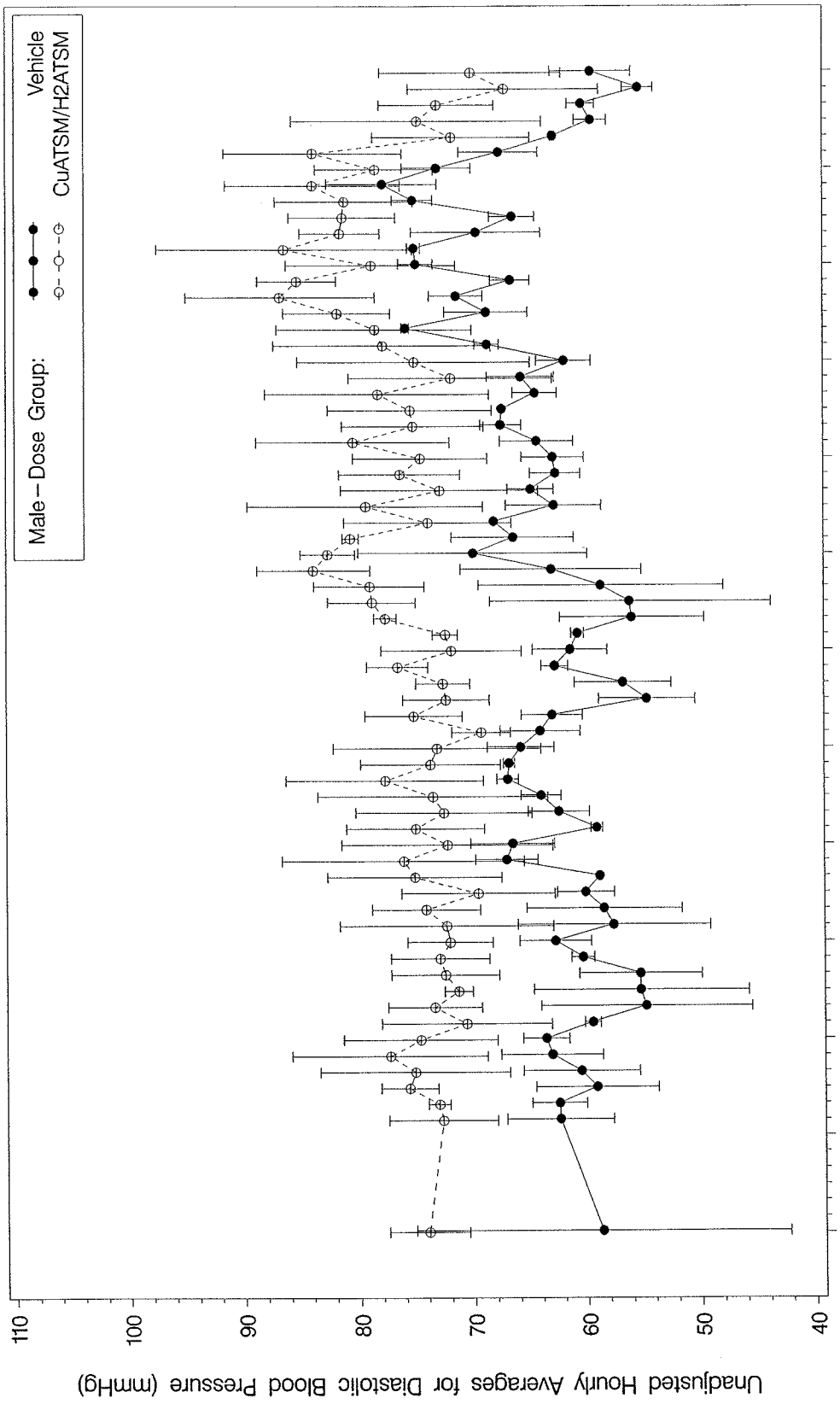


Figure U-18. Diastolic Blood Pressure (mmHg), Male Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle

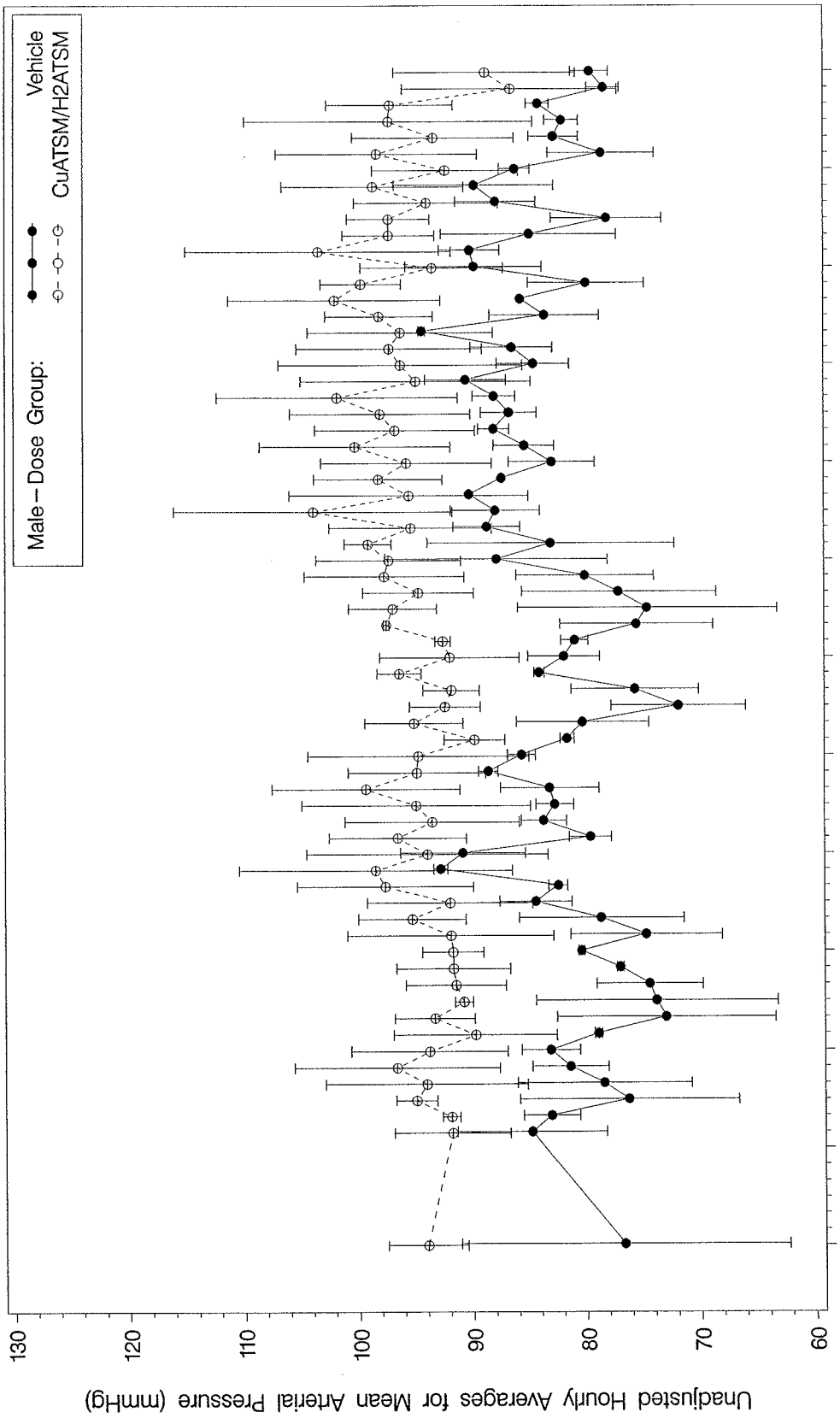


Figure U-19. **Mean Arterial Pressure (mmHg), Male Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle**

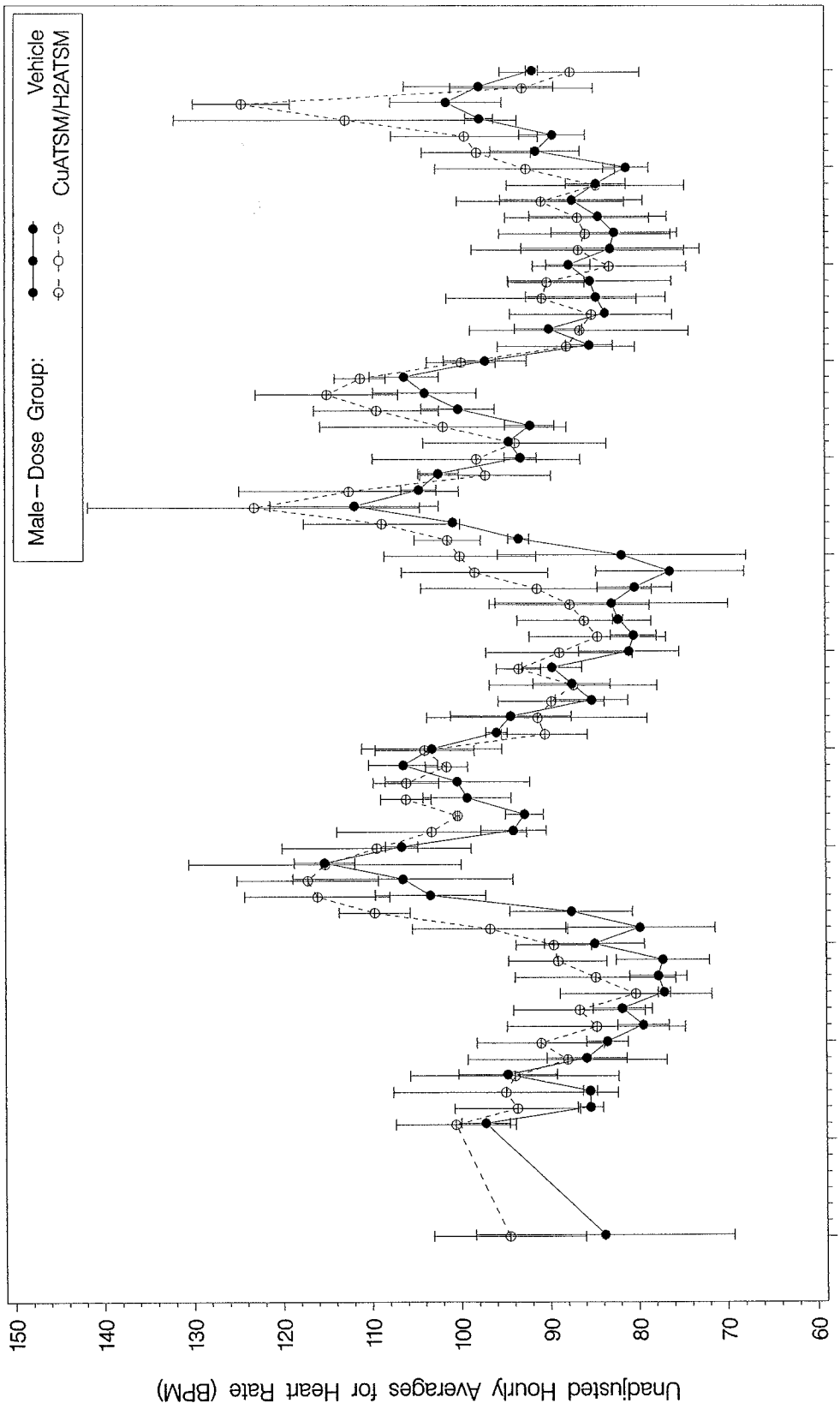


Figure U-20. **<u>Heart Rate</u> (BPM), <u>Male Animals</u>, <u>In-Cage</u> Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle**

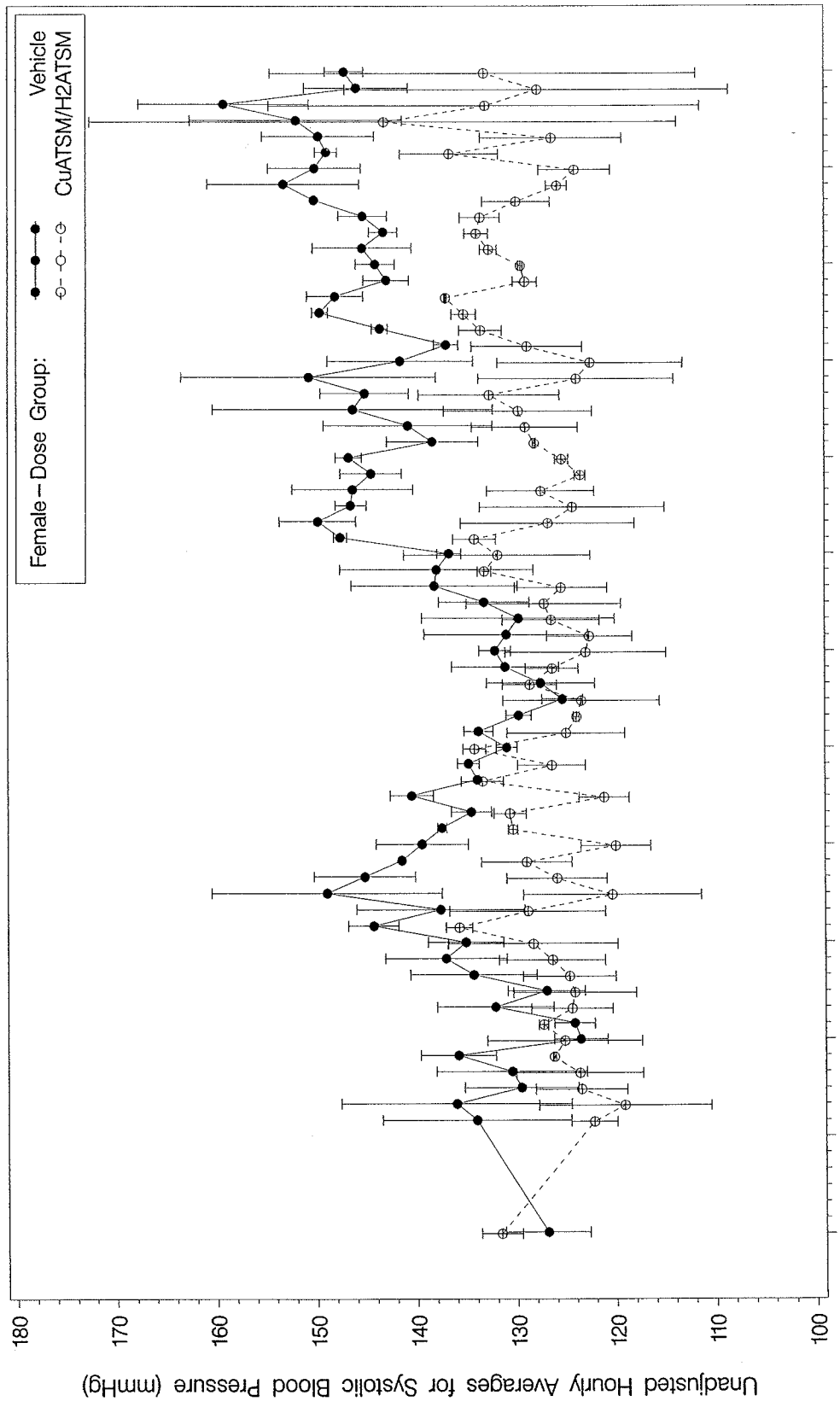


Figure U-21. Systolic Blood Pressure (mmHg), Female Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H$_2$ATSM or Vehicle

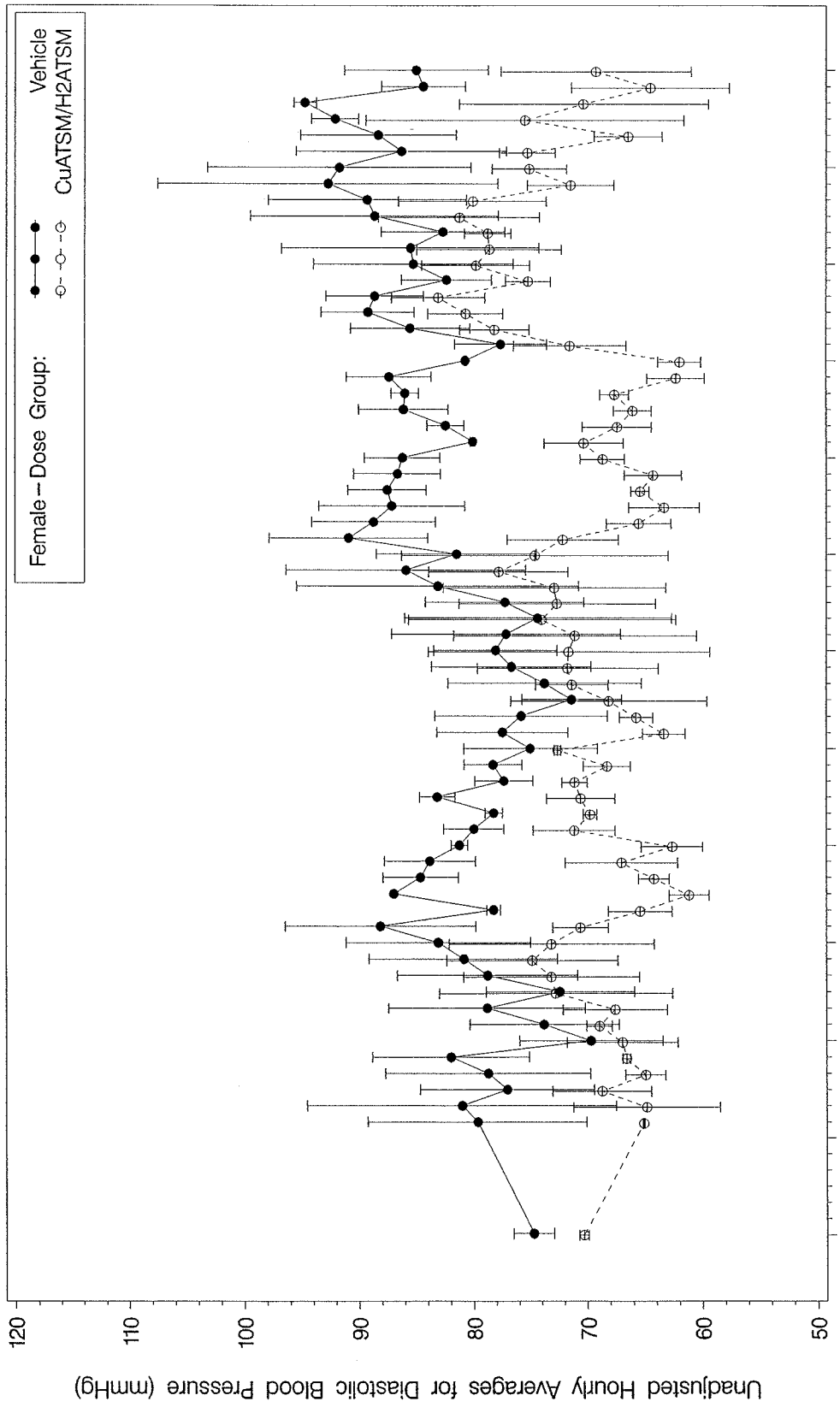


Figure U-22. Diastolic Blood Pressure (mmHg), Female Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle

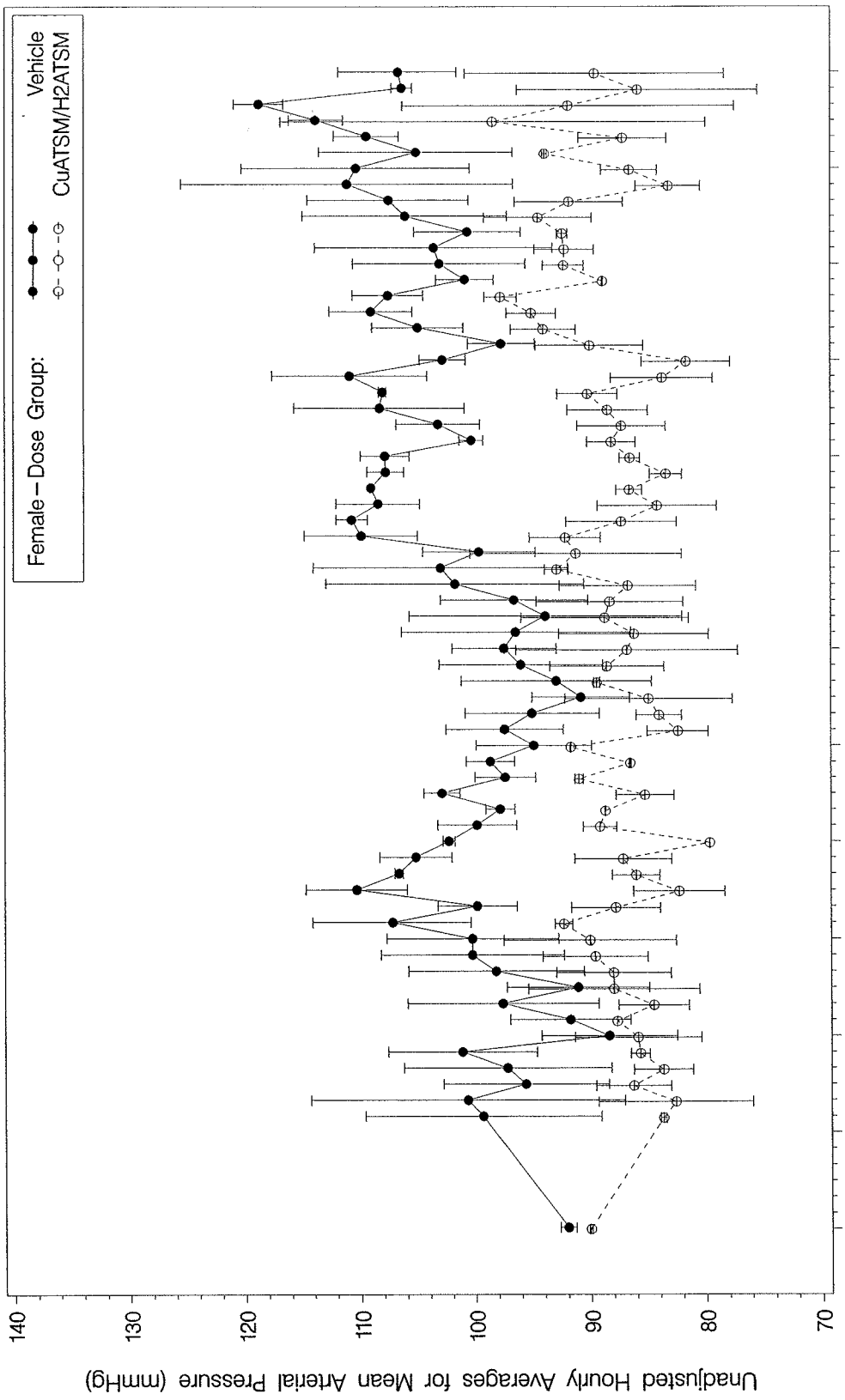


Figure U-23. Mean Arterial Pressure (mmHg), Female Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle

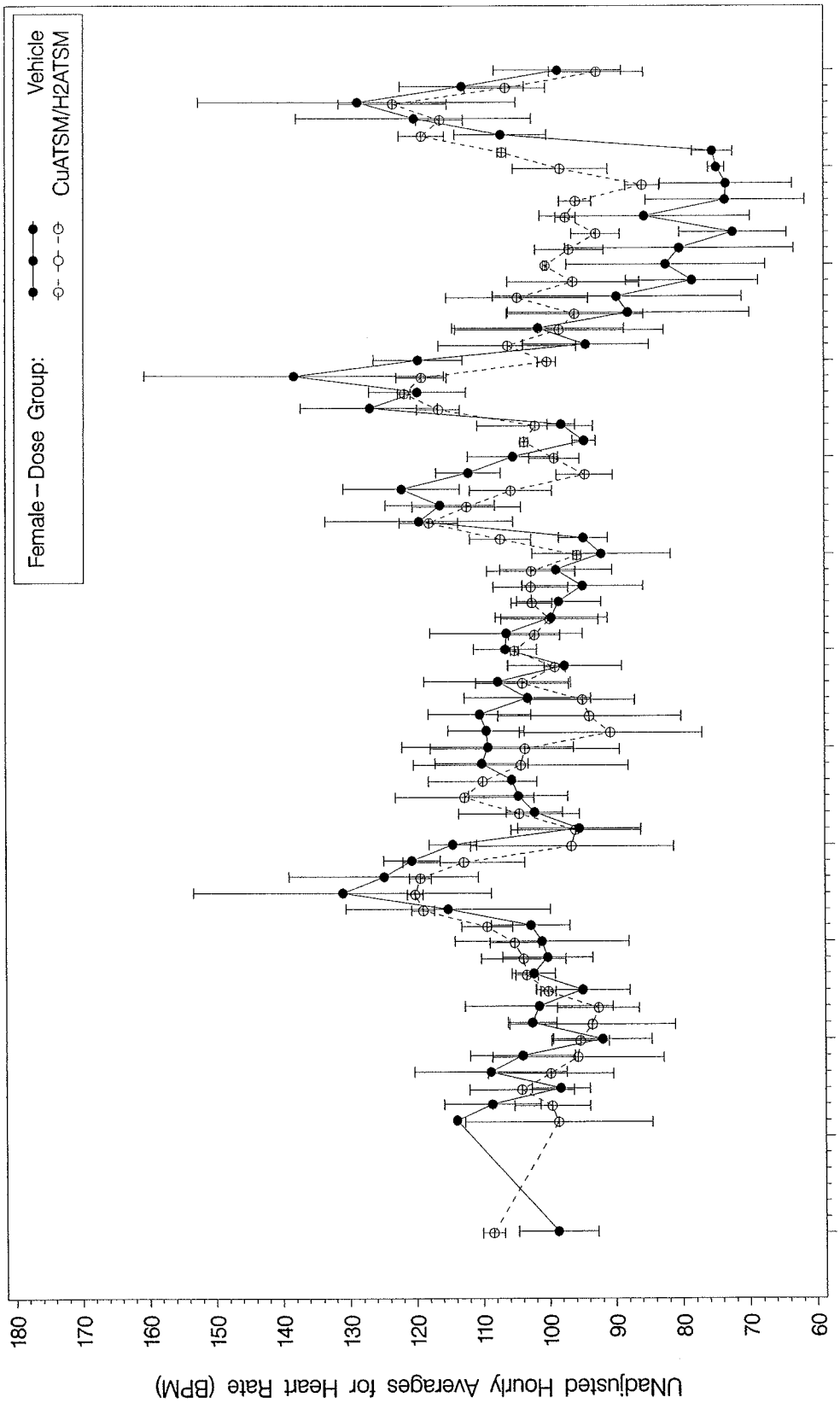


Figure U-24. **Heart Rate (BPM), Female Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Baseline Average and Unadjusted Hourly Averages Within a 66-Hour Period Following Dosing with CuATSM/H_2ATSM or Vehicle**

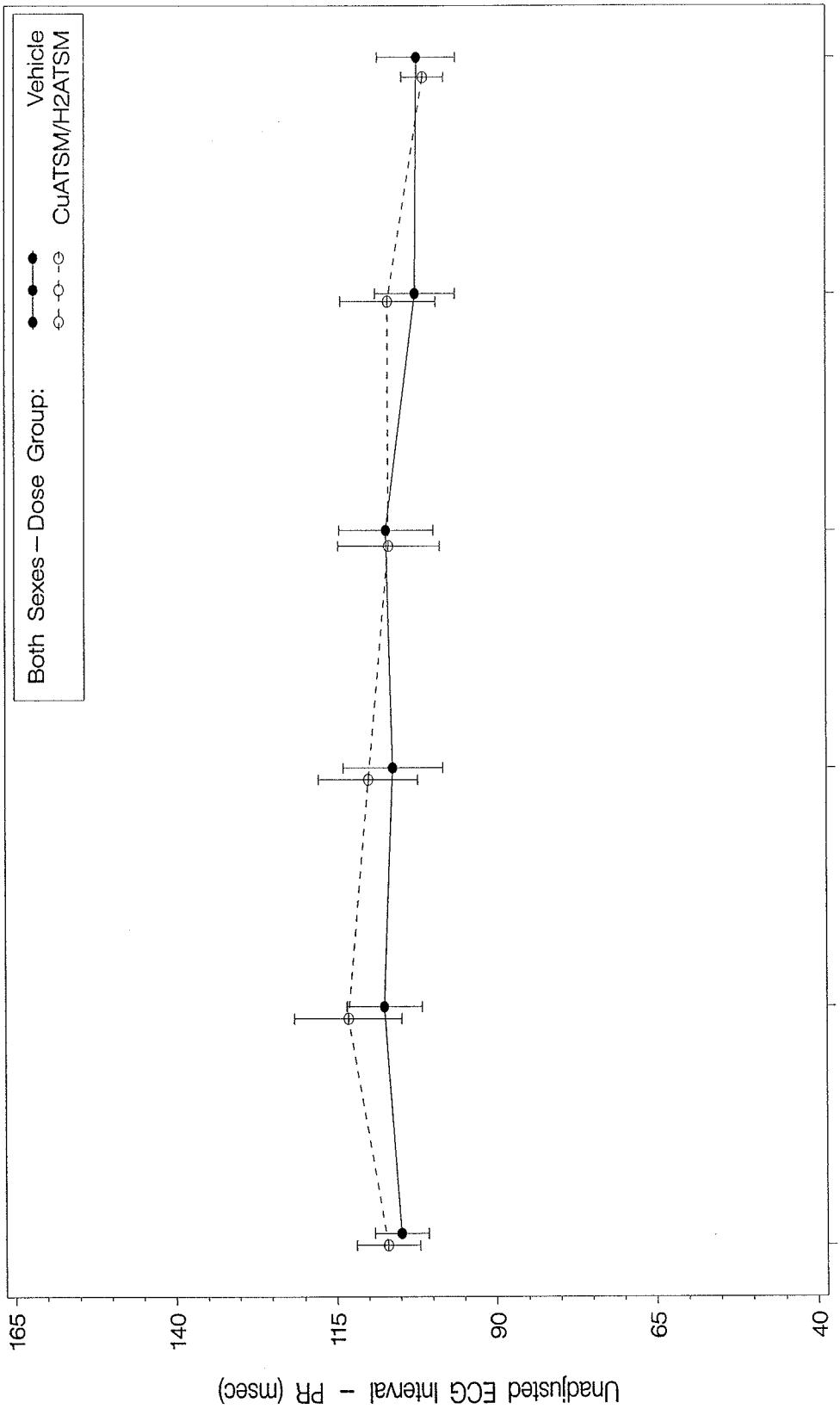


Figure U-25. PR Interval (msec), Both Sexes, In-Sling Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

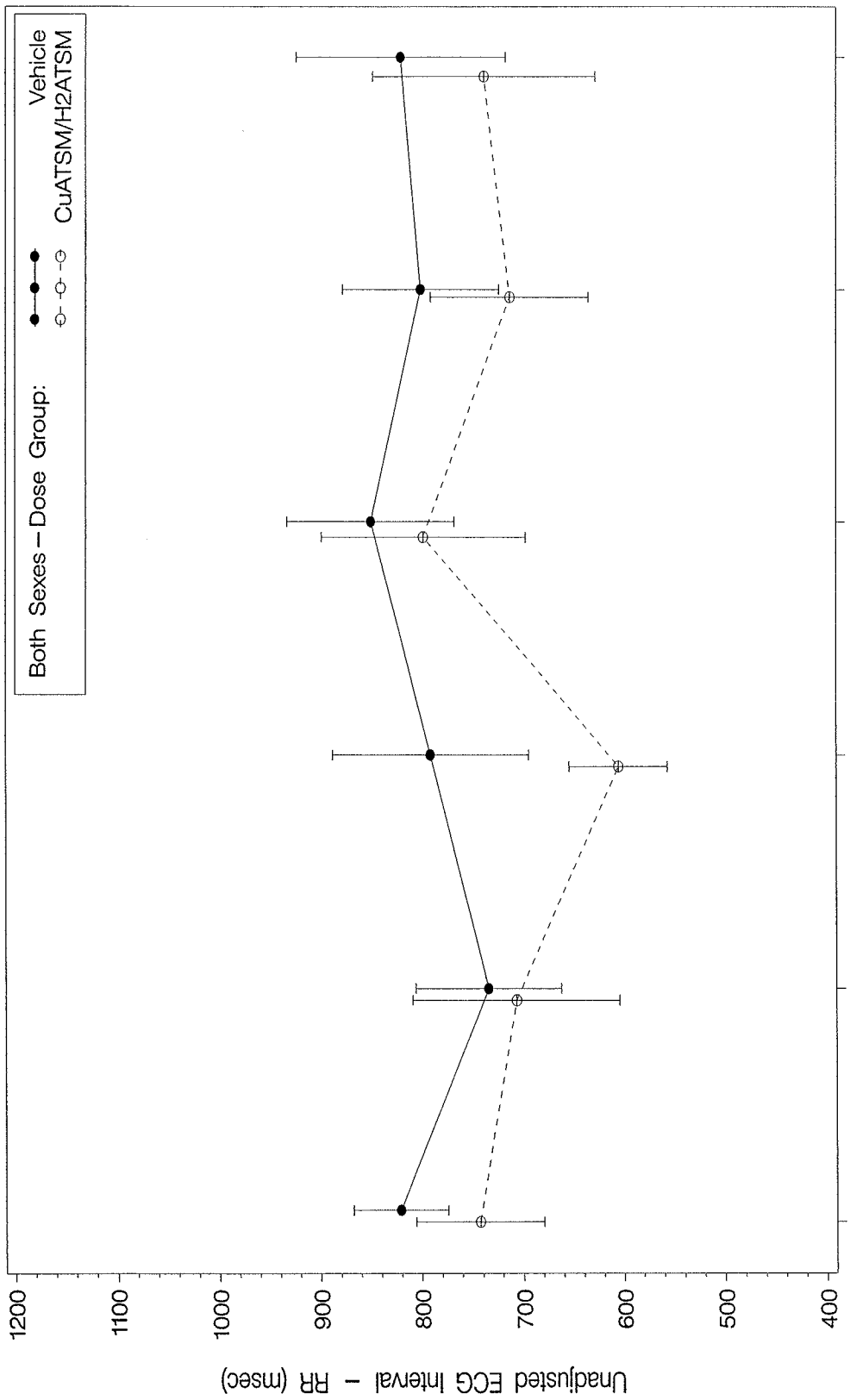


Figure U-26. RR Interval (msec), Both Sexes, In-Sling Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

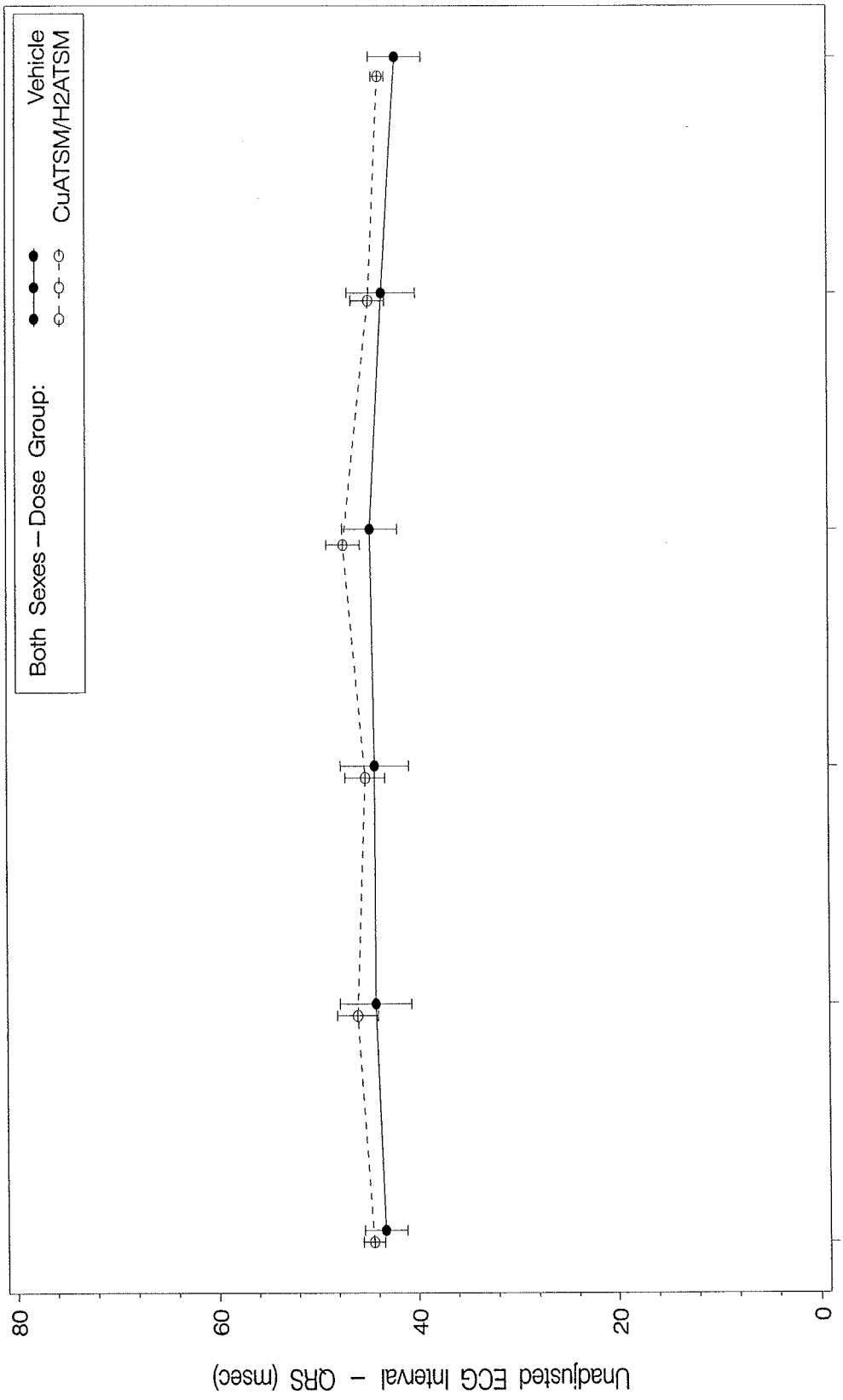


Figure U-27. QRS Interval (msec), Both Sexes, In-Sling Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the 4-Hour Period Immediately Following Dosing with $Cu^{II}ATSM/H_2ATSM$ or Vehicle

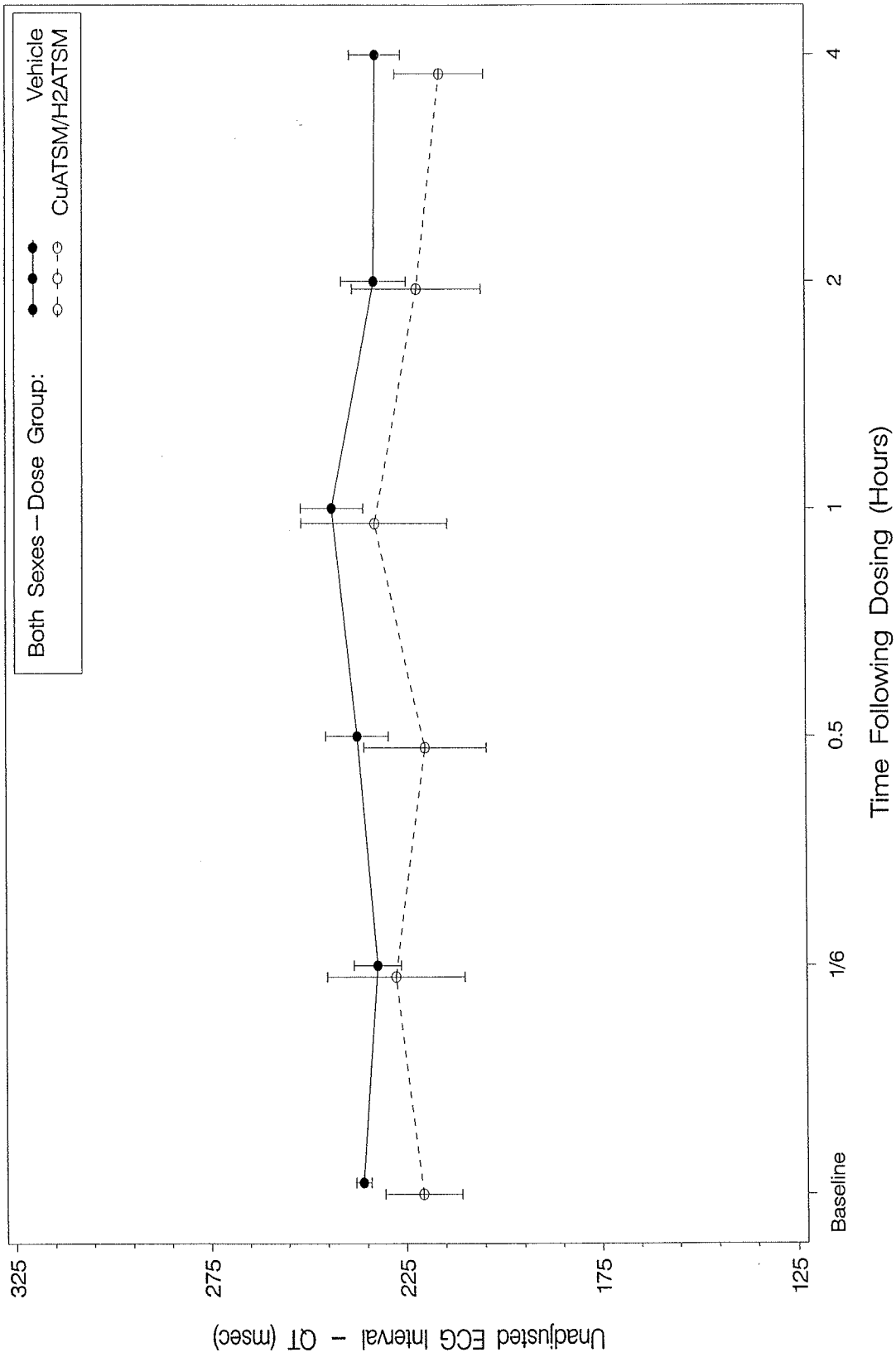


Figure U-28. QT Interval (msec), Both Sexes, In-Sling Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

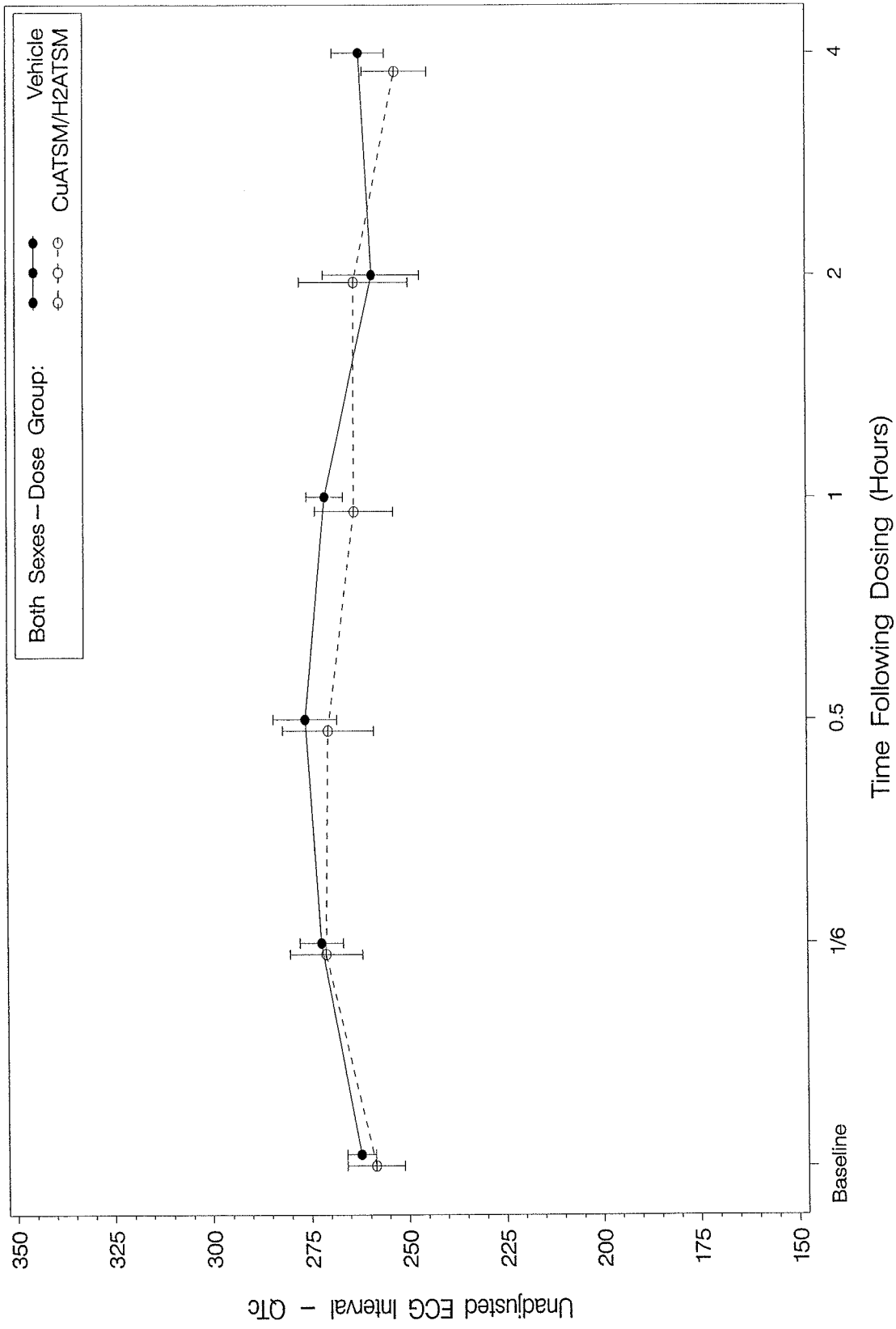


Figure U-29. Corrected QT Interval (QTc), Both Sexes, In-Sling Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

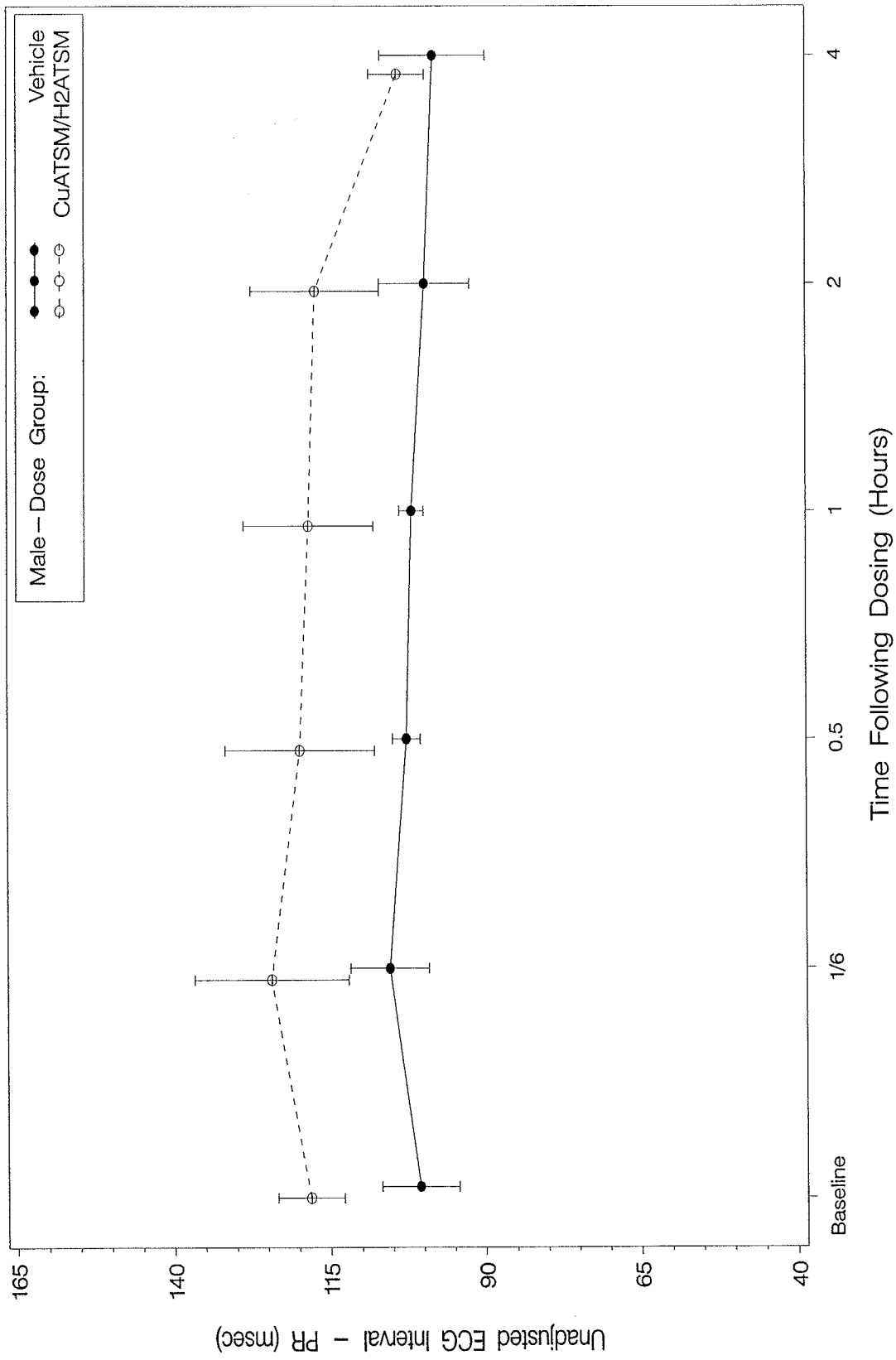


Figure U-30. **PR Interval (msec), Male Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

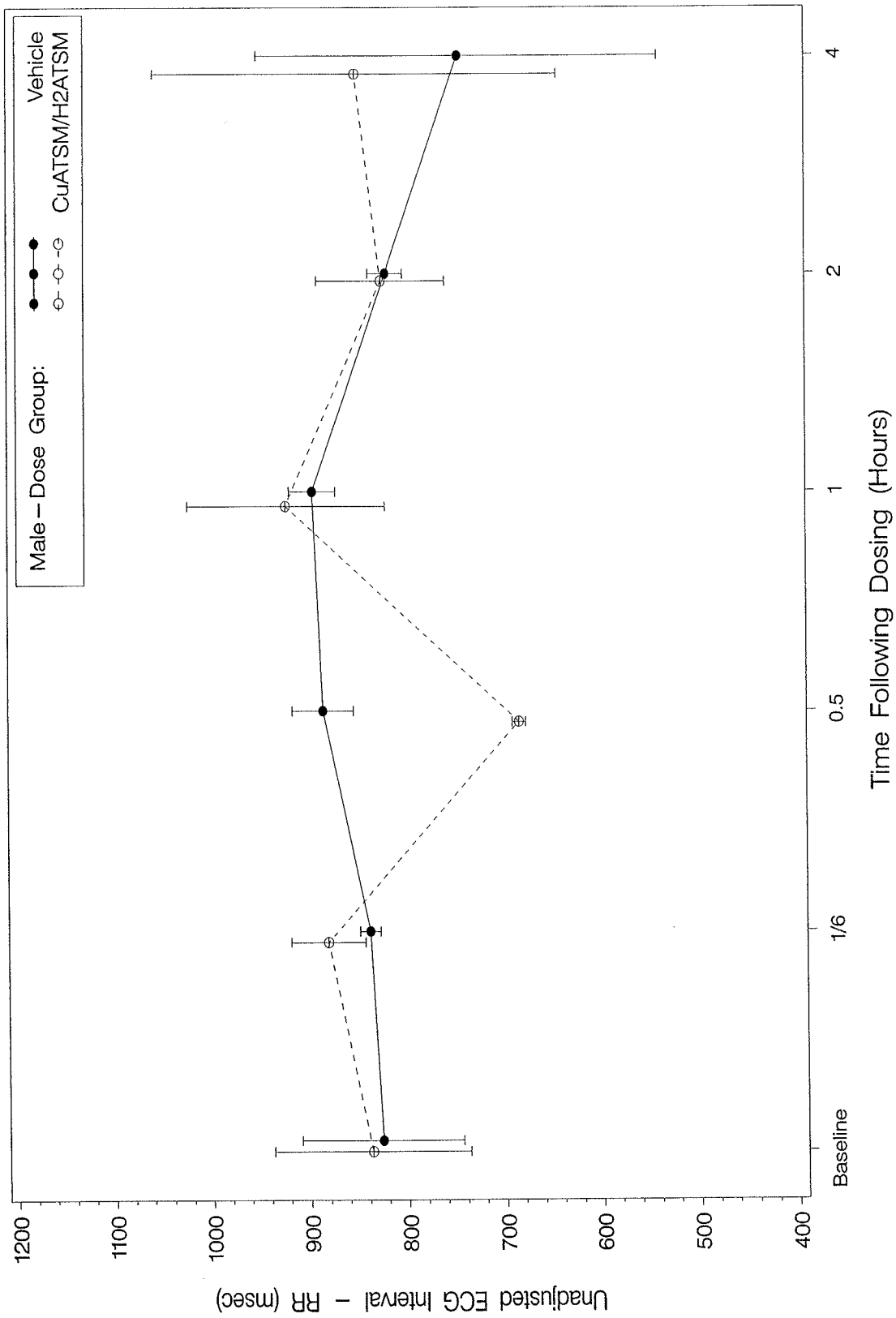


Figure U-31. RR Interval (msec), Male Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

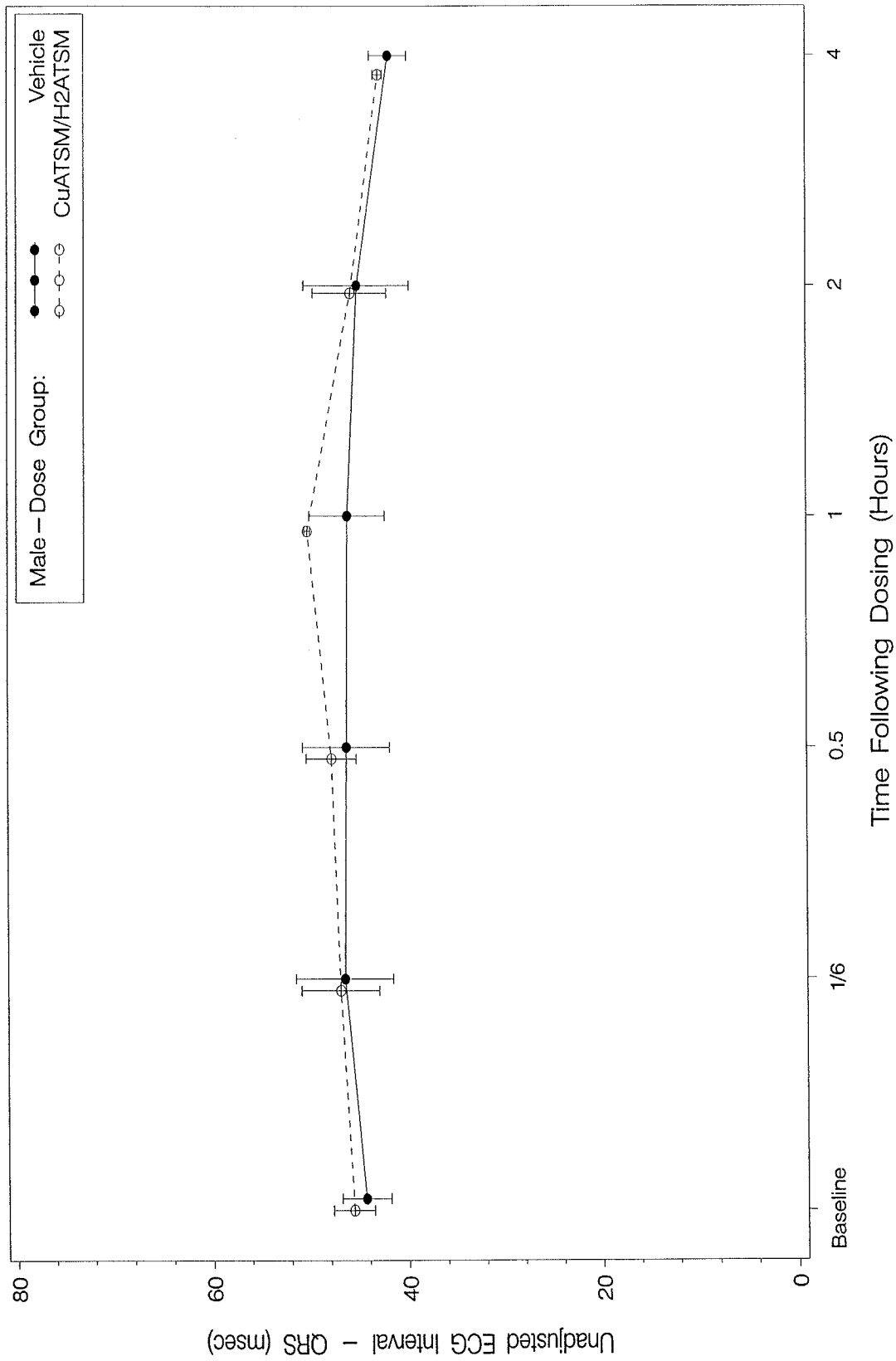


Figure U-32. QRS Interval (msec), Male Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

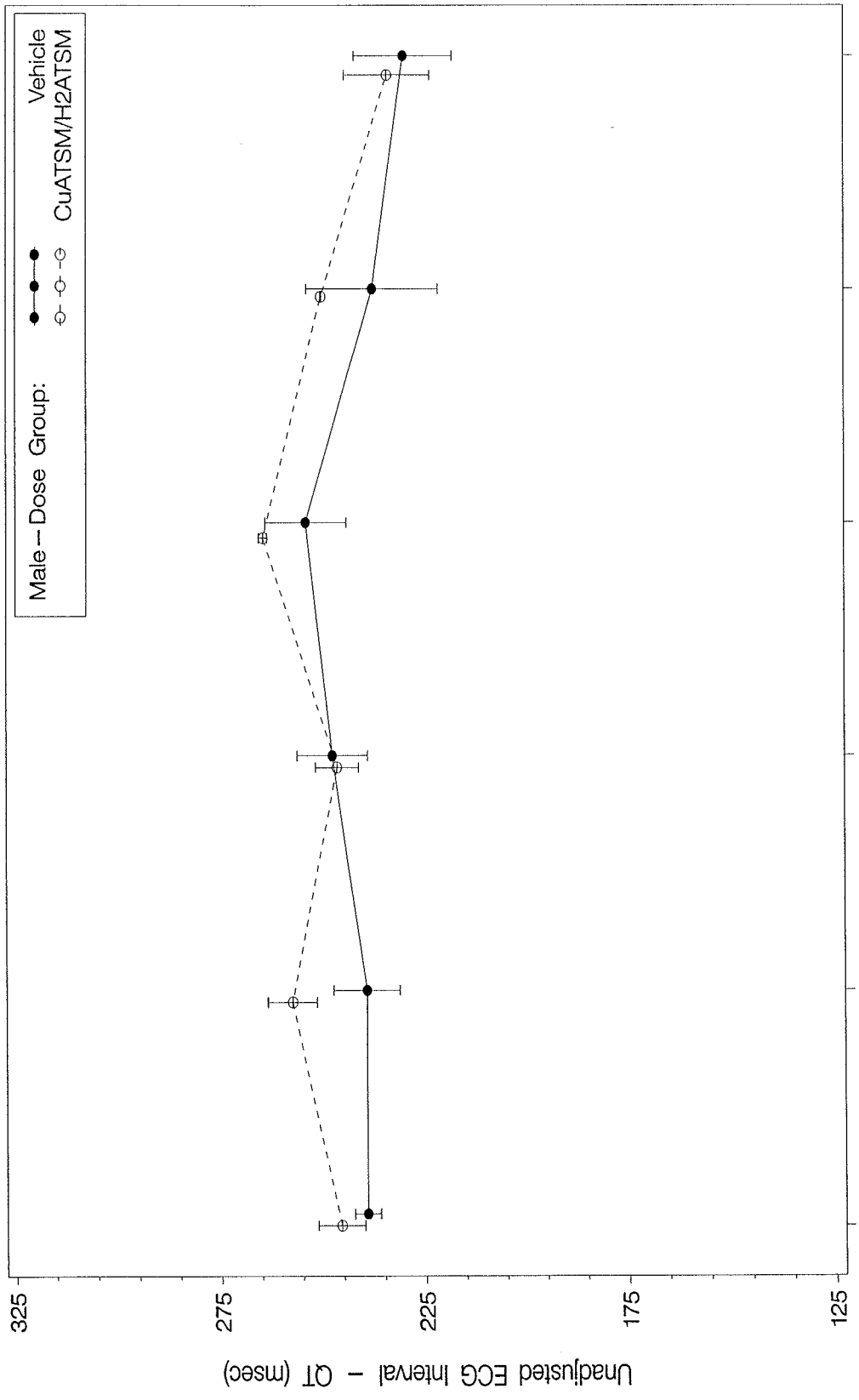


Figure U-33. QT Interval (msec), Male Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

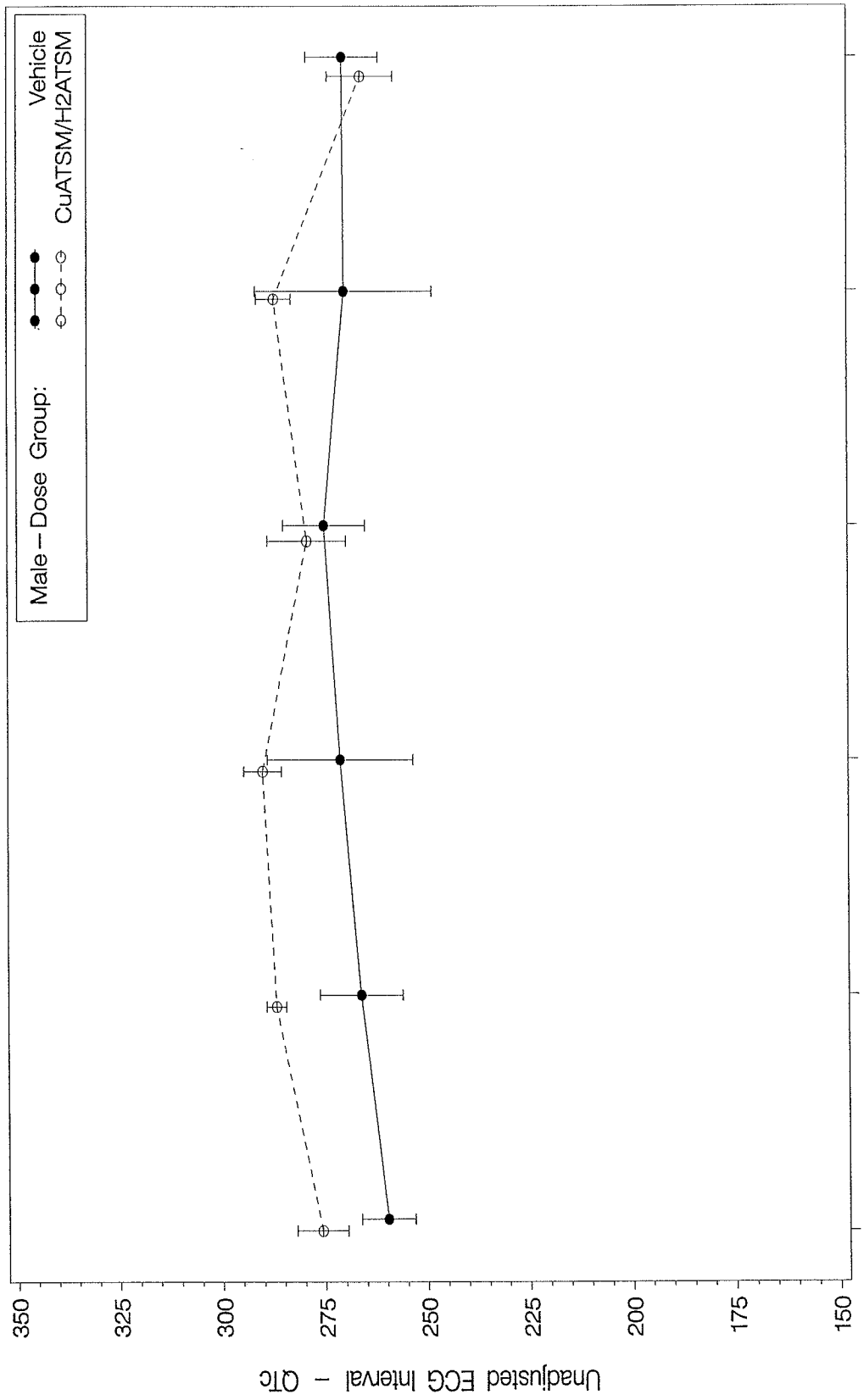


Figure U-34. **Corrected QT Interval (QTc), Male Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the 4-Hour Period Immediately Following Dosing with $CuATSM/H_2ATSM$ or Vehicle**

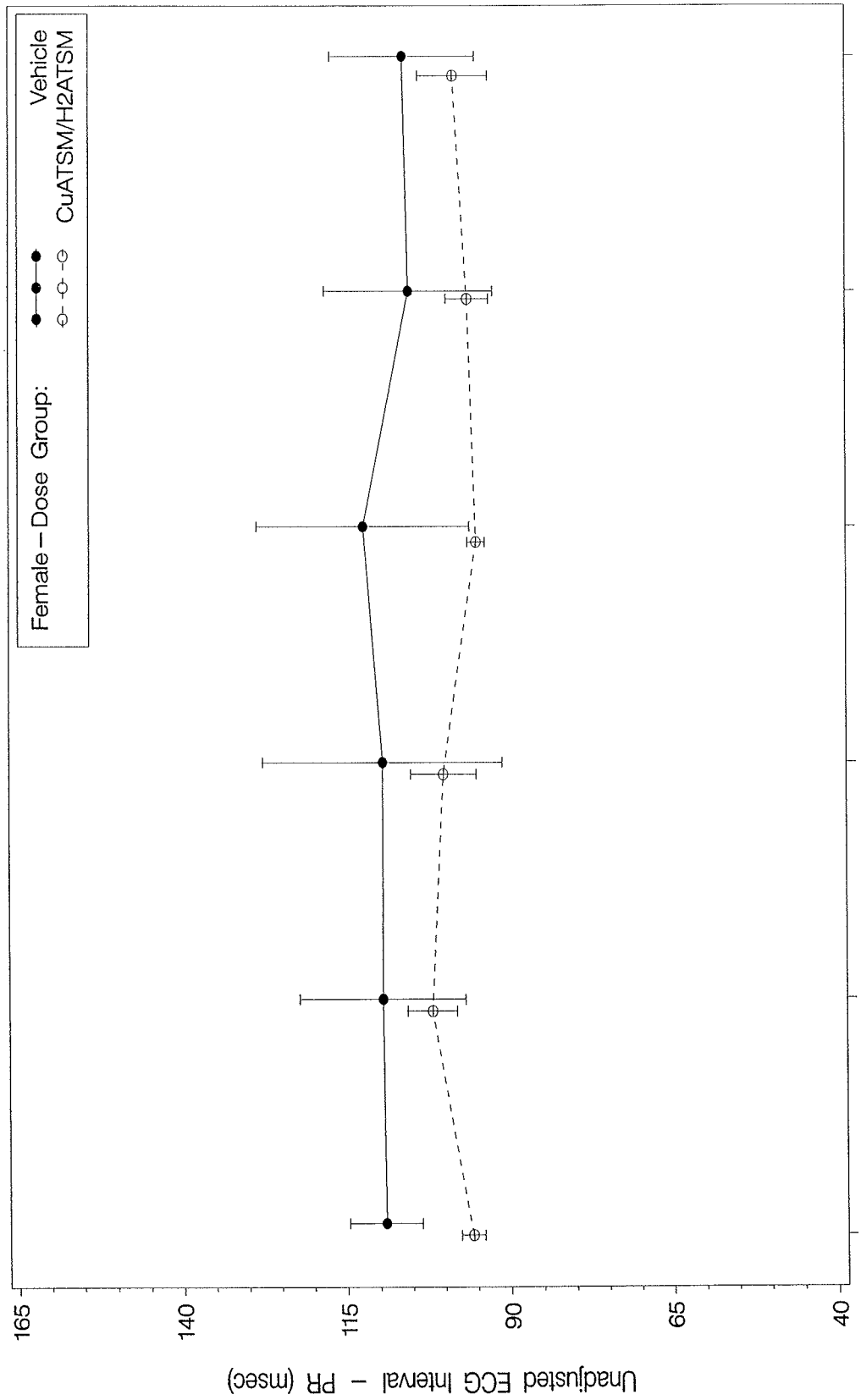


Figure U-35. PR Interval (msec), Female Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

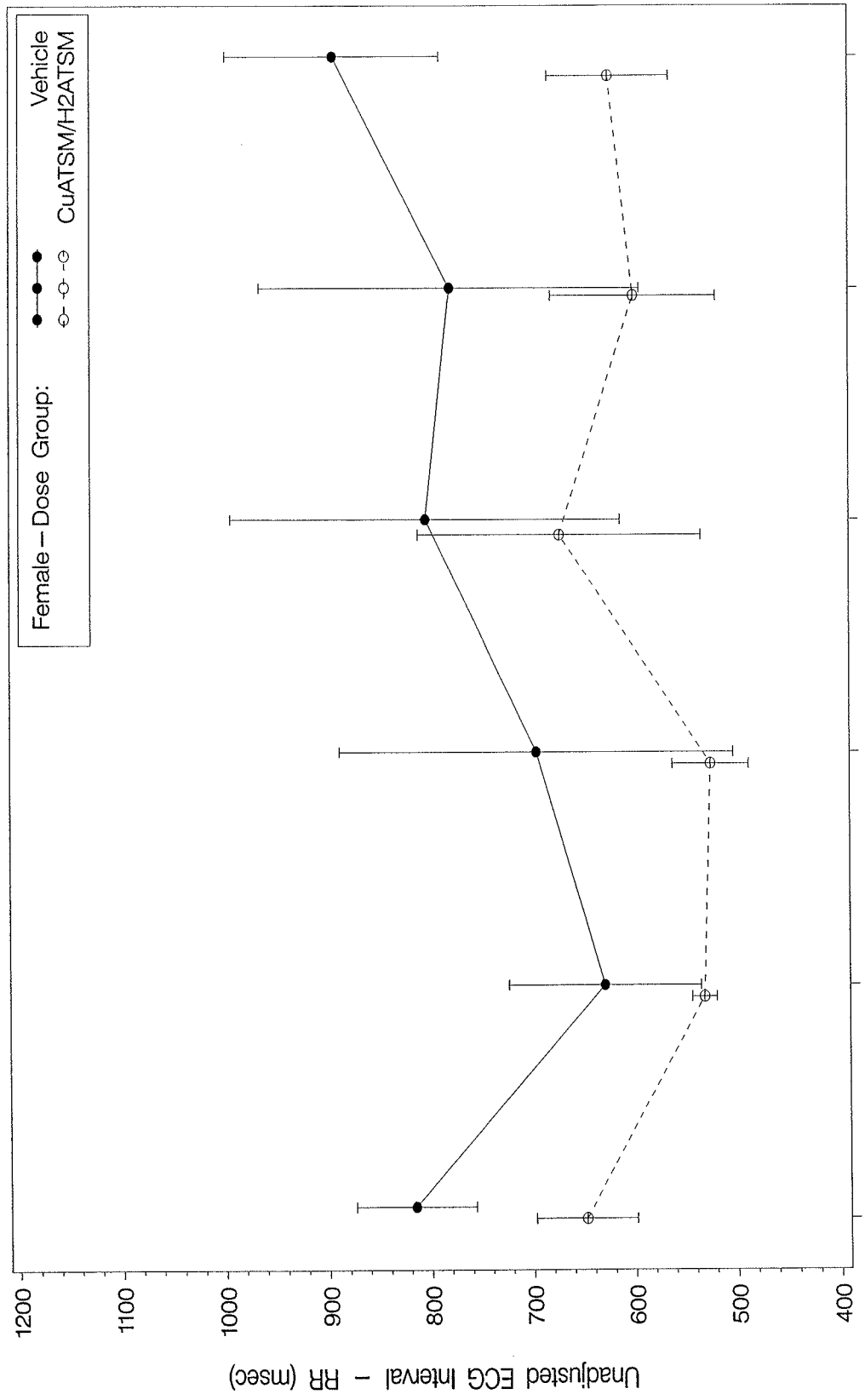


Figure U-36. RR Interval (msec), Female Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

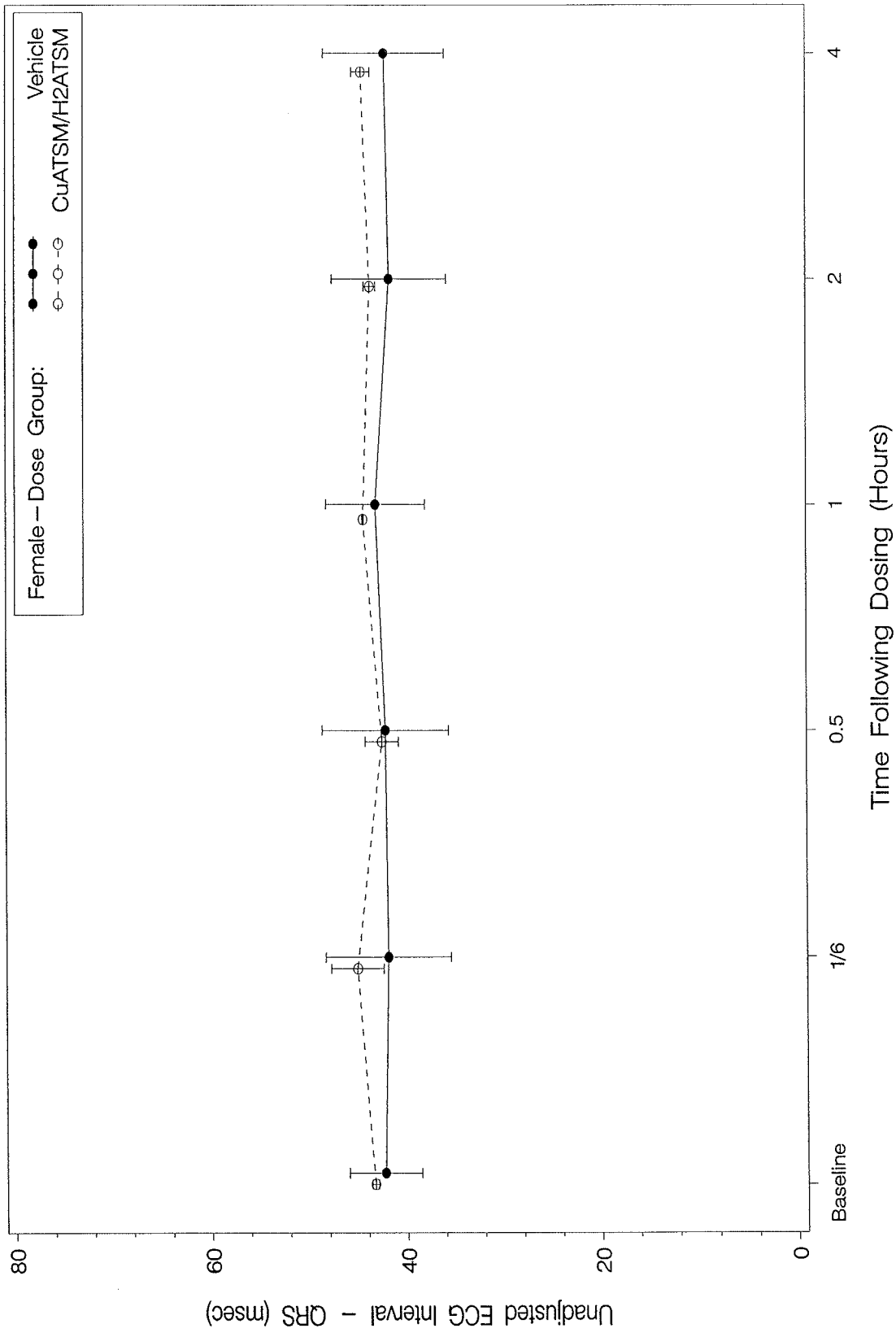


Figure U-37. QRS Interval (msec), Female Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

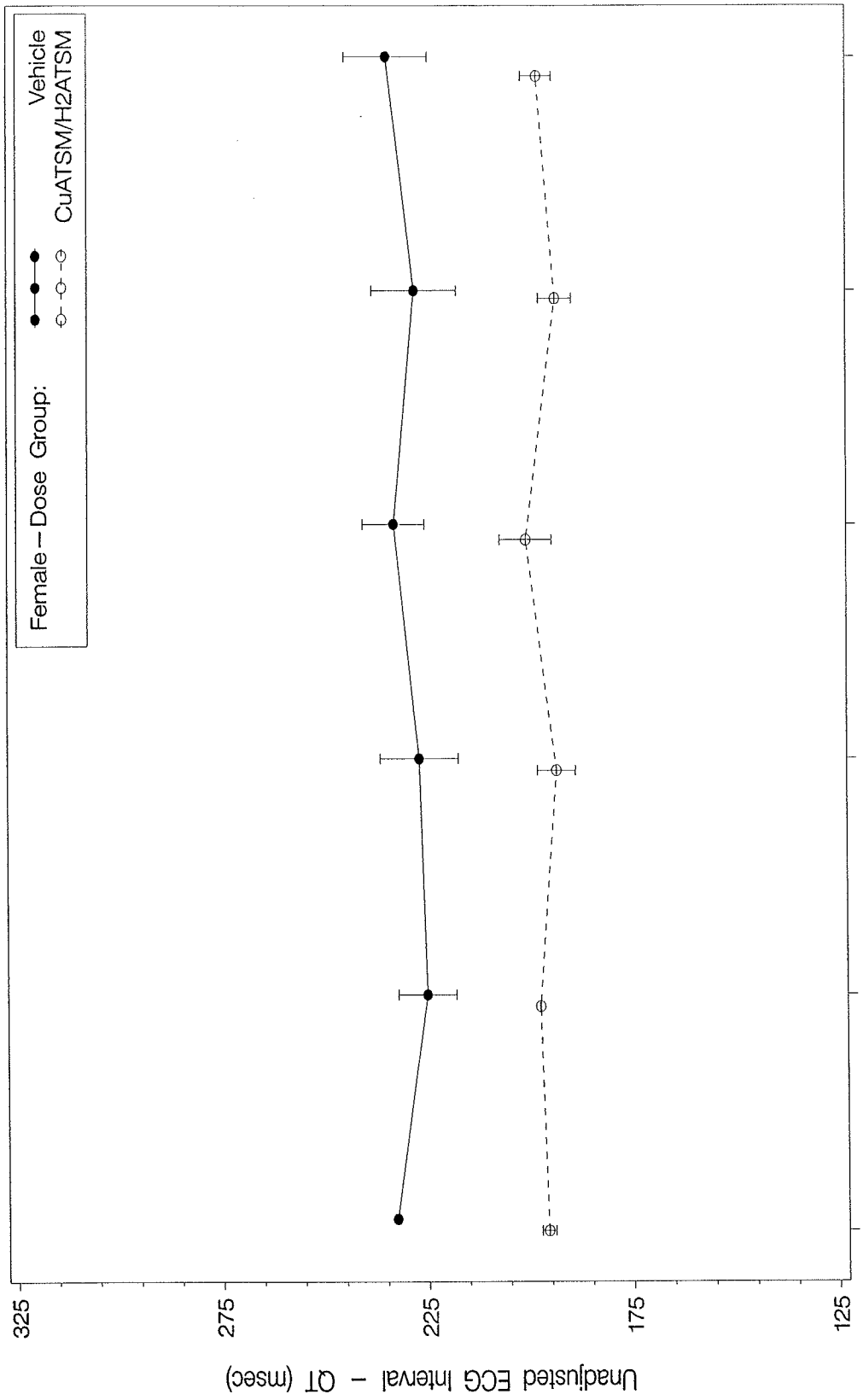


Figure U-38. QT Interval (msec), Female Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

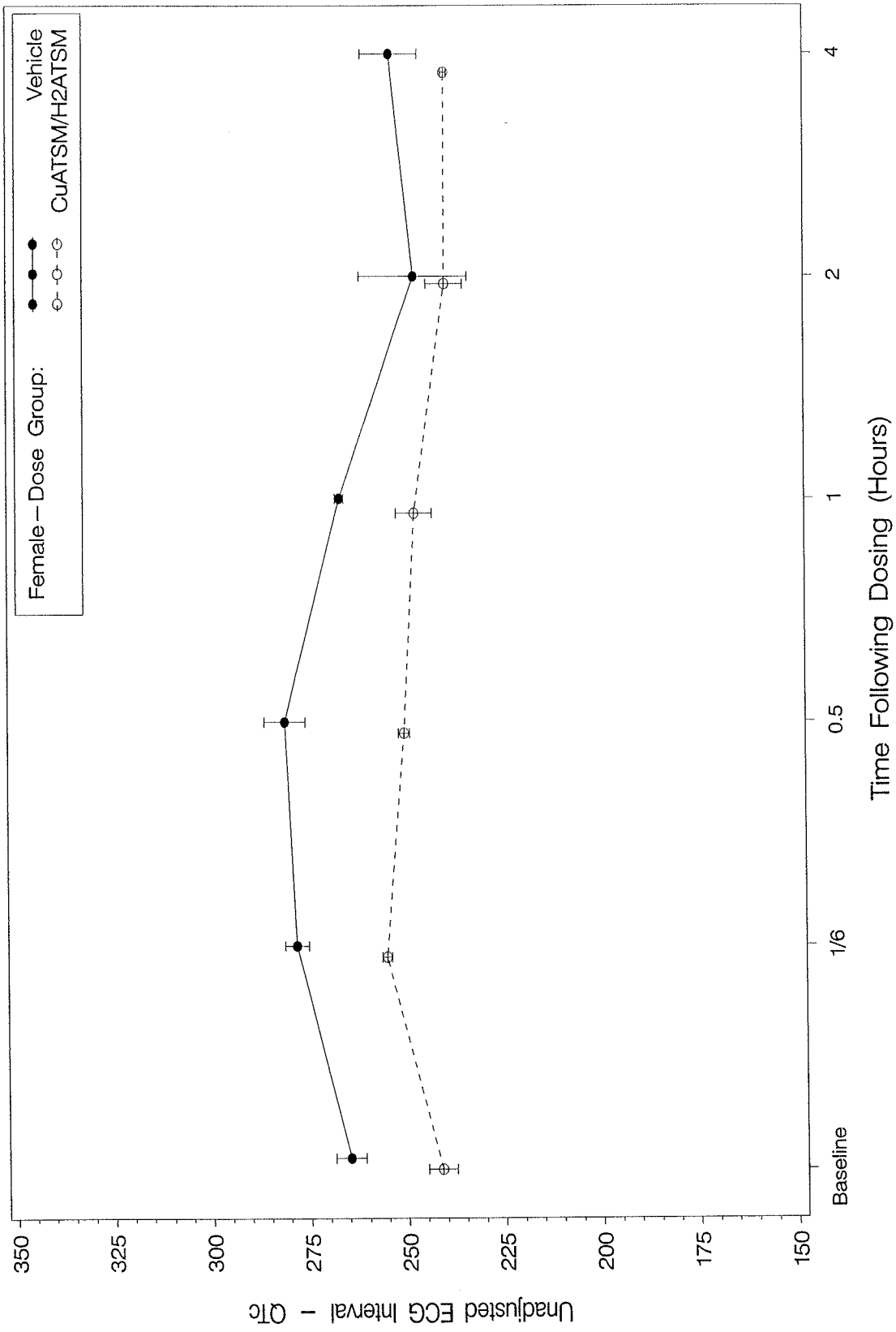


Figure U-39. Corrected QT Interval (QTc), Female Animals, In-Sling Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

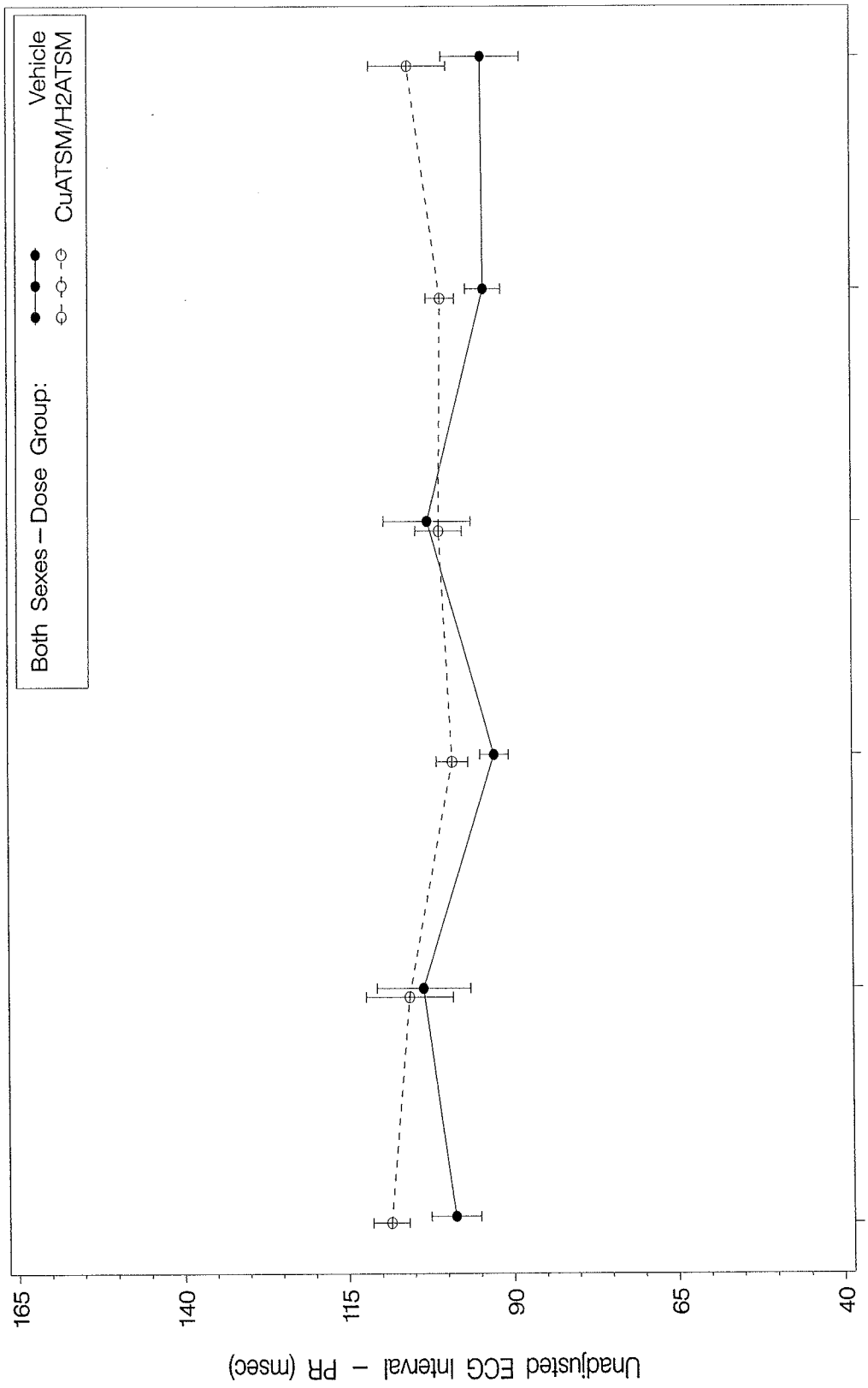


Figure U-40. PR Interval (msec), Both Sexes, In-Cage Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle

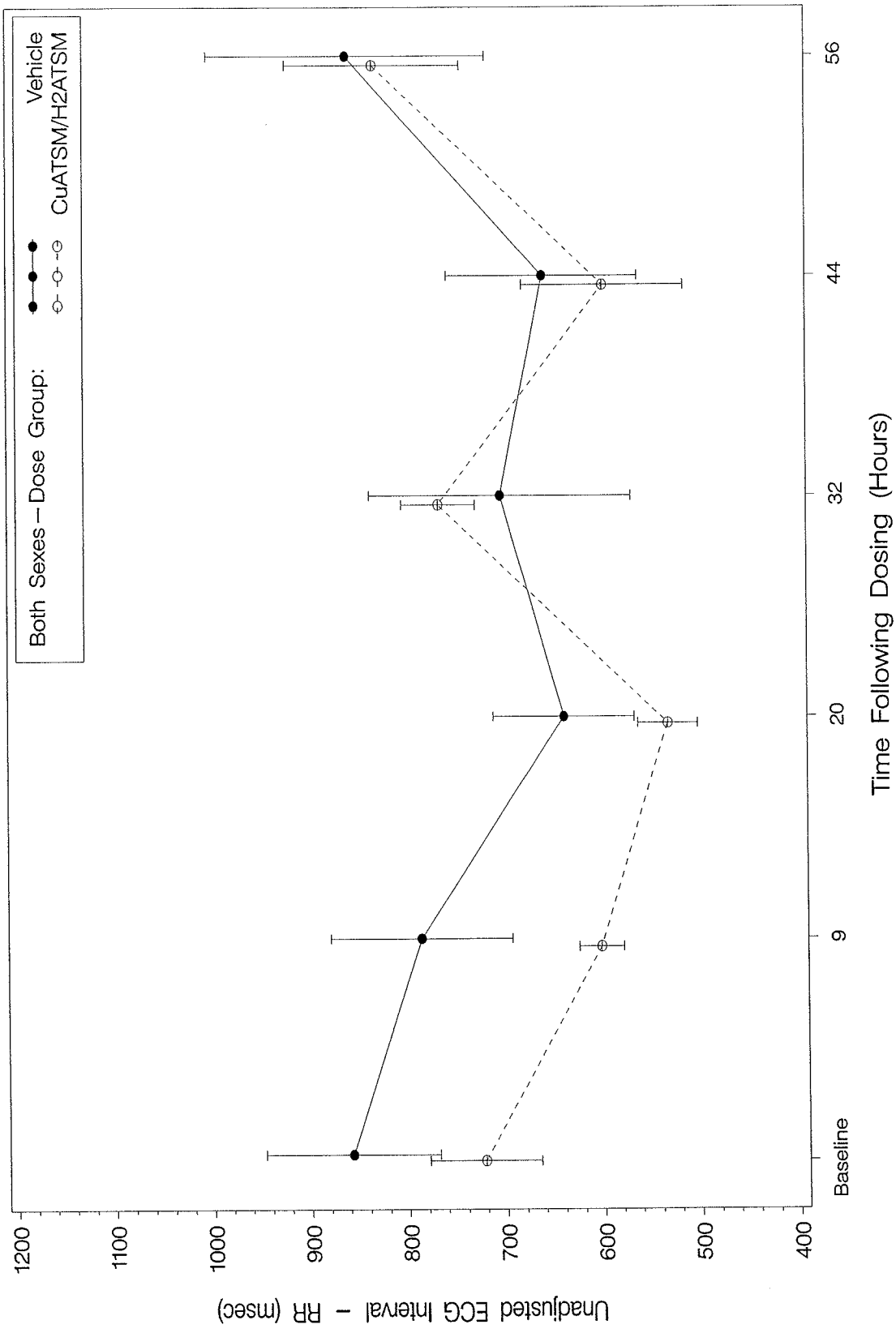


Figure U-41. **RR Interval (msec), Both Sexes, In-Cage Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

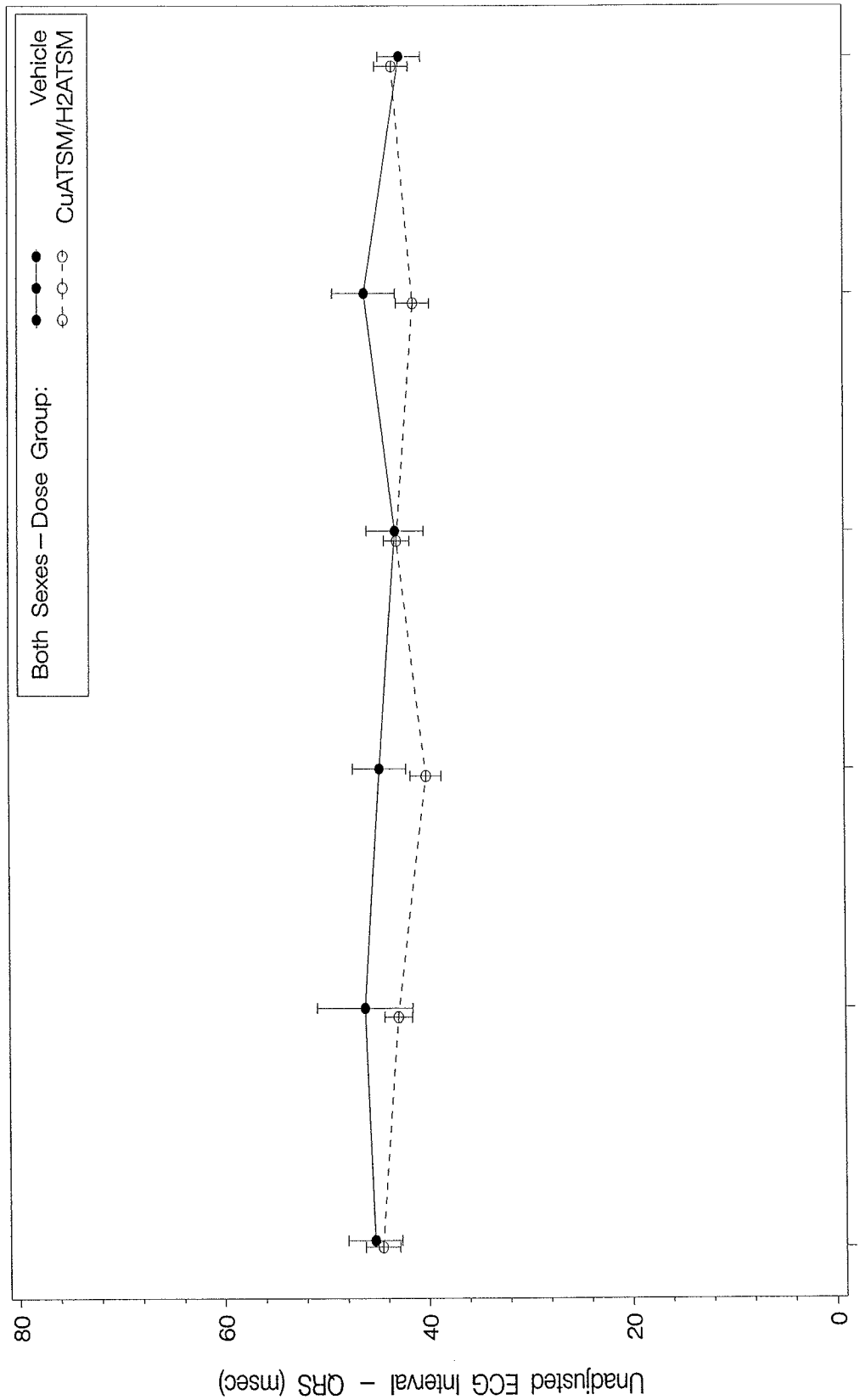


Figure U-42. **QRS Interval (msec), Both Sexes, In-Cage Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

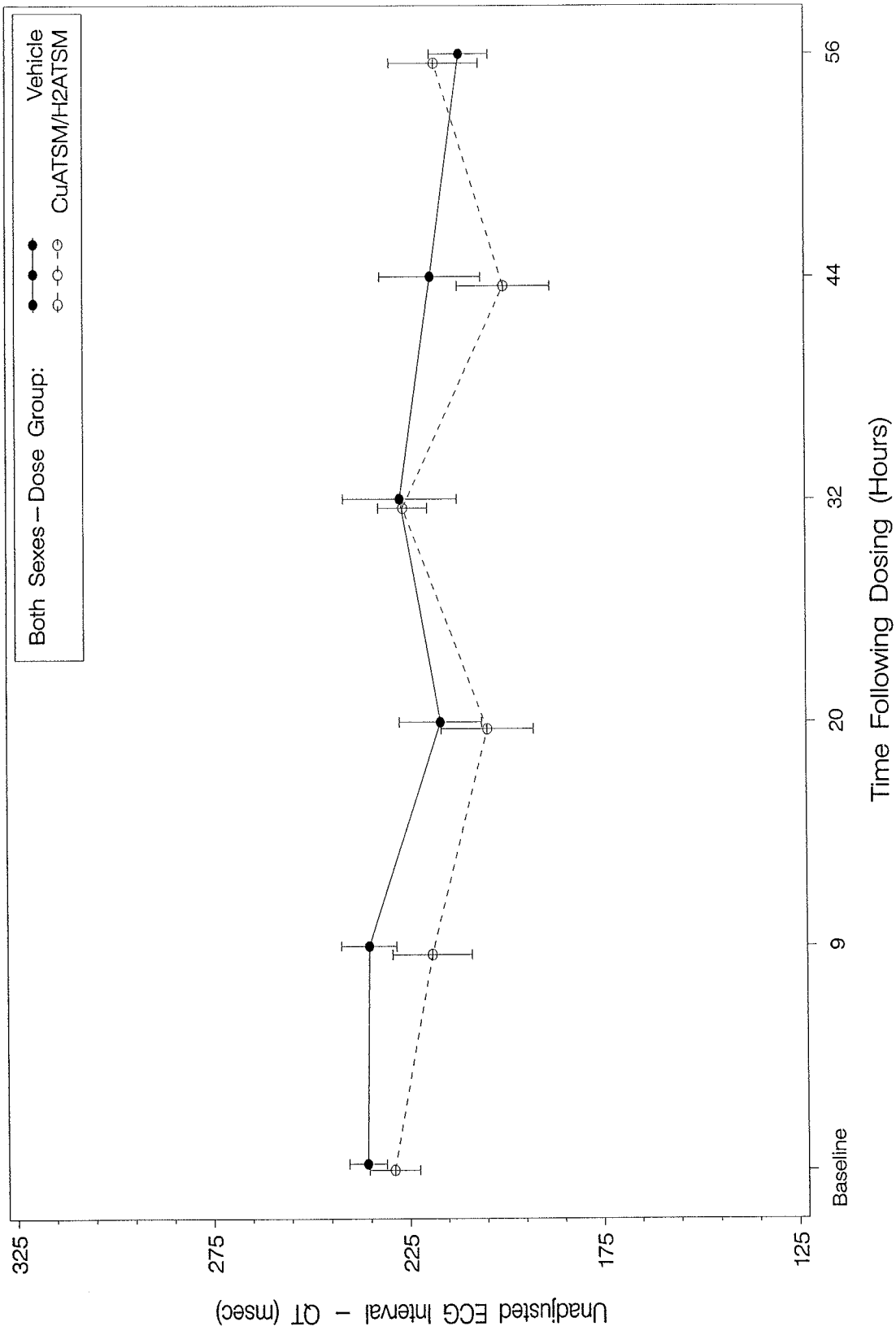


Figure U-43. QT Interval (msec), Both Sexes, In-Cage Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle

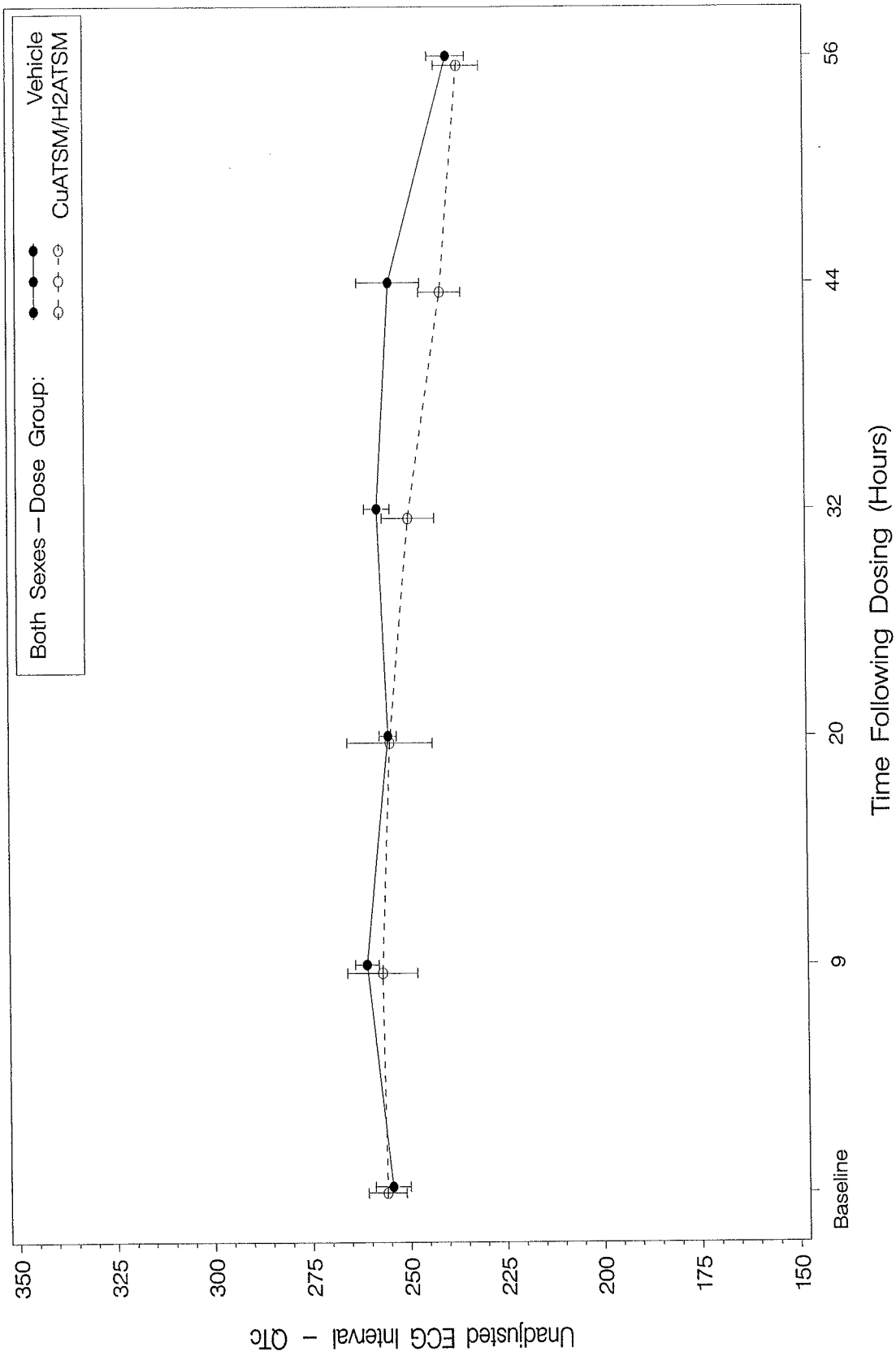


Figure U-44. **Corrected QT Interval (QTc), Both Sexes, In-Cage Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

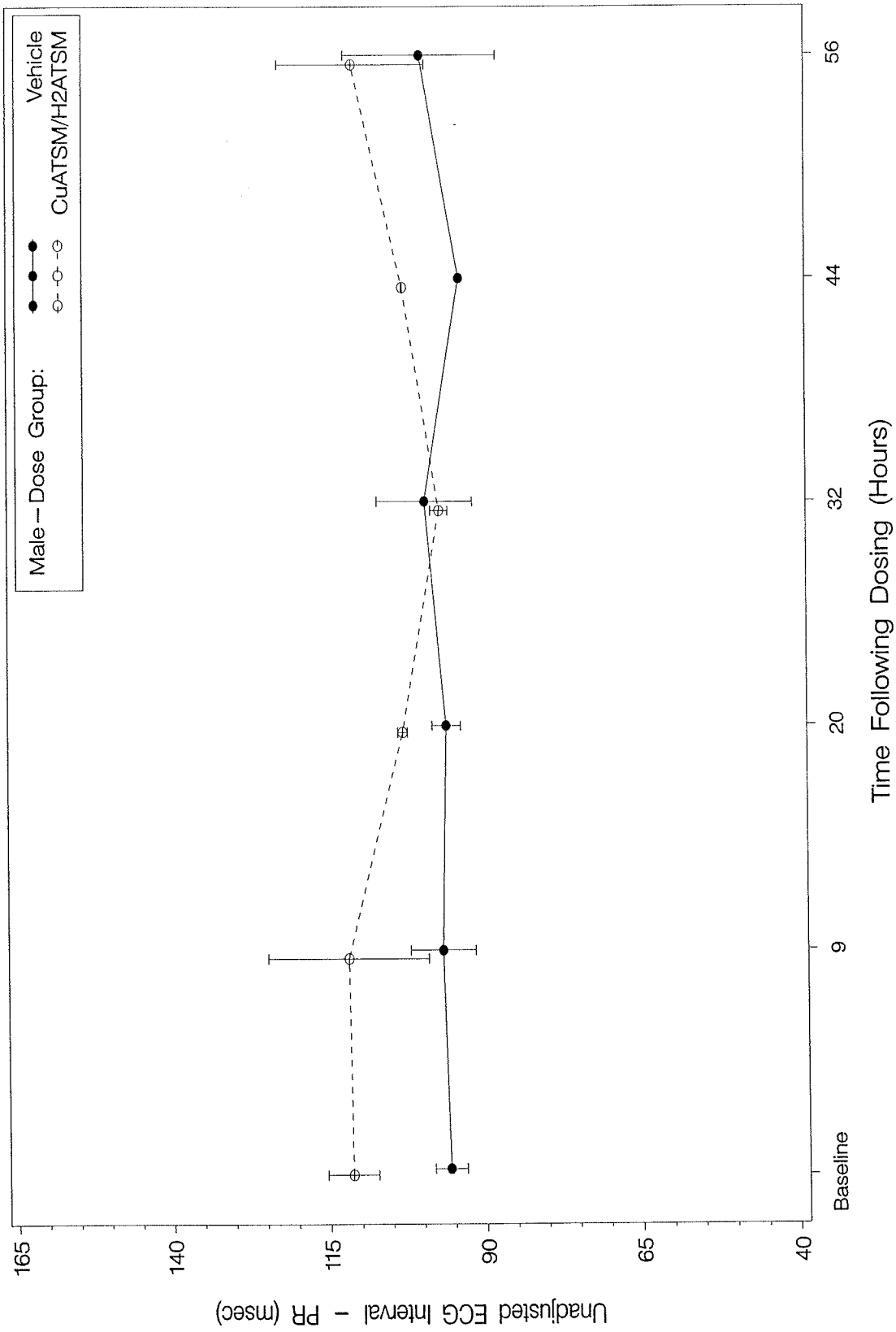


Figure U-45. **PR Interval (msec), Male Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with $CuATSM/H_2ATSM$ or Vehicle**

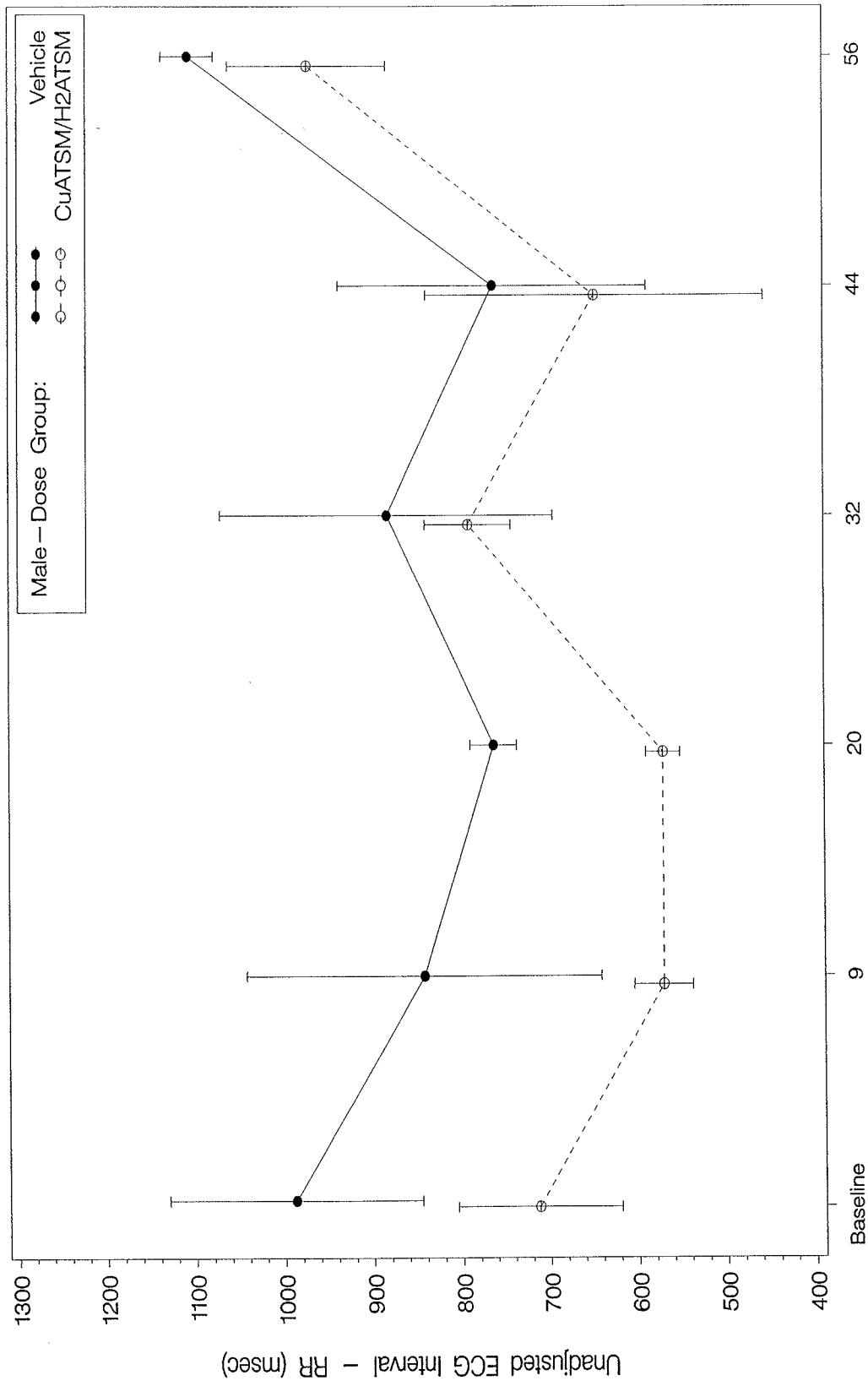


Figure U-46. **RR Interval (msec), Male Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

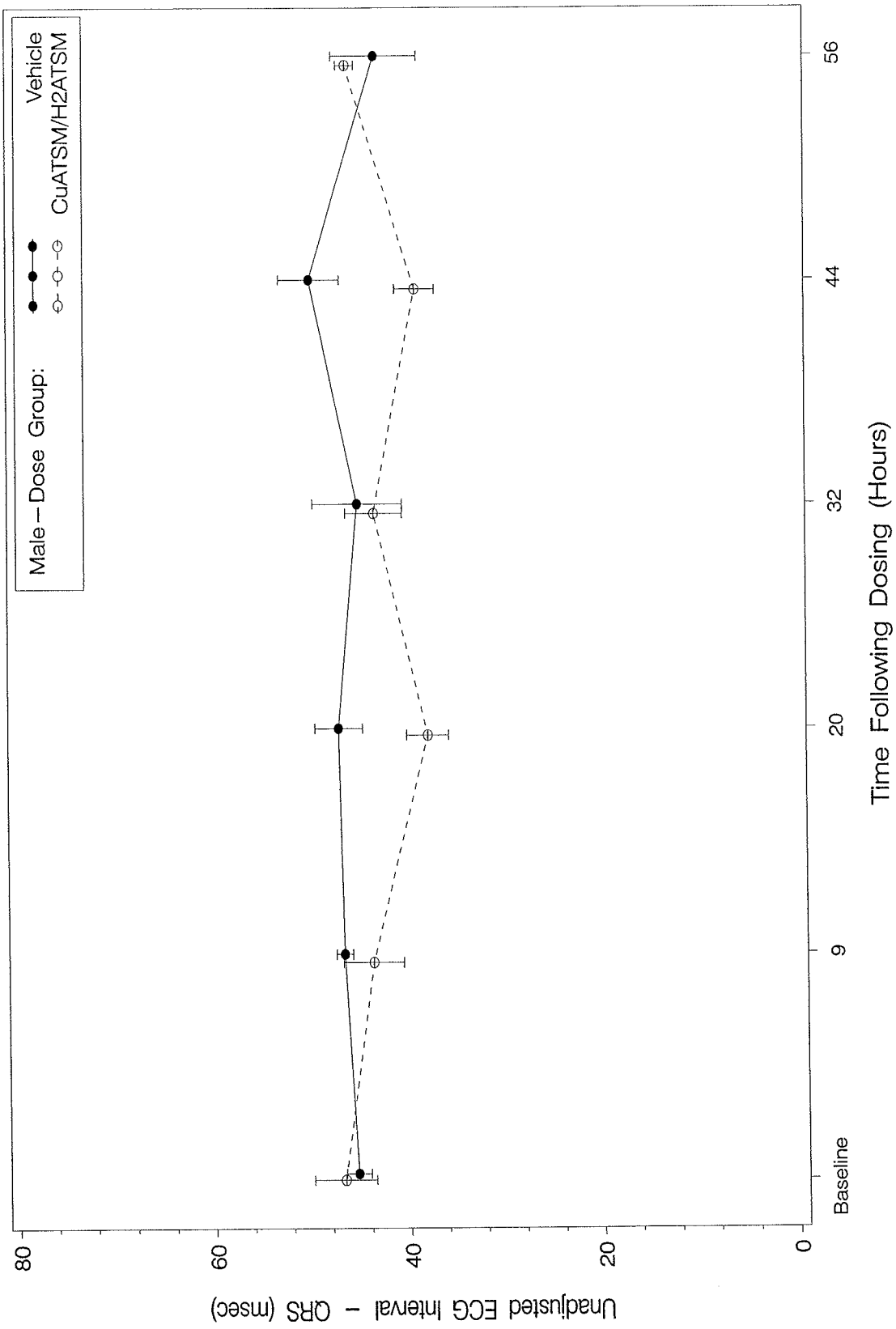


Figure U-47. QRS Interval (msec), Male Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle

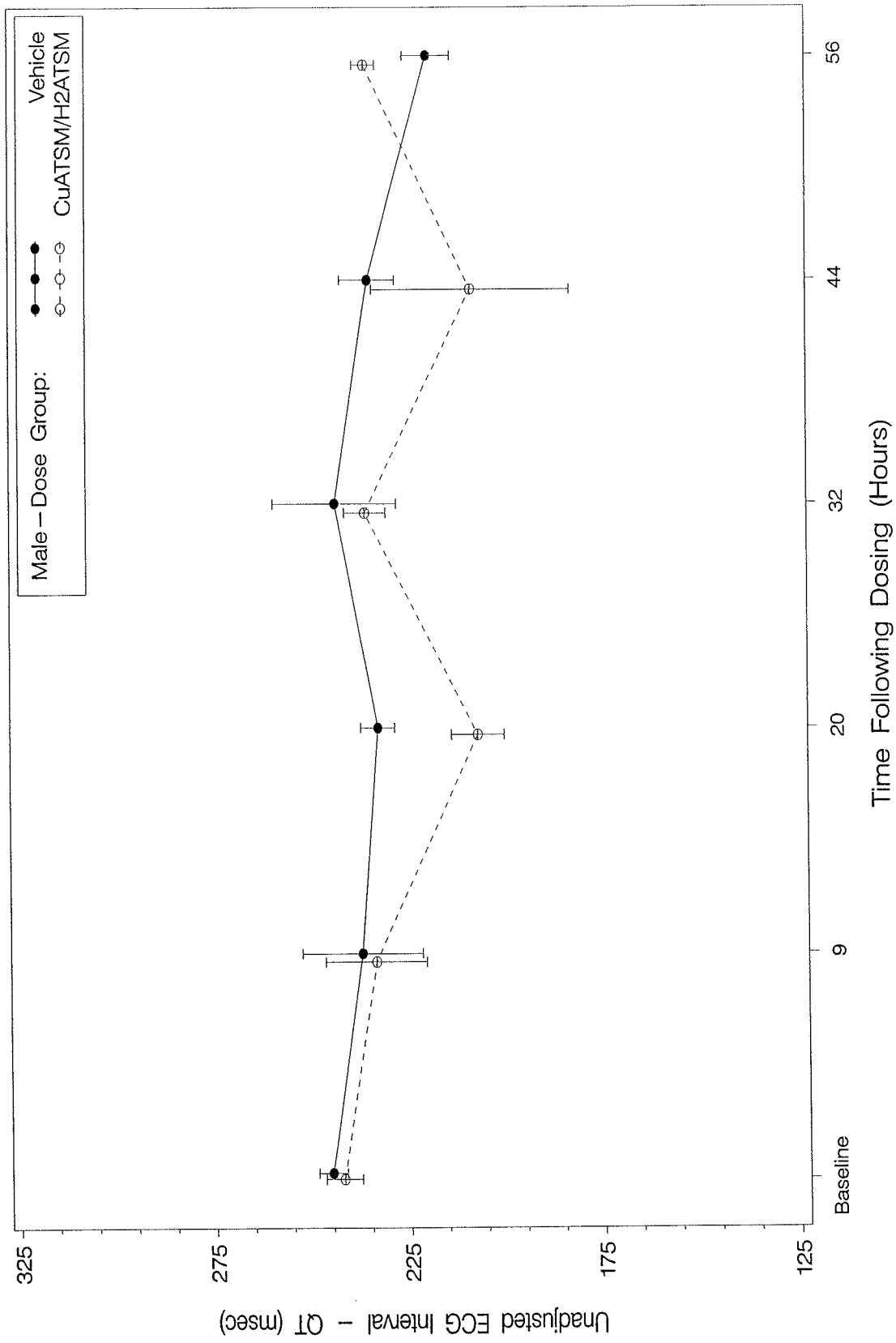


Figure U-48. **QT Interval (msec), Male Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

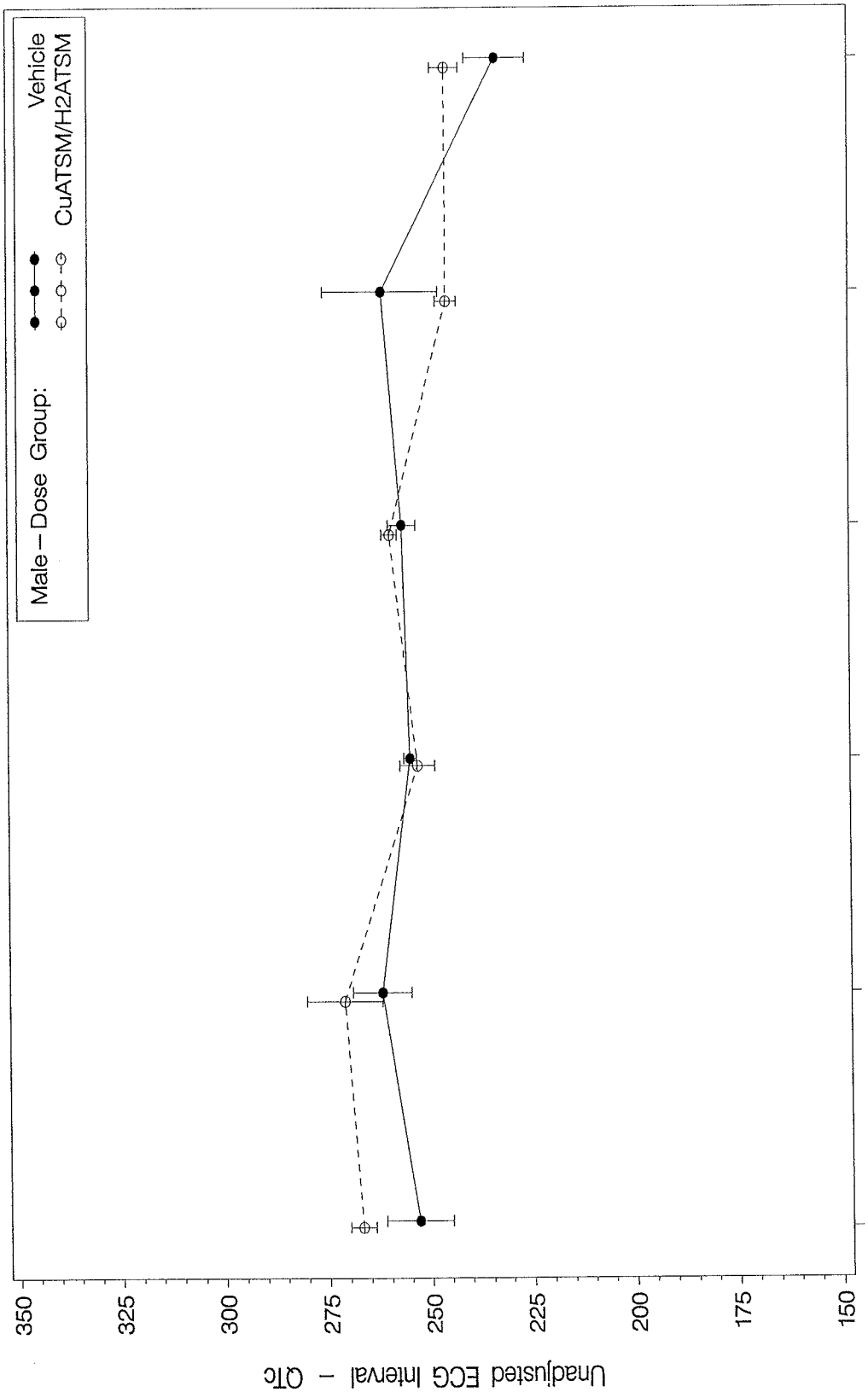


Figure U-49. Corrected QT Interval (QTc), Male Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle

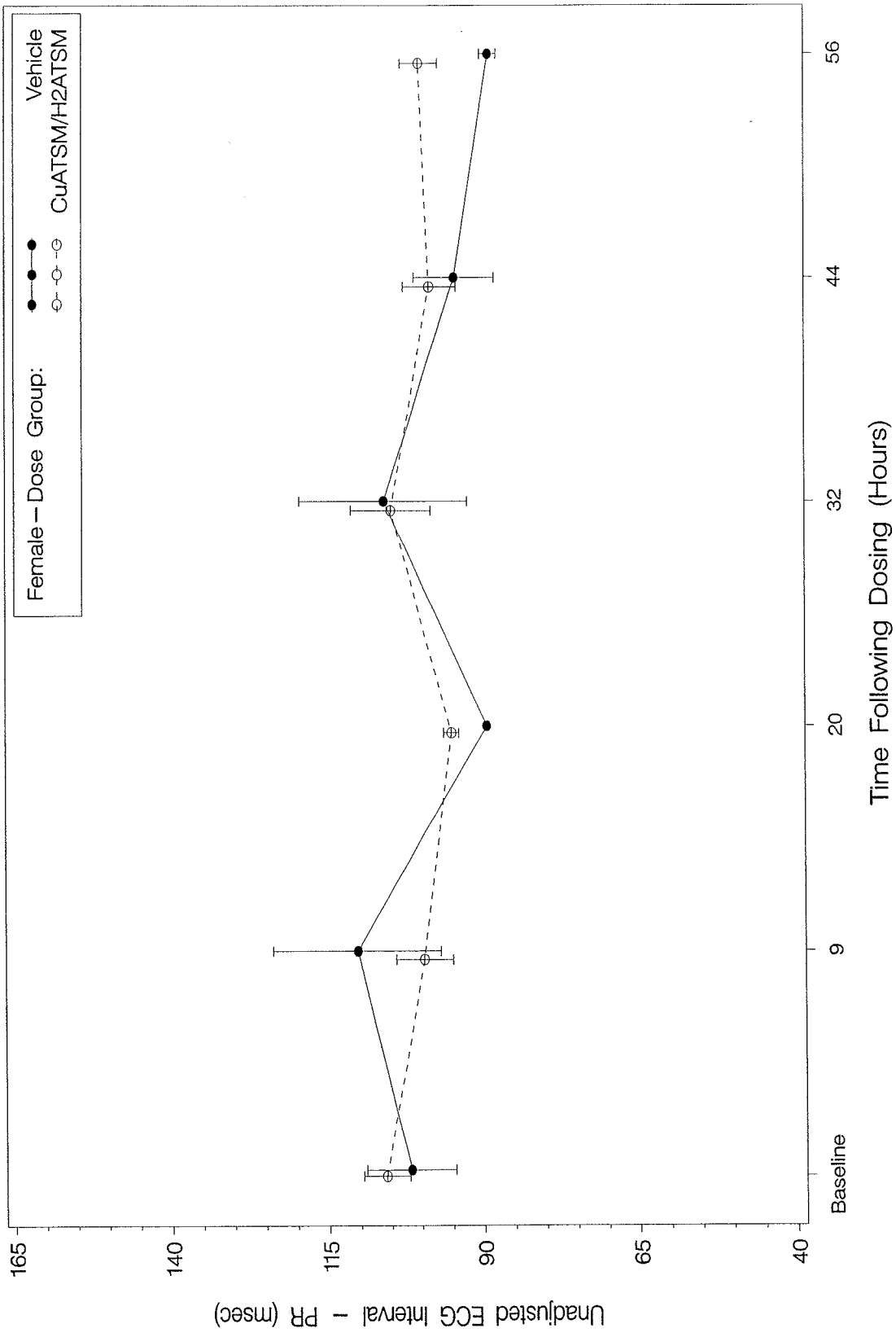


Figure U-50. PR Interval (msec), Female Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle

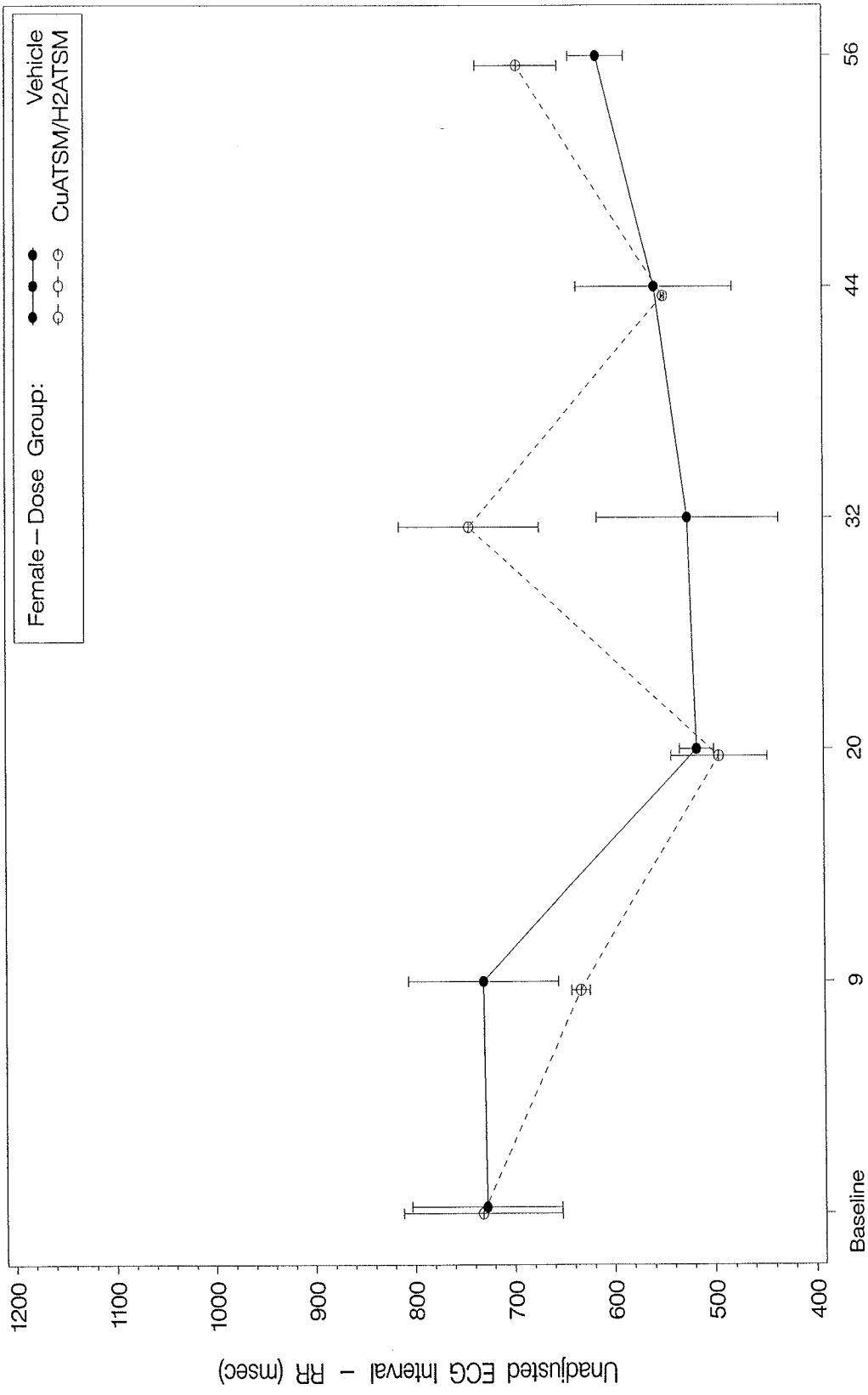


Figure U-51. **RR Interval (msec), Female Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

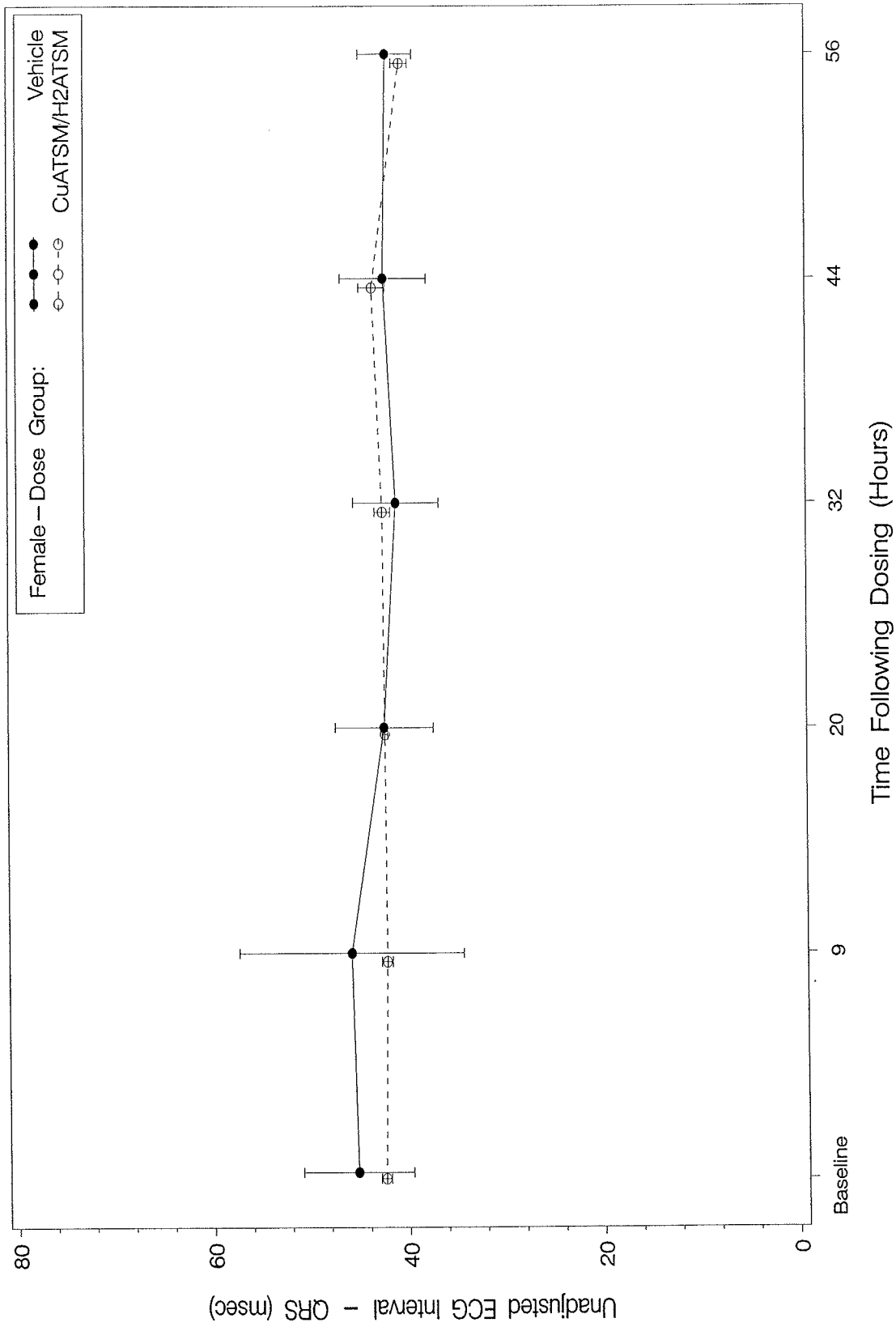


Figure U-52. **QRS Interval (msec), Female Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

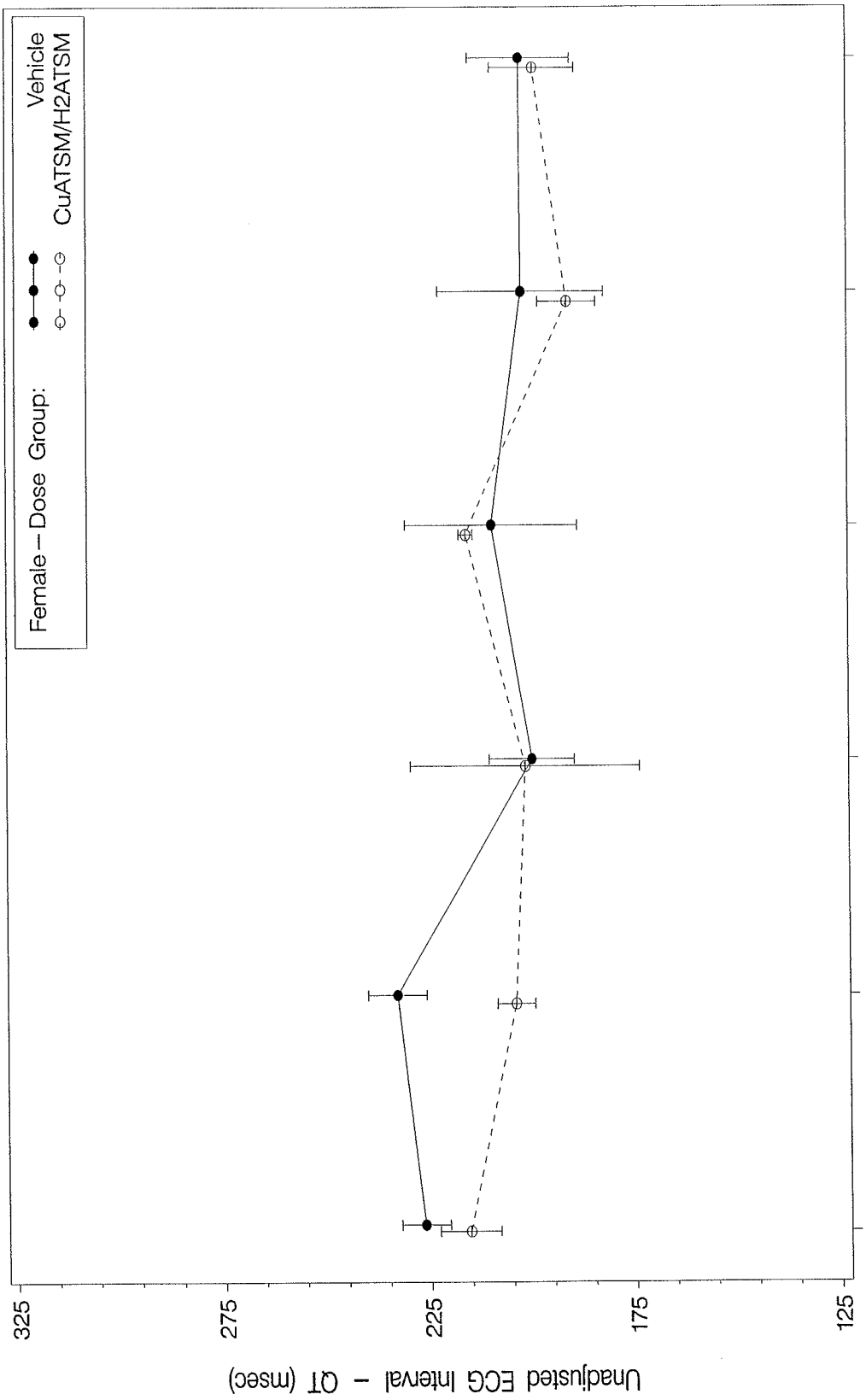


Figure U-53. **QT Interval (msec), Female Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

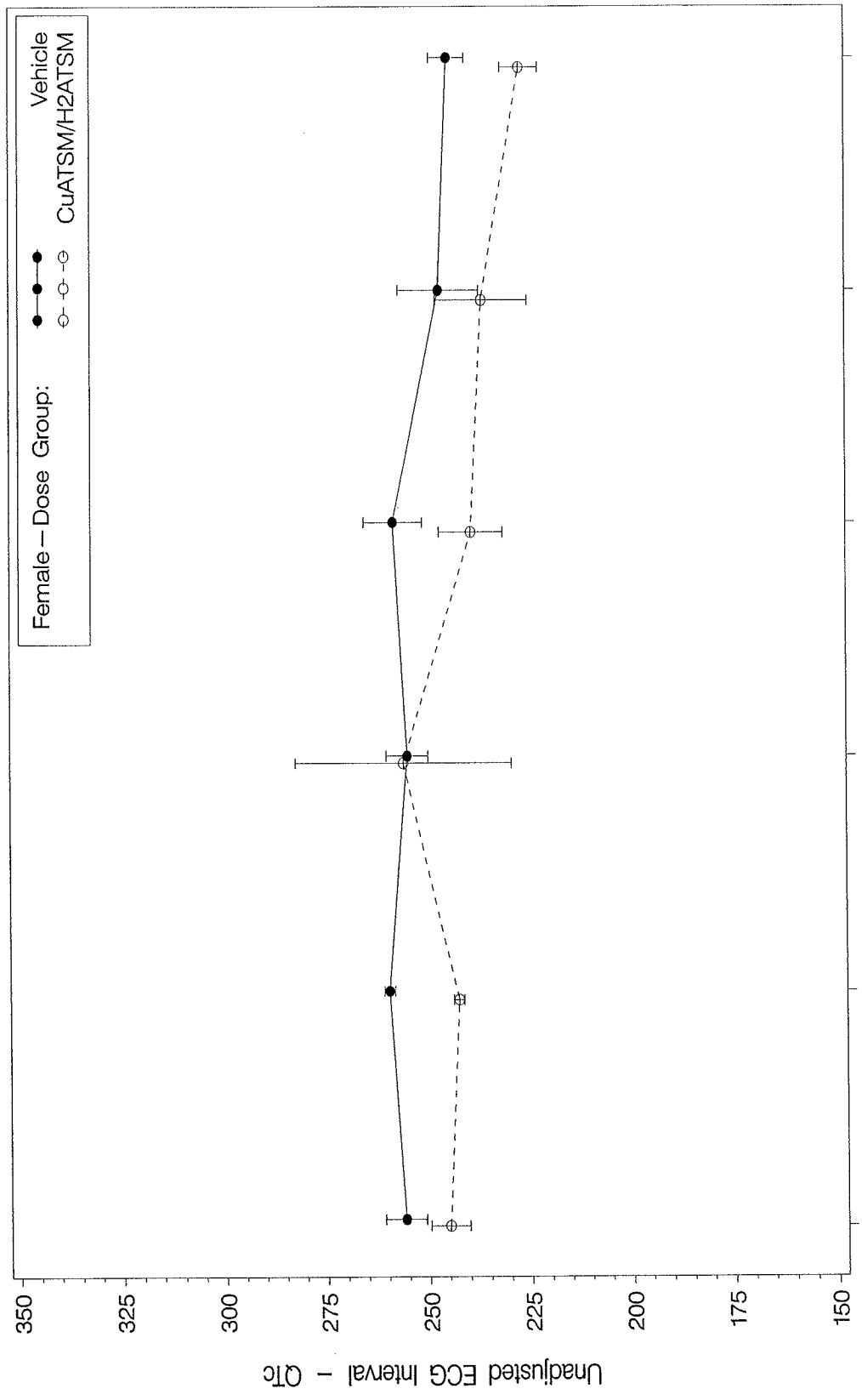


Figure U-54. **Corrected QT Interval (QTc), Female Animals, In-Cage Dose Group Means (with ± Standard Error Bars) of Unadjusted Averages at Baseline and Within the Period from 9 Hours Following Dosing to 56 Hours Following Dosing with CuATSM/H_2ATSM or Vehicle**

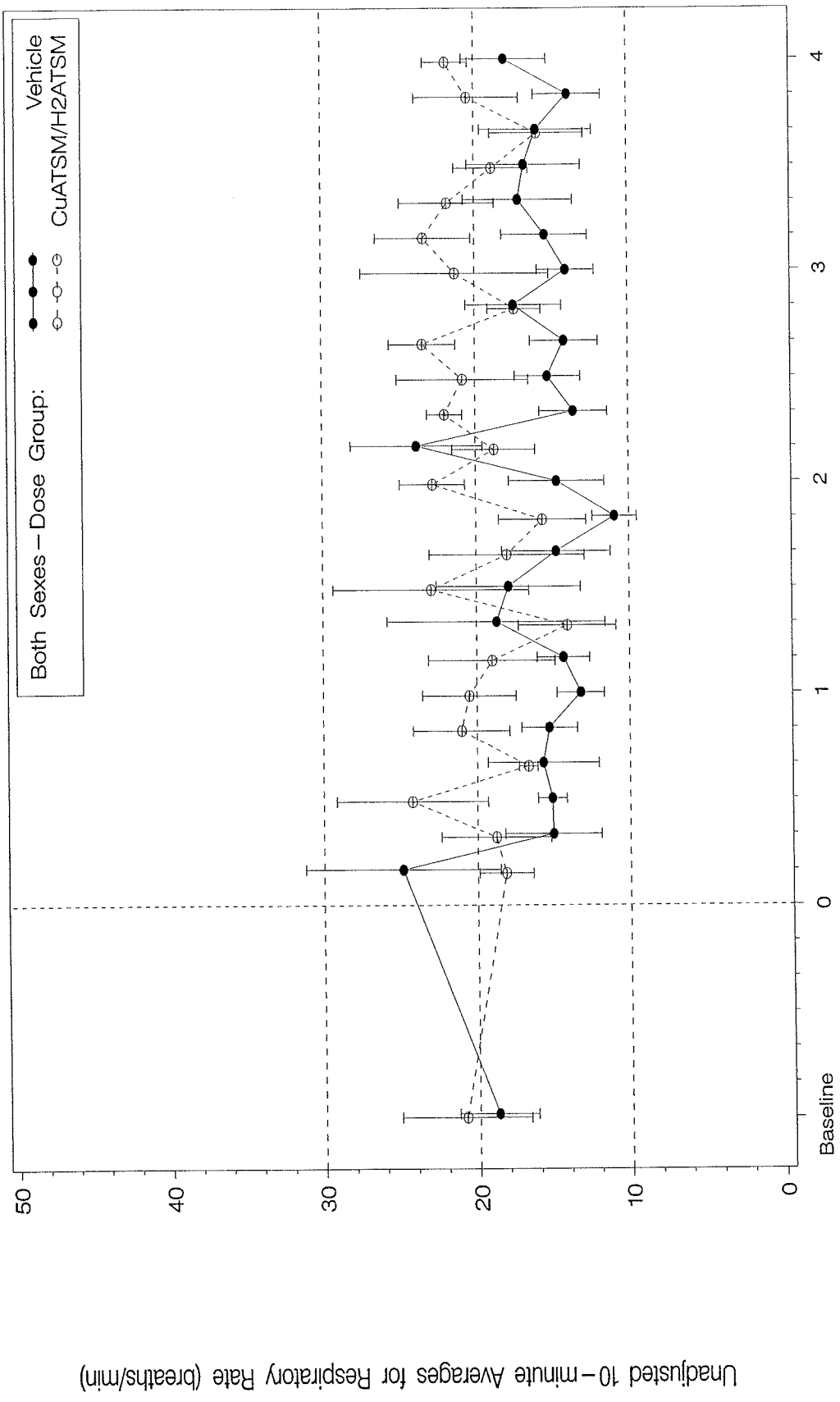


Figure U-55. **Respiratory Rate (breaths/min), Both Sexes, Dose Group Means (and Standard Errors) of Baseline Averages and Unadjusted 10-Minute Averages during the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

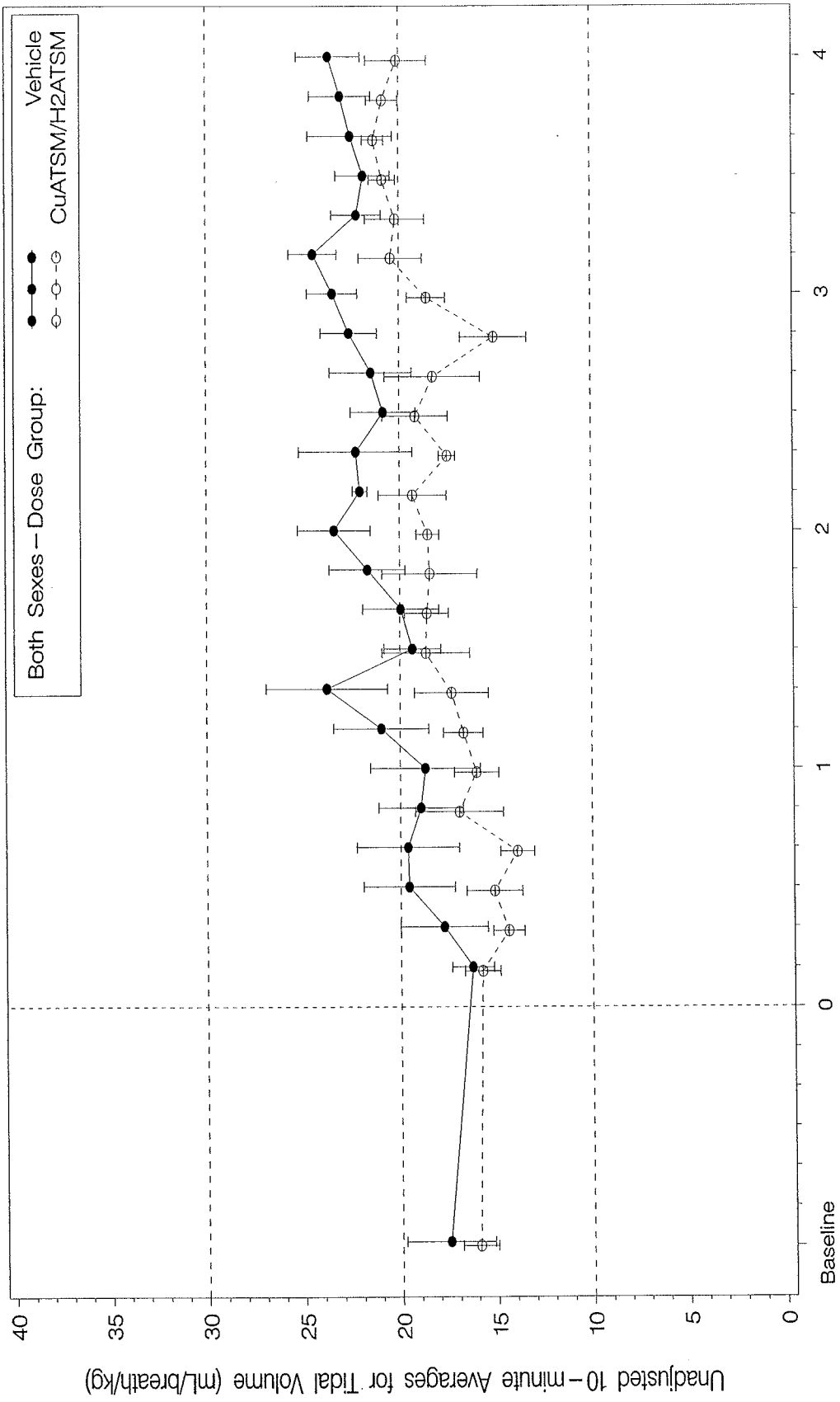


Figure U-56. Body Weight-Adjusted Tidal Volume (mL/breath/kg), Both Sexes Dose Group Means (and Standard Errors) of Baseline Averages and Unadjusted 10-Minute Averages during the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

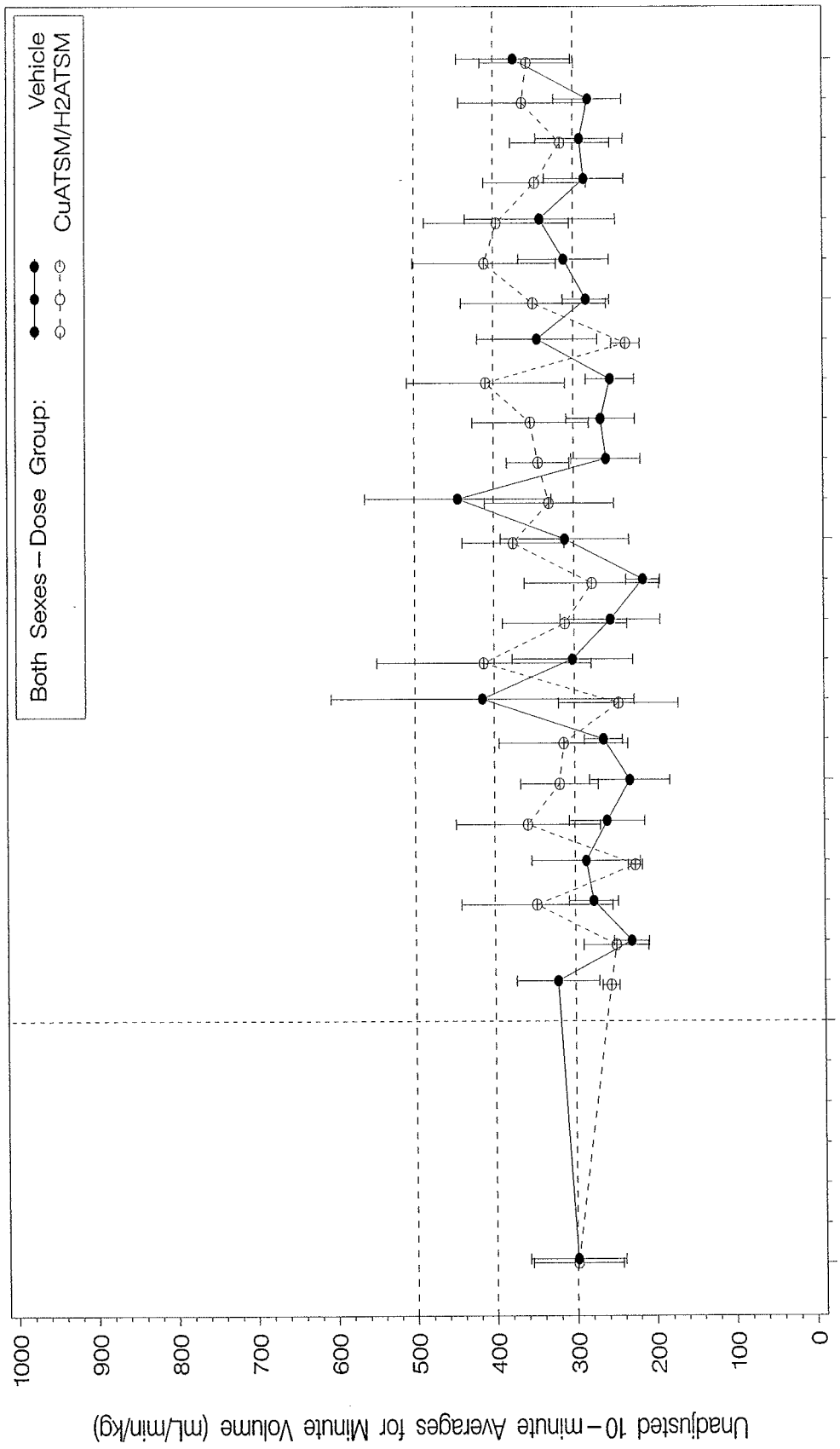


Figure U-57. Body Weight-Adjusted Minute Volume (mL/min/kg), Both Sexes, Dose Group Means (and Standard Errors) of Baseline Averages and Unadjusted 10-Minute Averages during the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

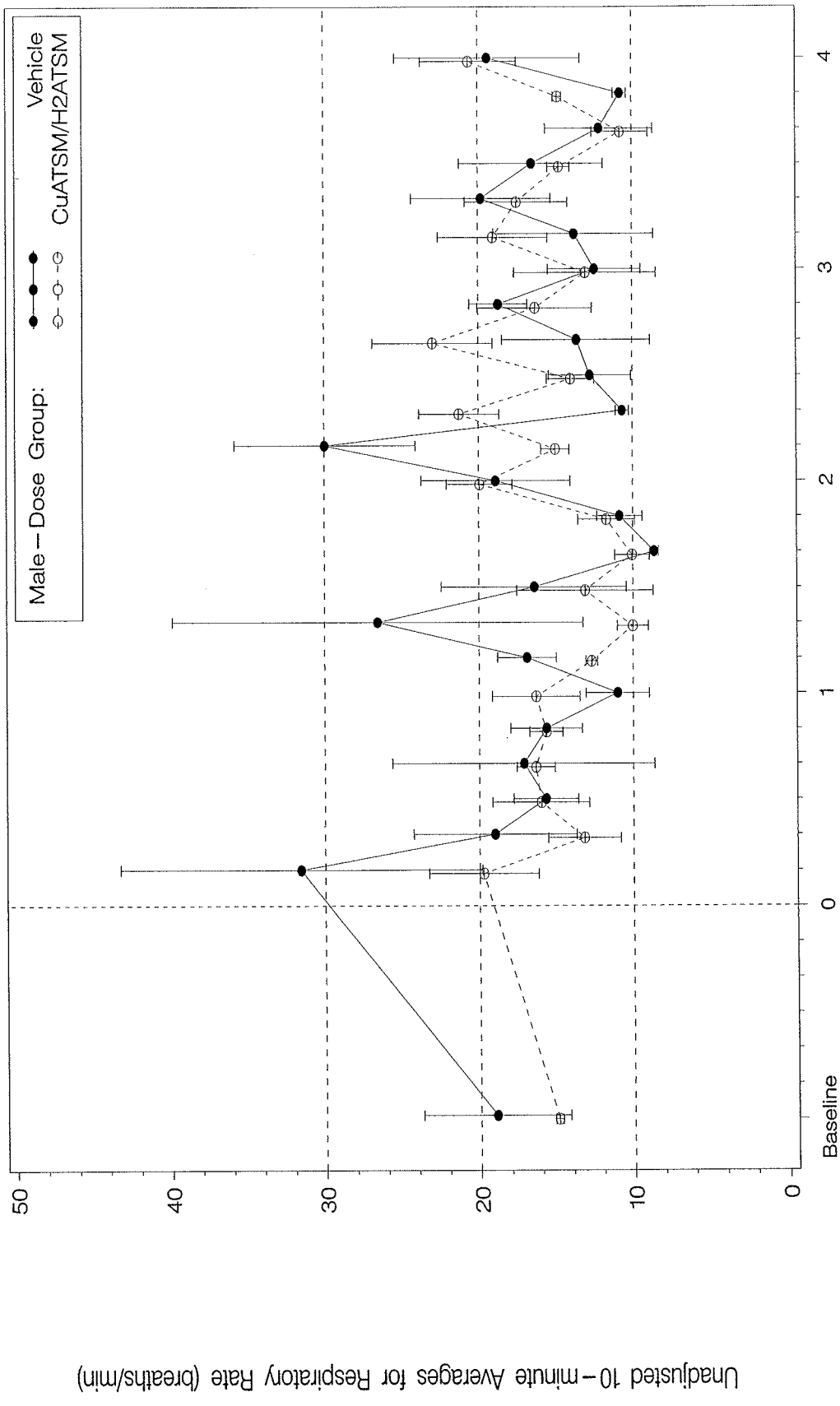


Figure U-58. **Respiratory Rate (breaths/min), Male Animals, Dose Group Means (and Standard Errors) of Baseline Averages and Unadjusted 10-Minute Averages during the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle**

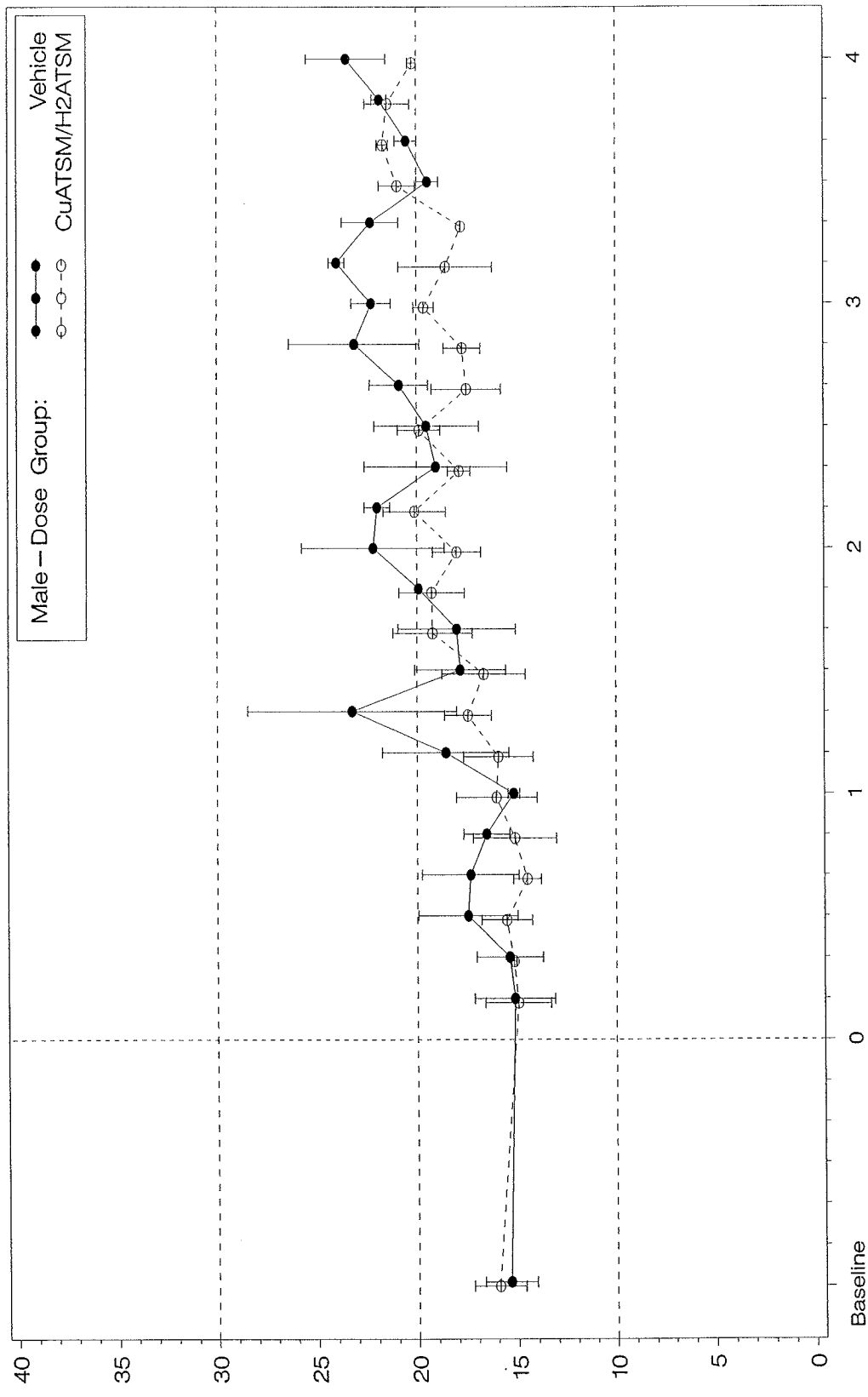


Figure U-59. Body Weight-Adjusted Tidal Volume (mL/breath/kg), Male Animals, Dose Group Means (and Standard Errors) of Baseline Averages and Unadjusted 10-Minute Averages during the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

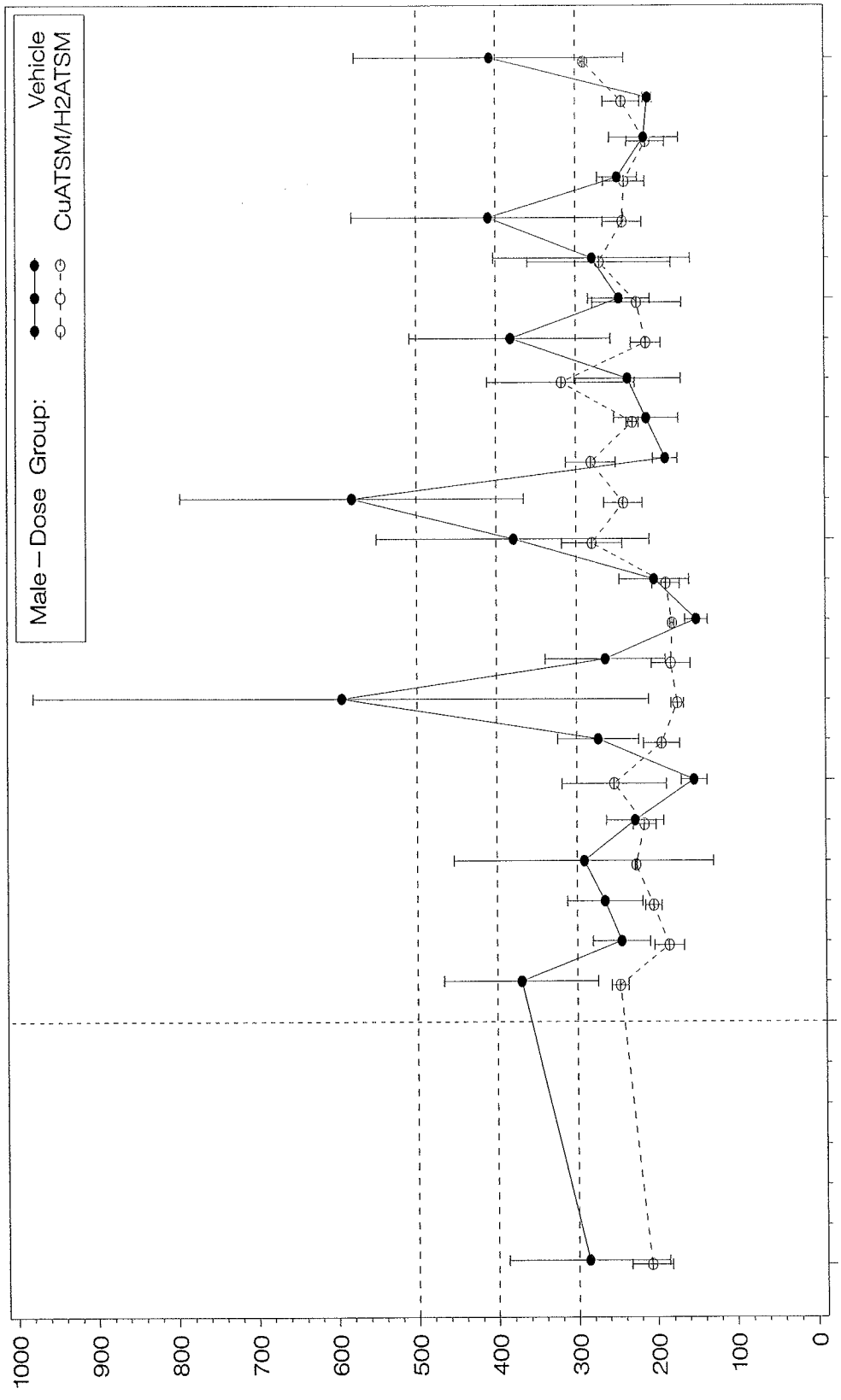


Figure U-60. Body Weight-Adjusted Minute Volume (mL/min/kg), Male Animals, Dose Group Means (and Standard Errors) of Baseline Averages and Unadjusted 10-Minute Averages during the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

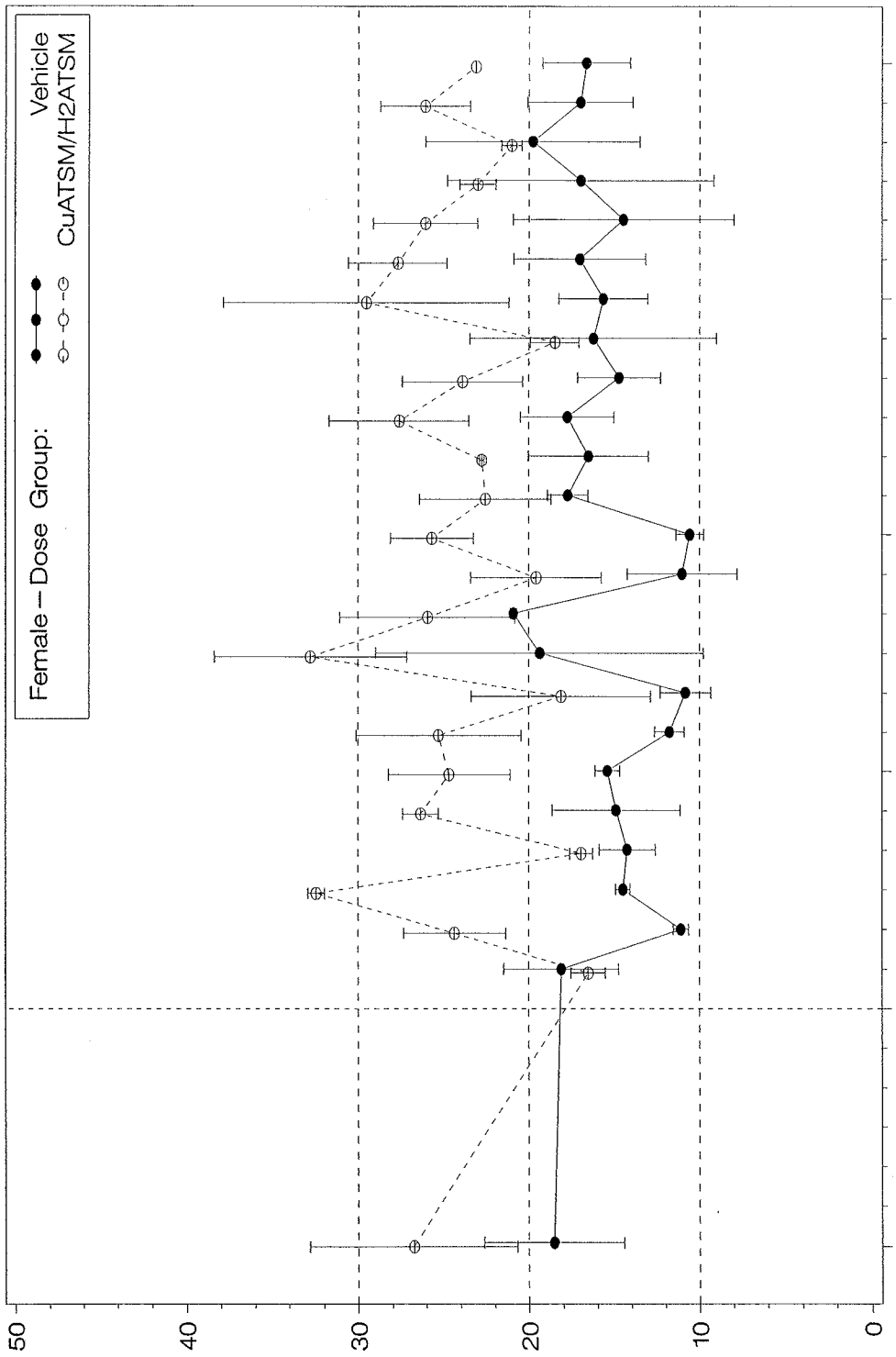


Figure U-61. Respiratory Rate (breaths/min), Female Animals, Dose Group Means (and Standard Errors) of Baseline Averages and Unadjusted 10-Minute Averages during the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

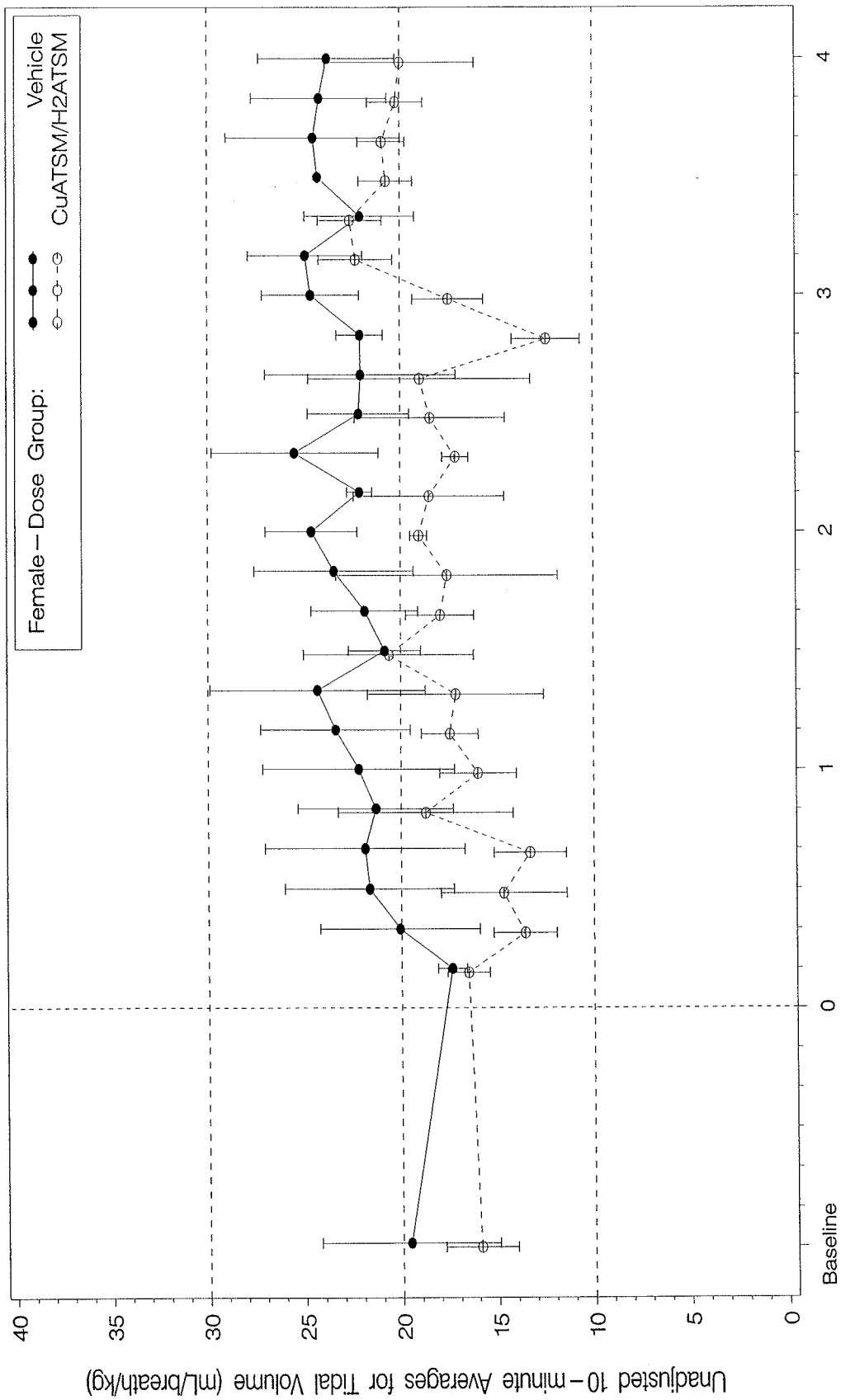


Figure U-62. Body Weight-Adjusted Tidal Volume (mL/breath/kg), Female Animals, Dose Group Means (and Standard Errors) of Baseline Averages and Unadjusted 10-Minute Averages during the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

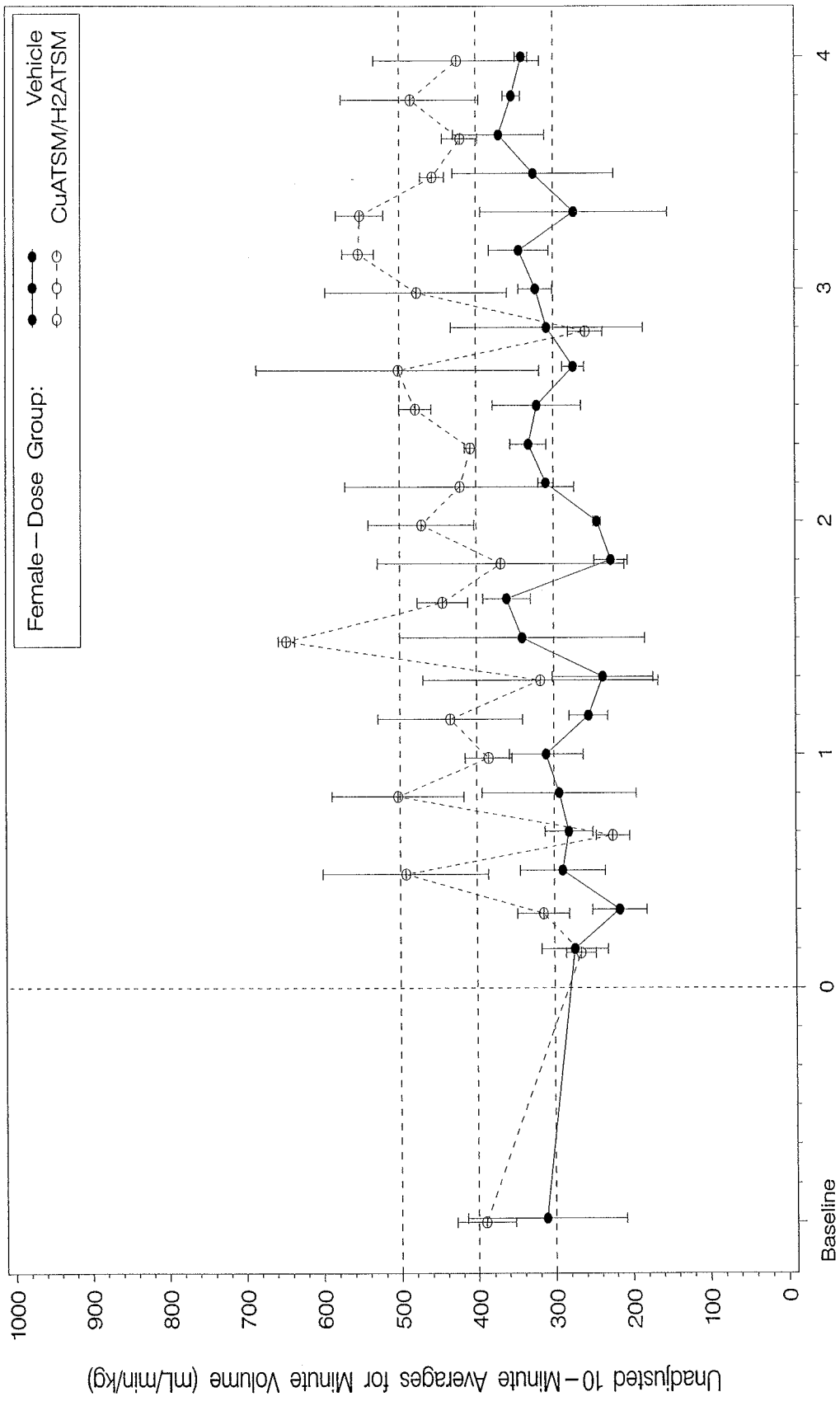


Figure U-63. Body Weight-Adjusted Minute Volume (mL/min/kg), Female Animals, Dose Group Means (and Standard Errors) of Baseline Averages and Unadjusted 10-Minute Averages during the 4-Hour Period Immediately Following Dosing with CuATSM/H_2ATSM or Vehicle

Table 1. In-Sling Baseline Averages for the Blood Pressure and Heart Rate Parameters, Calculated for Each Animal[a]

Sex	Animal ID	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Mean Arterial Pressure (mmHg)	Heart Rate (BPM)
Male	101	144.5	70.0	93.9	90.1
	102	141.4	87.0	101.3	88.0
	201	148.5	90.3	109.7	108.8
	202	159.1	85.3	106.2	72.7
Female	151	151.7	100.8	118.3	89.4
	152	169.3	99.6	119.2	94.7
	251	158.2	83.9	107.2	119.6
	252	158.0	90.1	111.0	105.9

a. Baseline averages were calculated for each animal by averaging data collected during the 30-minute interval from 10 to 40 minutes prior to dosing.

Table 2. In-Cage Baseline Averages for the Blood Pressure and Heart Rate Parameters, Calculated for Each Animal[a]

Sex	Animal ID	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Mean Arterial Pressure (mmHg)	Heart Rate (BPM)
Male	101	112.8	42.3	62.3	69.3
	102	132.5	75.1	91.1	98.4
	201	139.7	77.5	97.5	103.0
	202	136.1	70.5	90.5	86.0
Female	151	122.7	76.5	92.7	104.6
	152	131.2	72.9	91.3	92.7
	251	133.6	69.9	89.9	110.1
	252	129.5	70.7	90.2	106.8

a. Baseline averages were calculated for each animal by averaging data collected during the 1-hour interval from 5 to 6 hours prior to dosing.

Table 3. In-Sling Means (Standard Errors), Calculated by Sex and Dose Group, of the Animals' Baseline Average Responses for the Blood Pressure and Heart Rate Parameters[a]

Sex	Dose Group	Mean (Standard Error) Across Study Animals			
		Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Mean Arterial Pressure (mmHg)	Heart Rate (BPM)
Male	Vehicle (N = 2)	143.0 (1.5)	78.5 (8.5)	97.6 (3.7)	89.1 (1.0)
	CuATSM/H_2ATSM (0.3 mg/kg) (N = 2)	153.8 (5.3)	87.8 (2.5)	107.9 (1.7)	90.7 (18.0)
Female	Vehicle (N = 2)	160.5 (8.8)	100.2 (0.6)	118.8 (0.5)	92.1 (2.7)
	CuATSM/H_2ATSM (0.3 mg/kg) (N = 2)	158.1 (0.1)	87.0 (3.1)	109.1 (1.9)	112.8 (6.8)
All Animals	Vehicle (N = 4)	151.7 (6.2)	89.4 (7.2)	108.2 (6.3)	90.6 (1.5)
	CuATSM/H_2ATSM (0.3 mg/kg) (N = 4)	155.9 (2.5)	87.4 (1.7)	108.5 (1.1)	101.7 (10.1)

a. Summaries are of the baseline averages listed in Table 1. Comparisons between the two dose groups were made across all animals if the sex effect and the interaction between sex and dose group effects were not significant, and separately for each sex if the sex effect or the interaction between sex and dose group effects were significant. Significant differences between the two dose groups existed in baseline values for mean arterial pressure for both males and females, with comparisons were made separately for each sex.

Table 4. In-Cage Means (Standard Errors), Calculated by Sex and Dose Group, of the Animals' Baseline Average Responses for the Blood Pressure and Heart Rate Parameters[a]

Sex	Dose Group	Mean (Standard Error) Across Study Animals			
		Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Mean Arterial Pressure (mmHg)	Heart Rate (BPM)
Male	Vehicle (N = 2)	122.7 (9.8)	58.7 (16.4)	76.7 (14.4)	83.8 (14.5)
	CuATSM/H_2ATSM (0.3 mg/kg) (N = 2)	137.9 (1.8)	74.0 (3.5)	94.0 (3.5)	94.5 (8.5)
Female	Vehicle (N = 2)	126.9 (4.3)	74.7 (1.8)	92.0 (0.7)	98.7 (6.0)
	CuATSM/H_2ATSM (0.3 mg/kg) (N = 2)	131.6 (2.0)	70.3 (0.4)	90.0 (0.1)	108.4 (1.6)
All Animals	Vehicle (N = 4)	124.8 (4.5)	66.7 (8.2)	84.3 (7.4)	91.2 (7.7)
	CuATSM/H_2ATSM (0.3 mg/kg) (N = 4)	134.7 (2.1)	72.1 (1.8)	92.0 (1.8)	101.5 (5.4)

a. Summaries are of the baseline averages listed in Table 2. Comparisons between the two dose groups were made across all animals if the sex effect and the interaction between sex and dose group effects were not significant, and separately for each sex if the sex effect or the interaction between sex and dose group effects were significant. No significant differences in baseline values were observed between the two dose groups for any parameter across all animals.

Table 5. Systolic Blood Pressure (mmHg) In-Sling Means (Standard Errors) of Unadjusted and Baseline-Adjusted 10-Minute Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[a]

10-Minute Interval	Mean (Standard Error) of Unadjusted 10-Minute Averages (N=4)[b]		Mean (Standard Error) of Baseline-Adjusted 10-Minute Averages (N=4)[b]		Significant Differences Between Dose Groups?[c]
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	
0-10	161.2 (4.4)	171.1 (2.2)	9.4 (8.5)	15.1 (4.6)	
10-20	149.3 (5.4)	154.5 (5.8)	-2.4 (5.0)	-1.5 (7.1)	
20-30	149.0 (5.2)	152.0 (4.5)	-2.7 (2.7)	-3.9 (4.5)	
30-40	144.7 (5.9)	154.8 (8.0)	-7.1 (5.6)	-1.1 (7.2)	
40-50	144.9 (5.2)	156.2 (6.2)	-6.8 (5.4)	0.3 (6.3)	
50-60	146.4 (3.8)	151.1 (7.8)	-5.3 (4.6)	-4.9 (6.2)	
60-70	142.2 (3.5)	147.7 (5.9)	-9.5 (5.4)	-8.3 (4.1)	
70-80	145.6 (4.2)	144.1 (6.2)	-6.1 (6.2)	-11.8 (5.6)	
80-90	149.1 (5.9)	150.1 (4.8)	-2.6 (7.6)	-5.8 (5.0)	
90-100	148.0 (3.4)	147.1 (4.9)	-3.7 (6.3)	-8.8 (4.3)	
100-110	140.2 (3.6)	146.6 (5.3)	-11.5 (9.5)	-9.3 (5.4)	
110-120	147.7 (3.5)	156.6 (2.6)	-4.0 (9.0)	0.6 (1.5)	
120-130	150.9 (4.9)	153.7 (5.0)	-0.8 (9.4)	-2.2 (5.5)	
130-140	147.9 (5.9)	156.1 (4.6)	-3.8 (9.0)	0.2 (4.6)	
140-150	146.6 (1.7)	154.0 (4.0)	-5.1 (5.9)	-2.0 (3.9)	
150-160	142.2 (1.8)	155.4 (5.9)	-9.5 (6.8)	-0.5 (5.8)	
160-170	142.4 (3.5)	150.7 (5.8)	-9.4 (8.4)	-5.2 (5.7)	
170-180	151.6 (3.8)	153.6 (5.9)	-0.1 (8.9)	-2.4 (5.1)	
180-190	146.0 (2.9)	155.3 (6.7)	-5.7 (7.0)	-0.6 (4.5)	
190-200	148.6 (4.7)	154.9 (6.5)	-3.1 (8.3)	-1.0 (4.3)	
200-210	152.5 (4.2)	151.2 (5.0)	0.7 (7.3)	-4.7 (3.5)	
210-220	150.8 (1.9)	147.3 (4.5)	-1.0 (6.7)	-8.7 (4.1)	
220-230	146.1 (1.6)	157.0 (3.9)	-5.7 (7.0)	1.0 (1.5)	
230-240	147.8 (3.3)	157.2 (3.0)	-4.0 (8.5)	1.2 (3.1)	
240-250	153.1 (5.4)	158.8 (3.6)	1.3 (7.1)	2.9 (3.6)	
250-260	150.6 (2.2)	159.0 (3.8)	-1.1 (5.6)	3.1 (2.2)	
260-270	152.9 (3.1)	151.1 (9.6)	1.2 (7.9)	-4.1 (10.8)	

a. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted 10-minute averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for systolic blood pressure, F-tests for significant dose group effects were made across all animals, and not separately by sex.

b. N=3 for the CuATSM/H2ATSM group for the 10-minute interval ending at 270 minutes post-dosing.

c. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests for each interval so that the false discovery rate is no higher than 0.05 across all 27 intervals simultaneously. No significant dose group effects were observed at any 10-minute interval.

Table 6. Systolic Blood Pressure (mmHg) In-Sling Means (Standard Errors) of Unadjusted and Baseline-Adjusted 10-Minute Averages Following Dosing with CuATSM/H_2ATSM or Vehicle by Sex

10-Minute Interval	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted 10-Minute Averages (N=2)		Baseline-Adjusted 10-Minute Averages (N=2)		Unadjusted 10-Minute Averages (N=2)[a]		Baseline-Adjusted 10-Minute Averages (N=2)[a]	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
0-10	158.6 (0.2)	171.8 (5.2)	15.6 (1.7)	18.0 (10.5)	163.7 (10.1)	170.4 (0.4)	3.2 (18.9)	12.3 (0.5)
10-20	141.9 (8.0)	148.9 (10.7)	-1.0 (6.4)	-4.9 (16.0)	156.6 (1.4)	160.0 (5.1)	-3.9 (10.2)	1.9 (5.2)
20-30	142.9 (6.5)	148.7 (1.3)	-0.1 (5.0)	-5.1 (4.0)	155.1 (6.8)	155.3 (10.0)	-5.4 (2.0)	-2.8 (10.2)
30-40	140.4 (12.5)	158.6 (13.9)	-2.6 (11.0)	4.8 (8.6)	148.9 (3.9)	151.1 (12.9)	-11.6 (4.9)	-7.0 (13.0)
40-50	143.0 (10.3)	161.0 (6.7)	0.0 (8.8)	7.2 (1.5)	146.8 (6.9)	151.5 (11.7)	-13.6 (1.9)	-6.6 (11.8)
50-60	143.1 (7.3)	150.3 (15.4)	0.1 (5.8)	-3.5 (10.1)	149.7 (3.1)	151.8 (11.2)	-10.8 (5.7)	-6.2 (11.3)
60-70	141.8 (4.5)	141.6 (9.1)	-1.2 (6.0)	-12.2 (3.8)	142.6 (7.3)	153.8 (7.1)	-17.9 (1.5)	-4.3 (7.3)
70-80	147.6 (2.3)	139.4 (4.0)	4.6 (0.8)	-14.4 (1.3)	143.7 (9.6)	148.8 (13.0)	-16.8 (0.8)	-9.3 (13.2)
80-90	151.7 (10.9)	142.4 (4.0)	8.7 (9.3)	-11.4 (9.3)	146.5 (8.8)	157.9 (0.7)	-13.9 (0.0)	-0.2 (0.8)
90-100	147.1 (8.2)	139.3 (0.4)	4.1 (6.6)	-14.5 (4.9)	148.9 (0.1)	154.9 (4.6)	-11.5 (8.7)	-3.2 (4.7)
100-110	145.2 (4.0)	142.6 (0.1)	2.2 (2.5)	-11.2 (5.2)	135.2 (3.7)	150.7 (11.7)	-25.3 (12.5)	-7.4 (11.8)
110-120	153.1 (3.9)	154.1 (4.1)	10.1 (2.4)	0.3 (1.2)	142.3 (0.1)	159.1 (3.4)	-18.1 (8.9)	1.0 (3.5)
120-130	157.2 (7.6)	155.5 (2.3)	14.3 (6.1)	1.7 (3.0)	144.7 (2.8)	152.0 (11.9)	-15.8 (6.0)	-6.1 (12.0)
130-140	150.5 (14.0)	154.2 (2.4)	7.5 (12.5)	0.4 (2.9)	145.4 (0.1)	158.1 (10.7)	-15.1 (8.7)	-0.0 (10.9)
140-150	147.5 (0.1)	150.7 (1.2)	4.5 (1.4)	-3.1 (4.1)	145.7 (4.0)	157.2 (8.5)	-14.8 (4.8)	-0.9 (8.6)
150-160	144.4 (0.3)	156.3 (5.2)	1.4 (1.8)	2.5 (0.1)	140.0 (3.1)	154.5 (13.5)	-20.4 (5.7)	-3.6 (13.6)
160-170	147.6 (1.1)	149.8 (3.6)	4.7 (2.7)	-4.0 (1.7)	137.1 (4.0)	151.7 (13.8)	-23.4 (4.8)	-6.4 (13.9)
170-180	155.9 (6.9)	144.4 (1.5)	13.0 (5.3)	-9.4 (3.8)	147.2 (1.3)	162.8 (6.2)	-13.2 (10.1)	4.7 (6.3)
180-190	145.6 (6.6)	148.3 (12.3)	2.6 (5.1)	-5.5 (7.0)	146.4 (2.6)	162.4 (4.7)	-14.1 (11.4)	4.3 (4.8)
190-200	153.4 (7.4)	150.4 (13.4)	10.5 (5.9)	-3.4 (8.1)	143.7 (5.7)	159.4 (6.0)	-16.8 (3.1)	1.3 (6.1)
200-210	154.9 (8.5)	144.0 (5.4)	11.9 (7.0)	-9.8 (0.1)	150.0 (4.4)	158.5 (4.4)	-10.4 (4.4)	0.4 (4.5)
210-220	150.9 (4.4)	142.3 (2.0)	7.9 (2.8)	-11.5 (3.3)	150.7 (1.4)	152.2 (8.4)	-9.8 (10.2)	-5.9 (8.5)
220-230	148.1 (2.5)	153.4 (8.1)	5.1 (0.9)	-0.4 (2.8)	144.0 (1.2)	160.6 (1.1)	-16.5 (7.6)	2.5 (1.2)
230-240	152.6 (4.3)	155.5 (1.9)	9.6 (2.7)	1.7 (3.4)	142.9 (1.0)	158.9 (6.6)	-17.5 (7.8)	0.8 (6.7)
240-250	155.7 (8.2)	153.1 (1.1)	12.8 (6.7)	-0.7 (6.4)	150.4 (9.8)	164.6 (3.1)	-10.1 (1.0)	6.5 (3.2)
250-260	149.4 (5.1)	154.6 (5.2)	6.5 (3.5)	0.8 (0.0)	151.7 (1.1)	163.5 (4.1)	-8.7 (7.7)	5.4 (4.2)
260-270	157.2 (3.3)	160.4 (3.6)	14.3 (1.8)	6.6 (1.7)	148.6 (2.9)	132.4 (.)	-11.9 (5.9)	-25.5 (.)

a N=1 for the female CuATSM/H2ATSM group for the 10-minute interval ending at 270 minutes post-dosing.

Table 7. Diastolic Blood Pressure (mmHg) In-Sling Means (Standard Errors) of Unadjusted and Baseline-Adjusted 10-Minute Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[a]

10-Minute Interval	Mean (Standard Error) of Unadjusted 10-Minute Averages (N=4)[b]		Mean (Standard Error) of Baseline-Adjusted 10-Minute Averages (N=4)[b]		Significant Differences Between Dose Groups?[c]
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	
0-10	99.3 (6.1)	100.4 (5.2)	9.9 (4.9)	13.0 (4.2)	
10-20	89.8 (7.0)	91.8 (6.1)	0.4 (4.2)	4.4 (4.6)	
20-30	88.9 (6.3)	89.7 (4.5)	-0.5 (2.2)	2.3 (3.1)	
30-40	85.1 (4.9)	88.8 (6.0)	-4.3 (3.1)	1.4 (5.2)	
40-50	87.6 (4.2)	89.6 (5.8)	-1.7 (3.4)	2.2 (4.7)	
50-60	87.0 (5.8)	86.3 (4.9)	-2.4 (2.5)	-1.1 (4.3)	
60-70	85.3 (6.7)	83.4 (3.3)	-4.1 (2.1)	-4.0 (2.2)	
70-80	86.9 (5.6)	80.3 (5.4)	-2.5 (1.7)	-7.1 (3.9)	
80-90	88.1 (4.1)	85.4 (4.4)	-1.3 (4.2)	-2.0 (3.3)	
90-100	86.9 (4.6)	85.2 (3.9)	-2.5 (5.0)	-2.2 (2.7)	
100-110	86.0 (3.7)	82.6 (5.3)	-3.4 (4.3)	-4.8 (3.8)	
110-120	90.0 (4.0)	89.6 (3.5)	0.6 (4.5)	2.2 (2.0)	
120-130	89.2 (3.0)	87.8 (6.2)	-0.2 (4.9)	0.4 (4.8)	
130-140	88.7 (2.8)	88.0 (4.9)	-0.7 (5.9)	0.6 (3.5)	
140-150	86.7 (4.2)	88.1 (4.1)	-2.7 (3.0)	0.7 (2.6)	
150-160	84.4 (3.6)	89.7 (5.9)	-5.0 (3.7)	2.3 (4.5)	
160-170	85.8 (3.9)	87.2 (5.4)	-3.6 (4.1)	-0.2 (3.9)	
170-180	89.4 (3.8)	88.6 (3.3)	-0.0 (4.8)	1.2 (2.3)	
180-190	89.3 (5.1)	87.7 (3.4)	-0.1 (3.2)	0.3 (3.0)	
190-200	90.4 (3.8)	87.5 (3.3)	1.1 (4.4)	0.1 (2.6)	
200-210	91.2 (4.2)	86.3 (2.5)	1.9 (5.3)	-1.1 (1.4)	
210-220	89.8 (5.1)	84.0 (3.8)	0.4 (3.5)	-3.4 (2.2)	
220-230	87.9 (4.4)	89.2 (3.2)	-1.5 (4.8)	1.8 (1.6)	
230-240	89.4 (4.5)	88.1 (4.3)	0.0 (3.0)	0.7 (2.7)	
240-250	91.8 (4.3)	89.4 (4.2)	2.4 (3.5)	2.0 (2.8)	
250-260	89.8 (4.8)	90.6 (3.4)	0.4 (2.6)	3.2 (1.8)	
260-270	89.6 (2.7)	84.9 (7.1)	0.3 (5.3)	-3.7 (7.3)	

a. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted 10-minute averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for diastolic blood pressure, F-tests for significant dose group effects were made across all animals, and not separately by sex.

b. N=3 for the CuATSM/H2ATSM group for the 10-minute interval ending at 270 minutes post-dosing.

c. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests for each interval so that the false discovery rate is no higher than 0.05 across all 27 intervals simultaneously. No significant dose group effects were observed at any 10-minute interval.

Table 8. Diastolic Blood Pressure (mmHg) In-Sling Means (Standard Errors) of Unadjusted and Baseline-Adjusted 10-Minute Averages Following Dosing with CuATSM/H_2ATSM or Vehicle by Sex

10-Minute Interval	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted 10-Minute Averages (N=2)		Baseline-Adjusted 10-Minute Averages (N=2)		Unadjusted 10-Minute Averages (N=2)[a]		Baseline-Adjusted 10-Minute Averages (N=2)[a]	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
0-10	92.2 (4.2)	104.6 (11.2)	13.7 (4.3)	16.8 (8.7)	106.4 (10.4)	96.2 (2.2)	6.2 (9.8)	9.2 (0.9)
10-20	78.8 (0.4)	93.6 (12.8)	0.2 (8.1)	5.8 (10.2)	100.7 (7.1)	90.0 (7.5)	0.5 (6.5)	3.0 (4.4)
20-30	78.8 (4.6)	92.5 (2.1)	0.3 (3.9)	4.7 (0.4)	98.9 (4.0)	86.8 (9.9)	-1.3 (3.4)	-0.2 (6.8)
30-40	77.1 (2.7)	94.7 (2.9)	-1.5 (5.8)	6.9 (5.4)	93.1 (3.1)	82.9 (11.7)	-7.1 (2.5)	-4.1 (8.6)
40-50	81.0 (3.1)	96.1 (2.0)	2.4 (5.4)	8.3 (0.5)	94.3 (2.7)	83.1 (10.7)	-5.9 (2.1)	-3.9 (7.6)
50-60	77.7 (3.8)	89.5 (3.8)	-0.8 (4.7)	1.7 (6.3)	96.2 (3.8)	83.1 (10.4)	-4.0 (3.2)	-3.9 (7.3)
60-70	77.2 (11.6)	82.5 (1.0)	-1.4 (3.1)	-5.3 (1.5)	93.4 (1.9)	84.3 (7.9)	-6.9 (1.3)	-2.8 (4.8)
70-80	78.7 (7.0)	79.4 (5.1)	0.1 (1.5)	-8.4 (2.6)	95.1 (1.6)	81.1 (12.2)	-5.2 (1.0)	-5.9 (9.1)
80-90	81.4 (0.5)	82.4 (8.5)	2.8 (8.0)	-5.4 (5.9)	94.8 (3.3)	88.5 (5.3)	-5.4 (2.7)	1.4 (2.2)
90-100	80.6 (0.1)	82.4 (5.0)	2.0 (8.6)	-5.4 (2.5)	93.3 (6.8)	88.1 (7.1)	-6.9 (6.2)	1.1 (4.0)
100-110	81.0 (3.3)	82.1 (5.5)	2.4 (5.2)	-5.7 (2.9)	91.0 (4.6)	83.1 (11.7)	-9.2 (4.0)	-3.9 (8.6)
110-120	85.8 (5.4)	91.1 (3.0)	7.2 (3.1)	3.3 (0.5)	94.1 (5.4)	88.2 (7.7)	-6.1 (4.8)	1.2 (4.6)
120-130	85.0 (1.9)	91.7 (3.9)	6.4 (6.6)	3.9 (1.4)	93.3 (3.9)	83.9 (13.7)	-6.9 (3.3)	-3.1 (10.6)
130-140	85.0 (1.2)	87.4 (2.5)	6.4 (9.7)	-0.4 (0.0)	92.4 (4.2)	88.5 (11.6)	-7.8 (3.6)	1.5 (8.5)
140-150	80.3 (4.8)	89.1 (3.5)	1.8 (3.7)	1.3 (1.0)	93.1 (0.9)	87.1 (9.2)	-7.1 (0.3)	0.1 (6.1)
150-160	78.5 (2.9)	91.9 (2.8)	-0.0 (5.6)	4.1 (0.2)	90.2 (0.6)	87.5 (13.9)	-10.0 (0.0)	0.5 (10.8)
160-170	81.8 (7.1)	88.3 (5.0)	3.2 (1.4)	0.5 (2.5)	89.8 (3.2)	86.0 (12.2)	-10.5 (2.6)	-1.0 (9.1)
170-180	84.5 (2.0)	87.1 (0.5)	5.9 (6.5)	-0.7 (2.0)	94.3 (5.7)	90.1 (7.7)	-5.9 (5.1)	3.1 (4.6)
180-190	82.4 (5.8)	85.9 (2.5)	3.9 (2.7)	-1.9 (5.1)	96.2 (5.2)	89.6 (7.5)	-4.1 (4.6)	2.5 (4.4)
190-200	86.0 (4.7)	86.7 (1.3)	7.5 (3.8)	-1.1 (3.9)	94.9 (4.9)	88.3 (7.8)	-5.4 (4.3)	1.3 (4.7)
200-210	87.2 (3.5)	84.7 (3.3)	8.6 (5.0)	-3.1 (0.7)	95.3 (7.7)	87.9 (4.7)	-4.9 (7.1)	0.9 (1.6)
210-220	83.9 (7.5)	83.5 (5.4)	5.4 (1.0)	-4.3 (2.9)	95.7 (5.6)	84.5 (7.5)	-4.5 (5.0)	-2.5 (4.4)
220-230	83.1 (4.2)	90.1 (6.1)	4.6 (4.3)	2.3 (3.5)	92.7 (7.4)	88.3 (4.7)	-7.5 (6.8)	1.3 (1.6)
230-240	82.9 (5.0)	88.9 (8.2)	4.3 (3.5)	1.1 (5.6)	95.9 (2.9)	87.3 (6.7)	-4.3 (2.3)	0.2 (3.6)
240-250	84.5 (1.8)	87.6 (8.3)	6.0 (6.7)	-0.2 (5.8)	99.0 (1.2)	91.2 (5.3)	-1.2 (1.8)	4.2 (2.2)
250-260	83.1 (6.6)	90.3 (5.9)	4.6 (1.9)	2.5 (3.4)	96.4 (2.1)	90.9 (5.8)	-3.8 (1.5)	3.9 (2.7)
260-270	87.4 (5.0)	91.3 (5.2)	8.9 (3.5)	3.5 (2.6)	91.9 (2.9)	72.1 (.)	-8.4 (2.3)	-18.1 (.)

a. N=1 for the female CuATSM/H2ATSM group for the 10-minute interval ending at 270 minutes post-dosing.

Table 9. Mean Arterial Blood Pressure (mmHg) In-Sling Means (Standard Errors) of Unadjusted and Baseline-Adjusted 10-Minute Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[a]

10-Minute Interval	Mean (Standard Error) of Unadjusted 10-Minute Averages (N=4)[b]		Mean (Standard Error) of Baseline-Adjusted 10-Minute Averages (N=4)[b]		Significant Differences Between Dose Groups?[c]
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	
0-10	122.0 (5.9)	124.4 (4.5)	13.8 (5.8)	15.9 (4.0)	
10-20	110.1 (6.9)	113.2 (6.9)	1.9 (4.4)	4.7 (5.9)	
20-30	108.7 (5.1)	110.6 (4.6)	0.5 (2.4)	2.1 (3.7)	
30-40	103.8 (4.8)	110.5 (6.5)	-4.4 (4.1)	2.0 (6.4)	
40-50	105.7 (3.3)	111.5 (5.8)	-2.5 (4.3)	3.0 (5.4)	
50-60	105.8 (4.4)	106.9 (5.1)	-2.3 (3.4)	-1.6 (5.0)	
60-70	103.0 (4.6)	103.6 (3.7)	-5.1 (3.6)	-4.9 (2.9)	
70-80	105.0 (2.6)	99.6 (6.0)	-3.2 (3.7)	-8.9 (5.0)	
80-90	106.9 (3.4)	105.1 (6.0)	-1.3 (5.7)	-3.4 (5.0)	
90-100	105.1 (4.6)	104.1 (4.7)	-3.1 (5.9)	-4.4 (3.7)	
100-110	102.0 (2.9)	102.2 (5.9)	-6.2 (6.2)	-6.3 (4.8)	
110-120	107.2 (2.4)	110.9 (2.7)	-1.0 (6.5)	2.4 (1.9)	
120-130	108.0 (2.2)	108.5 (5.9)	-0.1 (7.0)	-0.0 (5.1)	
130-140	107.0 (3.8)	108.7 (5.0)	-1.2 (7.4)	0.2 (4.1)	
140-150	104.8 (2.5)	108.1 (4.2)	-3.4 (3.8)	-0.4 (3.2)	
150-160	100.9 (2.0)	110.0 (6.0)	-7.3 (4.7)	1.4 (5.2)	
160-170	102.3 (1.6)	106.0 (5.8)	-5.8 (6.0)	-2.6 (4.8)	
170-180	107.9 (3.3)	108.2 (4.6)	-0.2 (6.8)	-0.3 (3.8)	
180-190	105.5 (4.1)	108.9 (4.4)	-2.7 (5.0)	0.4 (4.2)	
190-200	107.3 (1.5)	108.6 (4.1)	-0.9 (6.0)	0.1 (3.8)	
200-210	109.7 (2.6)	106.3 (3.3)	1.5 (6.4)	-2.3 (2.5)	
210-220	108.1 (3.5)	102.9 (4.4)	-0.1 (4.8)	-5.6 (3.3)	
220-230	104.3 (3.1)	110.7 (2.0)	-3.9 (5.5)	2.2 (1.0)	
230-240	106.2 (2.2)	109.4 (3.6)	-2.0 (5.0)	0.9 (2.6)	
240-250	110.1 (3.6)	110.7 (4.9)	2.0 (5.1)	2.2 (3.9)	
250-260	107.4 (3.6)	111.9 (3.0)	-0.7 (3.3)	3.4 (2.0)	
260-270	109.1 (1.1)	106.3 (6.5)	0.9 (6.2)	-2.6 (7.2)	

a. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted 10-minute averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for mean arterial pressure, F-tests for significant dose group effects were made across all animals, and not separately by sex.

b. N=3 for the CuATSM/H2ATSM group for the 10-minute interval ending at 270 minutes post-dosing.

c. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests for each interval so that the false discovery rate is no higher than 0.05 across all 27 intervals simultaneously. No significant dose group effects were observed at any 10-minute interval.

Table 10. Mean Arterial Blood Pressure (mmHg) In-Sling Means (Standard Errors) of Unadjusted and Baseline-Adjusted 10-Minute Averages Following Dosing with CuATSM/H_2ATSM or Vehicle by Sex

10-Minute Interval	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted 10-Minute Averages (N=2)		Baseline-Adjusted 10-Minute Averages (N=2)		Unadjusted 10-Minute Averages (N=2)[a]		Baseline-Adjusted 10-Minute Averages (N=2)[a]	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
0-10	116.3 (1.9)	126.9 (10.5)	18.7 (1.8)	19.0 (8.8)	127.7 (12.0)	122.0 (0.8)	9.0 (12.4)	12.9 (1.1)
10-20	99.7 (3.9)	111.9 (15.2)	2.1 (7.6)	4.0 (13.4)	120.4 (7.3)	114.4 (7.2)	1.6 (7.7)	5.4 (5.3)
20-30	100.1 (0.5)	111.4 (3.3)	2.5 (4.2)	3.5 (1.5)	117.3 (2.7)	109.8 (10.7)	-1.4 (3.2)	0.7 (8.8)
30-40	96.3 (4.7)	116.4 (5.4)	-1.3 (8.4)	8.5 (7.1)	111.2 (2.8)	104.7 (12.6)	-7.5 (3.3)	-4.4 (10.6)
40-50	100.5 (3.4)	117.5 (1.2)	2.9 (7.0)	9.5 (0.5)	110.9 (1.3)	105.5 (11.3)	-7.9 (1.7)	-3.6 (9.4)
50-60	98.8 (1.6)	109.0 (5.3)	1.2 (5.3)	1.0 (7.0)	112.8 (3.7)	104.9 (11.1)	-5.9 (4.2)	-4.2 (9.1)
60-70	97.7 (8.4)	100.5 (0.9)	0.1 (4.7)	-7.4 (0.9)	108.3 (0.8)	106.7 (7.9)	-10.4 (1.2)	-2.3 (6.0)
70-80	100.8 (2.2)	96.4 (5.6)	3.2 (1.5)	-11.6 (3.9)	109.2 (0.3)	102.8 (12.8)	-9.6 (0.1)	-6.3 (10.9)
80-90	103.2 (6.3)	98.8 (10.8)	5.6 (9.9)	-9.1 (9.1)	110.7 (0.8)	111.3 (4.1)	-8.1 (1.2)	2.3 (2.2)
90-100	100.4 (5.5)	98.8 (5.7)	2.8 (9.2)	-9.2 (4.0)	109.7 (7.1)	109.4 (6.6)	-9.0 (7.6)	0.3 (4.7)
100-110	100.2 (1.4)	99.6 (6.0)	2.6 (5.1)	-8.3 (4.3)	103.8 (6.5)	104.7 (12.5)	-14.9 (7.0)	-4.3 (10.6)
110-120	106.6 (0.1)	111.1 (1.8)	9.0 (3.8)	3.1 (0.0)	107.8 (5.9)	110.8 (6.4)	-10.9 (6.3)	1.7 (4.5)
120-130	108.1 (3.6)	111.1 (3.1)	10.5 (7.3)	3.1 (1.4)	108.0 (3.9)	105.9 (13.5)	-10.7 (4.4)	-3.2 (11.6)
130-140	105.7 (7.8)	106.4 (2.5)	8.1 (11.5)	-1.6 (0.8)	108.3 (4.6)	111.0 (11.6)	-10.5 (5.1)	1.9 (9.6)
140-150	100.6 (1.2)	106.5 (3.8)	3.0 (2.4)	-1.5 (2.1)	109.1 (1.0)	109.7 (9.2)	-9.7 (1.5)	0.6 (7.3)
150-160	97.6 (1.0)	110.9 (1.5)	0.0 (4.7)	3.0 (0.2)	104.1 (1.7)	109.0 (14.4)	-14.7 (2.1)	-0.1 (12.5)
160-170	102.0 (3.3)	105.2 (4.8)	4.4 (0.4)	-2.8 (3.0)	102.7 (1.9)	106.7 (13.2)	-16.1 (2.4)	-2.3 (11.3)
170-180	106.5 (4.1)	102.4 (2.5)	8.9 (7.8)	-5.5 (0.8)	109.3 (6.5)	114.0 (7.5)	-9.4 (7.0)	4.9 (5.6)
180-190	100.8 (0.8)	104.2 (5.1)	3.2 (4.5)	-3.8 (6.8)	110.2 (7.4)	113.7 (6.8)	-8.6 (7.9)	4.6 (4.9)
190-200	106.1 (1.7)	105.6 (4.6)	8.5 (5.4)	-2.4 (6.4)	108.5 (2.6)	111.6 (7.8)	-10.2 (3.1)	2.5 (5.9)
200-210	108.2 (3.0)	101.8 (1.7)	10.6 (6.7)	-6.1 (0.0)	111.2 (5.2)	110.7 (4.7)	-7.6 (5.7)	1.6 (2.7)
210-220	104.1 (1.5)	99.8 (5.5)	6.5 (2.1)	-8.1 (3.8)	112.0 (6.5)	106.0 (8.1)	-6.8 (6.9)	-3.1 (6.1)
220-230	101.4 (0.3)	109.1 (3.3)	3.8 (4.0)	1.2 (1.5)	107.2 (6.4)	112.2 (3.1)	-11.5 (6.9)	3.1 (1.2)
230-240	103.3 (0.3)	108.7 (6.3)	5.7 (3.9)	0.8 (4.5)	109.1 (3.3)	110.1 (6.2)	-9.6 (3.8)	1.0 (4.3)
240-250	105.6 (5.1)	105.9 (8.5)	8.0 (8.8)	-2.0 (6.8)	114.7 (3.4)	115.5 (4.8)	-4.1 (3.0)	6.4 (2.9)
250-260	101.6 (0.7)	109.2 (4.0)	4.0 (3.0)	1.3 (2.2)	113.3 (2.8)	114.5 (5.1)	-5.5 (3.3)	5.4 (3.2)
260-270	108.9 (0.9)	112.3 (4.1)	11.3 (2.8)	4.4 (2.3)	109.3 (2.4)	94.3 (.)	-9.4 (2.9)	-16.7 (.)

a. N=1 for the female CuATSM/H2ATSM group for the 10-minute interval ending at 270 minutes post-dosing.

Table 11. Heart Rate (BPM) In-Sling Means (Standard Errors) of Unadjusted and Baseline-Adjusted 10-Minute Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[a]

10-Minute Interval	Mean (Standard Error) of Unadjusted 10-Minute Averages (N=4)[b]		Mean (Standard Error) of Baseline-Adjusted 10-Minute Averages (N=4)[b]		Significant Differences Between Dose Groups?[c]
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	
0-10	116.2 (6.8)	118.5 (13.9)	25.6 (7.2)	16.8 (6.9)	
10-20	104.6 (6.1)	121.6 (13.0)	14.0 (5.9)	19.9 (4.7)	
20-30	105.4 (5.4)	118.7 (11.0)	14.8 (5.8)	16.9 (7.1)	
30-40	100.9 (4.3)	107.5 (6.9)	10.3 (4.5)	5.7 (4.1)	
40-50	105.6 (2.6)	111.0 (12.4)	15.0 (2.6)	9.2 (6.9)	
50-60	99.4 (5.1)	109.6 (9.9)	8.8 (5.3)	7.9 (4.5)	
60-70	97.6 (8.7)	106.9 (12.4)	7.0 (9.1)	5.2 (5.5)	
70-80	102.9 (6.2)	101.5 (12.0)	12.3 (6.1)	-0.3 (6.9)	
80-90	108.5 (11.7)	110.8 (14.4)	17.9 (11.8)	9.1 (8.3)	
90-100	95.6 (7.5)	106.7 (10.9)	5.0 (7.3)	4.9 (5.1)	
100-110	98.2 (8.9)	104.2 (11.1)	7.6 (8.2)	2.4 (6.8)	
110-120	99.9 (3.1)	113.2 (7.4)	9.3 (3.0)	11.5 (5.7)	
120-130	104.3 (6.9)	110.9 (8.3)	13.7 (6.8)	9.2 (6.4)	
130-140	107.9 (6.3)	105.2 (10.4)	17.3 (6.3)	3.4 (2.3)	
140-150	97.0 (7.8)	110.8 (11.7)	6.4 (7.2)	9.0 (4.6)	
150-160	96.8 (8.5)	110.3 (10.8)	6.2 (7.5)	8.6 (6.4)	
160-170	96.0 (5.5)	100.8 (9.8)	5.4 (4.9)	-0.9 (1.8)	
170-180	102.0 (7.3)	111.6 (10.1)	11.4 (7.0)	9.9 (4.6)	
180-190	104.0 (5.8)	107.4 (11.5)	13.4 (5.1)	5.7 (8.4)	
190-200	98.9 (2.4)	109.2 (10.0)	8.3 (2.5)	7.5 (5.4)	
200-210	102.1 (5.5)	107.2 (8.4)	11.5 (5.6)	5.5 (4.2)	
210-220	100.2 (5.2)	103.7 (9.4)	9.6 (5.1)	1.9 (4.2)	
220-230	94.4 (6.4)	109.2 (10.4)	3.8 (6.3)	7.5 (2.9)	
230-240	97.9 (8.0)	106.8 (10.4)	7.3 (7.3)	5.0 (1.1)	
240-250	102.2 (7.6)	113.5 (13.5)	11.6 (7.4)	11.8 (4.7)	
250-260	96.3 (6.7)	108.4 (9.6)	5.7 (6.2)	6.7 (1.0)	
260-270	99.2 (2.0)	110.9 (17.3)	8.6 (1.4)	15.1 (7.7)	

a. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted 10-minute averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for heart rate, F-tests for significant dose group effects were made across all animals, and not separately by sex.

b. N=3 for the CuATSM/H2ATSM group for the 10-minute interval ending at 270 minutes post-dosing.

c. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests for each interval so that the false discovery rate is no higher than 0.05 across all 27 intervals simultaneously. No significant dose group effects were observed at any 10-minute interval.

Table 12. Heart Rate (BPM) In-Sling Means (Standard Errors) of Unadjusted and Baseline-Adjusted 10-Minute Averages Following Dosing with CuATSM/H_2ATSM or Vehicle by Sex

10-Minute Interval	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted 10-Minute Averages (N=2)		Baseline-Adjusted 10-Minute Averages (N=2)		Unadjusted 10-Minute Averages (N=2)[a]		Baseline-Adjusted 10-Minute Averages (N=2)[a]	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
0-10	109.4 (4.7)	100.9 (12.3)	20.3 (3.7)	10.2 (5.8)	123.0 (12.8)	136.2 (19.6)	30.9 (15.5)	23.4 (12.8)
10-20	98.4 (10.0)	104.8 (21.1)	9.3 (9.0)	14.1 (3.0)	110.8 (6.6)	138.4 (0.6)	18.7 (9.3)	25.6 (7.4)
20-30	99.2 (0.3)	100.9 (9.0)	10.1 (0.7)	10.2 (9.0)	111.6 (10.0)	136.4 (4.8)	19.5 (12.6)	23.6 (11.6)
30-40	97.5 (7.1)	99.9 (9.5)	8.5 (6.1)	9.2 (8.5)	104.2 (6.2)	115.0 (8.8)	12.1 (8.9)	2.3 (2.0)
40-50	102.0 (3.0)	90.6 (9.3)	12.9 (1.9)	-0.1 (8.7)	109.2 (2.5)	131.3 (0.7)	17.1 (5.2)	18.6 (6.1)
50-60	92.3 (0.9)	94.1 (9.2)	3.3 (2.0)	3.4 (8.8)	106.4 (7.6)	125.1 (4.6)	14.3 (10.3)	12.4 (2.2)
60-70	88.2 (10.9)	87.4 (11.7)	-0.8 (12.0)	-3.3 (6.3)	107.0 (12.5)	126.4 (5.6)	14.9 (15.2)	13.6 (1.2)
70-80	95.2 (6.2)	83.6 (13.8)	6.2 (5.2)	-7.2 (4.2)	110.6 (8.4)	119.4 (6.3)	18.5 (11.1)	6.6 (13.1)
80-90	108.6 (27.4)	86.9 (10.0)	19.5 (26.3)	-3.8 (8.1)	108.4 (8.8)	134.7 (2.1)	16.3 (11.5)	21.9 (4.7)
90-100	86.7 (9.9)	89.4 (10.7)	-2.4 (8.9)	-1.3 (7.3)	104.6 (8.8)	123.9 (2.2)	12.5 (11.4)	11.2 (4.7)
100-110	82.9 (2.4)	87.5 (11.7)	-6.2 (3.4)	-3.2 (6.3)	113.6 (0.0)	120.8 (6.4)	21.5 (2.6)	8.1 (13.2)
110-120	95.3 (2.0)	101.0 (4.9)	6.2 (1.0)	10.2 (13.1)	104.5 (3.2)	125.5 (2.2)	12.4 (5.9)	12.7 (4.6)
120-130	102.7 (15.9)	100.6 (12.1)	13.6 (14.8)	9.8 (6.0)	106.0 (5.1)	121.3 (7.6)	13.9 (7.7)	8.5 (14.4)
130-140	107.1 (15.0)	91.1 (15.1)	18.1 (13.9)	0.4 (2.9)	108.6 (3.7)	119.2 (4.6)	16.6 (6.3)	6.5 (2.2)
140-150	83.6 (2.6)	93.5 (15.2)	-5.5 (1.6)	2.8 (2.8)	110.3 (2.5)	128.0 (0.4)	18.2 (5.1)	15.3 (6.4)
150-160	82.4 (3.0)	95.7 (14.7)	-6.6 (2.0)	4.9 (3.3)	111.1 (3.5)	125.0 (7.5)	19.0 (0.9)	12.3 (14.4)
160-170	87.2 (5.0)	89.9 (18.1)	-1.9 (6.0)	-0.8 (0.1)	104.7 (1.2)	111.7 (2.5)	12.7 (1.5)	-1.0 (4.3)
170-180	96.9 (15.7)	95.8 (10.2)	7.8 (14.7)	5.1 (7.8)	107.2 (4.8)	127.4 (2.4)	15.1 (7.5)	14.7 (4.4)
180-190	94.5 (4.3)	87.9 (5.1)	5.4 (5.3)	-2.8 (12.9)	113.4 (2.3)	126.9 (3.6)	21.3 (0.4)	14.2 (10.4)
190-200	95.7 (2.6)	94.1 (11.3)	6.6 (1.5)	3.3 (6.8)	102.1 (2.7)	124.4 (2.9)	10.0 (5.3)	11.6 (9.7)
200-210	102.5 (13.1)	94.6 (10.1)	13.4 (12.0)	3.8 (7.9)	101.7 (3.4)	119.9 (0.8)	9.6 (6.1)	7.2 (6.0)
210-220	92.3 (3.3)	89.6 (11.7)	3.2 (4.4)	-1.1 (6.3)	108.2 (4.7)	117.7 (0.1)	16.1 (7.3)	4.9 (6.9)
220-230	84.7 (0.5)	97.4 (19.3)	-4.4 (1.6)	6.7 (1.2)	104.1 (7.5)	121.0 (0.2)	12.0 (10.2)	8.2 (7.0)
230-240	84.1 (0.9)	96.8 (19.6)	-5.0 (0.1)	6.1 (1.6)	111.6 (1.8)	116.7 (8.2)	19.6 (4.4)	3.9 (1.4)
240-250	97.4 (16.2)	97.5 (24.1)	8.3 (15.1)	6.8 (6.0)	106.9 (6.4)	129.5 (0.1)	14.8 (9.0)	16.8 (6.9)
250-260	86.2 (8.0)	98.9 (18.5)	-2.9 (9.0)	8.2 (0.4)	106.4 (1.0)	118.0 (5.5)	14.3 (1.6)	5.2 (1.3)
260-270	97.4 (4.2)	98.2 (20.3)	8.3 (3.1)	7.5 (2.3)	101.0 (1.1)	136.3 (.)	8.9 (1.5)	30.4 (.)

a. N=1 for the female CuATSM/H2ATSM group for the 10-minute interval ending at 270 minutes post-dosing.

Table 13. Systolic Blood Pressure (mmHg) In-Cage Means (Standard Errors) of Unadjusted and Baseline-Adjusted Hourly Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[a]

Hourly Interval	Mean (Standard Error) of Unadjusted Hourly Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Hourly Averages (N=4)		Sig. Differences Between Dose Groups?[b]
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	
6-7	131.1 (6.4)	125.7 (2.7)	6.3 (10.5)	-9.0 (1.9)	
7-8	132.5 (5.8)	124.9 (5.0)	7.7 (9.4)	-9.8 (5.0)	
8-9	125.5 (5.0)	129.5 (4.2)	0.7 (4.2)	-5.2 (3.8)	
9-10	125.4 (5.0)	129.0 (4.4)	0.6 (5.3)	-5.7 (3.8)	
10-11	130.0 (3.9)	132.4 (4.1)	5.2 (6.5)	-2.3 (2.3)	
11-12	125.1 (1.5)	130.3 (4.5)	0.3 (5.0)	-4.4 (4.2)	
12-13	124.0 (1.1)	129.8 (1.9)	-0.8 (5.5)	-5.0 (1.2)	
13-14	124.3 (6.0)	130.7 (4.0)	-0.5 (5.3)	-4.0 (3.4)	
14-15	123.5 (4.6)	130.2 (4.8)	-1.3 (3.4)	-4.5 (4.7)	
15-16	127.9 (4.7)	130.6 (3.9)	3.1 (5.6)	-4.2 (3.4)	
16-17	130.5 (4.6)	131.0 (3.5)	5.7 (6.7)	-3.7 (3.1)	
17-18	129.7 (3.7)	131.3 (3.9)	4.8 (6.4)	-3.4 (4.4)	
18-19	132.8 (6.9)	134.6 (3.2)	8.0 (6.7)	-0.1 (3.4)	
19-20	131.1 (5.5)	132.0 (4.3)	6.3 (3.5)	-2.7 (2.8)	
20-21	138.1 (8.2)	125.9 (5.6)	13.3 (8.8)	-8.8 (3.8)	
21-22	134.5 (6.9)	131.6 (4.7)	9.7 (8.1)	-3.1 (2.7)	
22-23	138.8 (2.3)	134.0 (5.8)	13.9 (6.0)	-0.8 (4.2)	
23-24	136.8 (4.7)	127.5 (6.4)	12.0 (8.0)	-7.3 (5.1)	
24-25	130.2 (4.3)	135.0 (3.5)	5.4 (6.0)	0.3 (1.8)	
25-26	131.9 (3.2)	133.2 (3.8)	7.1 (6.7)	-1.6 (2.7)	
26-27	133.5 (4.3)	128.8 (6.5)	8.7 (6.0)	-5.9 (5.1)	
27-28	130.8 (2.1)	137.2 (4.1)	6.0 (3.4)	2.5 (2.7)	
28-29	133.8 (1.5)	132.1 (4.6)	9.0 (5.5)	-2.7 (3.5)	
29-30	129.5 (1.9)	135.4 (3.9)	4.7 (6.1)	0.7 (3.6)	
30-31	130.3 (2.8)	129.1 (3.4)	5.5 (6.4)	-5.6 (3.4)	
31-32	127.0 (1.9)	130.8 (4.0)	2.2 (3.9)	-3.9 (2.3)	
32-33	120.8 (2.9)	129.4 (4.8)	-4.0 (4.2)	-5.3 (4.6)	
33-34	123.6 (3.4)	131.7 (2.3)	-1.2 (5.0)	-3.0 (1.7)	
34-35	129.4 (2.5)	132.4 (3.7)	4.6 (6.2)	-2.4 (3.0)	
35-36	129.7 (1.6)	129.1 (5.0)	4.9 (4.4)	-5.6 (4.5)	
36-37	128.9 (3.8)	130.3 (5.0)	4.1 (7.5)	-4.4 (4.3)	
37-38	125.7 (5.1)	134.7 (5.7)	0.9 (6.1)	-0.0 (5.1)	
38-39	126.7 (4.9)	134.4 (5.2)	1.9 (4.6)	-0.4 (4.8)	
39-40	130.4 (6.2)	131.0 (3.7)	5.6 (6.3)	-3.8 (3.2)	
40-41	132.5 (5.3)	134.7 (1.5)	7.7 (6.5)	0.0 (1.2)	
41-42	136.3 (2.8)	134.2 (4.7)	11.5 (2.7)	-0.6 (4.9)	
42-43	139.4 (6.7)	138.3 (2.6)	14.6 (4.1)	3.6 (1.8)	
43-44	142.5 (4.7)	132.2 (5.3)	17.7 (4.1)	-2.5 (3.5)	
44-45	139.2 (4.3)	135.3 (8.8)	14.4 (5.1)	0.6 (6.7)	
45-46	141.3 (4.2)	132.4 (5.8)	16.5 (5.9)	-2.3 (4.2)	
46-47	138.3 (4.3)	132.8 (5.8)	13.5 (6.4)	-2.0 (3.9)	
47-48	137.2 (5.6)	132.1 (5.0)	12.4 (5.9)	-2.6 (3.2)	
48-49	134.3 (3.1)	136.0 (5.5)	9.5 (4.7)	1.2 (3.7)	
49-50	137.0 (4.2)	134.5 (4.5)	12.2 (5.3)	-0.3 (2.5)	
50-51	138.4 (7.4)	134.9 (5.4)	13.6 (6.9)	0.2 (3.5)	
51-52	138.8 (4.2)	138.4 (6.3)	14.0 (5.6)	3.7 (4.6)	
52-53	143.9 (7.5)	130.2 (7.2)	19.1 (8.9)	-4.5 (5.5)	
53-54	135.5 (5.8)	130.6 (7.7)	10.7 (7.9)	-4.1 (5.8)	
54-55	135.0 (1.4)	136.1 (5.0)	10.1 (3.7)	1.4 (2.9)	
55-56	142.8 (1.0)	138.1 (3.0)	18.0 (5.1)	3.4 (0.9)	
56-57	139.9 (5.8)	139.7 (2.6)	15.0 (5.4)	5.0 (1.7)	
57-58	140.8 (4.5)	141.4 (3.4)	16.0 (4.4)	6.6 (1.9)	
58-59	135.7 (5.3)	135.5 (3.7)	10.9 (3.2)	0.8 (2.4)	
59-60	139.5 (4.0)	133.4 (2.2)	14.7 (3.1)	-1.3 (1.2)	
60-61	141.7 (3.7)	140.9 (5.6)	16.9 (4.2)	6.2 (3.7)	
61-62	138.5 (4.6)	138.0 (2.4)	13.7 (2.8)	3.2 (0.8)	
62-63	135.6 (6.3)	137.1 (2.2)	10.7 (5.4)	2.3 (1.9)	
63-64	142.1 (5.0)	132.6 (2.1)	17.3 (4.5)	-2.1 (2.3)	

Hourly Interval	Mean (Standard Error) of Unadjusted Hourly Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Hourly Averages (N=4)		Sig. Differences Between Dose Groups?[b]
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	
64-65	144.8 (6.8)	134.8 (5.2)	20.0 (6.1)	0.1 (3.6)	
65-66	142.0 (5.1)	129.2 (3.6)	17.2 (6.8)	-5.5 (1.4)	
66-67	136.0 (7.8)	137.8 (3.8)	11.2 (6.9)	3.1 (3.0)	
67-68	139.8 (6.2)	132.2 (5.2)	15.0 (5.7)	-2.5 (3.2)	
68-69	139.4 (8.5)	141.0 (13.1)	14.6 (7.6)	6.3 (12.4)	
69-70	144.1 (9.6)	135.9 (9.3)	19.2 (9.5)	1.2 (8.1)	
70-71	134.1 (7.3)	126.7 (9.0)	9.3 (7.5)	-8.1 (8.3)	
71-72	135.5 (7.0)	131.4 (9.4)	10.7 (8.4)	-3.3 (8.8)	

a. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted hourly averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for systolic blood pressure, F-tests for significant dose group effects were made across all animals, and not separately by sex.

b. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests for each interval so that the false discovery rate is no higher than 0.05 across all 66 hourly intervals simultaneously. No significant dose group effects were observed at any hourly interval.

Table 14. Systolic Blood Pressure (mmHg) In-Cage Means (Standard Errors) of Unadjusted and Baseline-Adjusted Hourly Averages Following Dosing with CuATSM/H_2ATSM or Vehicle by Sex

Hourly Interval	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Hourly Averages (N=2)		Baseline-Adjusted Hourly Averages (N=2)		Unadjusted Hourly Averages (N=2)		Baseline-Adjusted Hourly Averages (N=2)	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
6-7	128.1 (11.9)	129.2 (3.6)	5.4 (21.7)	-8.6 (1.8)	134.0 (9.4)	122.2 (2.3)	7.1 (13.7)	-9.3 (4.4)
7-8	129.0 (6.7)	130.7 (2.7)	6.3 (16.5)	-7.2 (4.5)	136.0 (11.5)	119.1 (8.7)	9.1 (15.8)	-12.4 (10.7)
8-9	121.4 (9.0)	135.6 (3.5)	-1.2 (0.8)	-2.3 (5.3)	129.6 (5.7)	123.5 (4.6)	2.6 (10.0)	-8.0 (6.7)
9-10	120.4 (6.4)	134.3 (4.4)	-2.3 (3.4)	-3.6 (2.6)	130.5 (7.5)	123.7 (6.4)	3.6 (11.8)	-7.9 (8.4)
10-11	124.0 (2.8)	138.6 (5.1)	1.4 (12.6)	0.7 (3.3)	135.9 (3.7)	126.3 (0.1)	8.9 (8.0)	-5.3 (1.9)
11-12	126.7 (1.3)	135.4 (3.2)	4.0 (8.5)	-2.5 (1.4)	123.6 (2.7)	125.2 (7.8)	-3.4 (7.0)	-6.4 (9.9)
12-13	123.7 (1.7)	132.2 (3.1)	1.1 (11.5)	-5.7 (1.3)	124.2 (2.0)	127.3 (0.5)	-2.7 (6.3)	-4.2 (2.5)
13-14	116.5 (7.8)	137.0 (1.5)	-6.2 (2.0)	-0.9 (3.3)	132.2 (5.8)	124.5 (4.1)	5.2 (10.1)	-7.1 (6.1)
14-15	120.1 (9.2)	136.3 (5.1)	-2.6 (0.6)	-1.6 (6.9)	127.0 (3.9)	124.2 (6.2)	0.1 (8.1)	-7.4 (8.2)
15-16	121.4 (3.4)	136.4 (1.1)	-1.3 (6.5)	-1.5 (2.9)	134.3 (6.3)	124.7 (4.7)	7.4 (10.6)	-6.9 (6.7)
16-17	123.9 (1.1)	135.6 (1.6)	1.2 (10.9)	-2.2 (0.2)	137.1 (6.1)	126.4 (5.4)	10.2 (10.4)	-5.2 (7.4)
17-18	124.2 (2.7)	134.3 (0.5)	1.5 (12.5)	-3.6 (2.3)	135.1 (3.8)	128.3 (8.5)	8.2 (8.1)	-3.2 (10.6)
18-19	121.3 (3.2)	133.4 (7.4)	-1.4 (6.7)	-4.5 (5.7)	144.3 (2.5)	135.8 (1.3)	17.4 (6.8)	4.2 (0.7)
19-20	124.6 (5.3)	135.2 (5.3)	2.0 (4.5)	-2.7 (3.5)	137.6 (8.4)	128.9 (7.8)	10.7 (4.1)	-2.7 (5.8)
20-21	127.2 (6.2)	131.5 (6.8)	4.5 (16.1)	-6.3 (5.0)	149.0 (11.5)	120.4 (9.0)	22.0 (7.2)	-11.2 (6.9)
21-22	123.8 (5.7)	137.3 (6.6)	1.1 (15.6)	-0.6 (4.8)	145.2 (5.1)	125.9 (5.0)	18.3 (0.8)	-5.6 (3.0)
22-23	136.0 (4.2)	139.0 (11.5)	13.3 (14.1)	1.1 (9.7)	141.5 (0.0)	129.0 (4.6)	14.6 (4.3)	-2.6 (2.5)
23-24	134.2 (9.8)	134.9 (11.1)	11.5 (19.6)	-3.0 (9.3)	139.5 (4.6)	120.0 (3.5)	12.5 (0.3)	-11.6 (5.6)
24-25	122.9 (2.0)	139.7 (5.4)	0.2 (11.8)	1.8 (3.6)	137.4 (0.5)	130.3 (0.5)	10.5 (4.7)	-1.2 (1.6)
25-26	129.2 (6.5)	135.7 (8.5)	6.5 (16.3)	-2.2 (6.7)	134.5 (2.0)	130.6 (1.6)	7.6 (2.3)	-0.9 (0.4)
26-27	126.5 (3.0)	136.4 (11.6)	3.8 (12.8)	-1.5 (9.8)	140.5 (2.2)	121.2 (2.5)	13.6 (2.1)	-10.4 (4.6)
27-28	127.7 (2.7)	141.0 (8.3)	5.0 (7.2)	3.1 (6.5)	133.9 (0.1)	133.4 (2.1)	7.0 (4.1)	1.8 (0.1)
28-29	132.7 (3.2)	137.7 (7.3)	10.0 (13.1)	-0.2 (5.5)	134.8 (1.1)	126.4 (3.4)	7.9 (3.2)	-5.1 (5.5)
29-30	128.1 (4.0)	136.6 (9.4)	5.4 (13.8)	-1.3 (7.6)	131.0 (1.0)	134.2 (1.1)	4.0 (5.3)	2.6 (3.2)
30-31	126.8 (4.6)	133.3 (0.4)	4.1 (14.5)	-4.6 (1.4)	133.8 (1.4)	125.0 (5.9)	6.9 (5.7)	-6.6 (8.0)
31-32	124.2 (2.0)	137.6 (0.5)	1.6 (7.8)	-0.3 (1.3)	129.8 (1.3)	123.9 (0.3)	2.8 (5.5)	-7.6 (1.8)
32-33	116.2 (2.4)	135.4 (1.9)	-6.5 (7.4)	-2.5 (3.7)	125.4 (2.1)	123.5 (7.9)	-1.6 (6.3)	-8.1 (9.9)
33-34	119.6 (2.7)	134.7 (2.3)	-3.1 (7.1)	-3.2 (4.1)	127.6 (5.5)	128.7 (2.7)	0.6 (9.7)	-2.9 (0.6)
34-35	127.6 (2.0)	138.3 (2.1)	4.9 (11.8)	0.4 (3.9)	131.1 (5.4)	126.4 (2.7)	4.2 (9.6)	-5.2 (4.7)
35-36	127.3 (0.9)	135.2 (2.8)	4.7 (8.9)	-2.7 (1.0)	132.1 (1.6)	123.0 (8.1)	5.2 (5.9)	-8.6 (10.1)
36-37	126.9 (3.6)	138.0 (3.6)	4.2 (13.4)	0.1 (5.4)	131.0 (8.2)	122.6 (4.3)	4.0 (12.5)	-8.9 (6.4)
37-38	121.6 (5.2)	142.9 (5.8)	-1.1 (4.6)	5.0 (7.6)	129.8 (9.7)	126.5 (4.9)	2.8 (13.9)	-5.1 (6.9)
38-39	120.2 (6.2)	141.5 (1.3)	-2.5 (3.7)	3.6 (3.1)	133.2 (4.5)	127.2 (7.8)	6.3 (8.8)	-4.4 (9.8)
39-40	122.5 (6.3)	136.4 (0.9)	-0.1 (3.5)	-1.5 (2.7)	138.2 (8.3)	125.5 (4.7)	11.3 (12.6)	-6.1 (6.7)
40-41	127.0 (3.5)	136.3 (2.9)	4.3 (6.3)	-1.6 (1.1)	138.0 (9.7)	133.2 (0.7)	11.0 (14.0)	1.6 (1.4)
41-42	135.8 (6.8)	136.5 (5.7)	13.2 (3.0)	-1.4 (3.9)	136.7 (1.2)	131.9 (9.4)	9.8 (5.5)	0.3 (11.4)
42-43	131.2 (11.8)	142.5 (1.1)	8.6 (1.9)	4.6 (0.7)	147.6 (0.7)	134.2 (2.1)	20.7 (4.9)	2.6 (4.2)
43-44	135.1 (3.0)	137.6 (6.1)	12.4 (6.8)	-0.3 (4.3)	149.8 (3.8)	126.8 (8.7)	22.9 (0.4)	-4.8 (6.7)
44-45	131.9 (0.1)	146.2 (11.6)	9.2 (9.7)	8.4 (9.8)	146.6 (1.5)	124.3 (9.3)	19.6 (2.7)	-7.2 (7.3)
45-46	136.2 (3.9)	137.3 (11.3)	13.6 (13.7)	-0.5 (9.5)	146.4 (6.1)	127.5 (5.4)	19.4 (1.8)	-4.0 (3.4)
46-47	132.1 (4.7)	142.0 (5.5)	9.4 (14.5)	4.1 (3.7)	144.5 (3.1)	123.5 (0.5)	17.6 (1.2)	-8.0 (1.5)
47-48	127.6 (0.2)	138.8 (7.7)	4.9 (9.6)	0.9 (5.9)	146.8 (1.3)	125.4 (0.7)	19.8 (2.9)	-6.1 (1.4)
48-49	130.2 (1.3)	143.8 (7.6)	7.5 (11.1)	5.9 (5.8)	138.4 (4.6)	128.2 (0.1)	11.4 (0.3)	-3.4 (2.2)
49-50	133.1 (2.3)	139.8 (5.8)	10.5 (12.2)	1.9 (4.0)	140.8 (8.4)	129.1 (5.3)	13.9 (4.2)	-2.5 (3.3)
50-51	130.5 (1.3)	140.1 (7.9)	7.8 (11.2)	2.2 (6.1)	146.3 (14.0)	129.8 (7.5)	19.4 (9.8)	-1.8 (5.4)
51-52	132.5 (2.5)	144.2 (11.1)	9.8 (12.4)	6.3 (9.3)	145.1 (4.4)	132.7 (7.0)	18.2 (0.2)	1.1 (5.0)
52-53	137.0 (9.0)	136.4 (11.8)	14.3 (18.8)	-1.5 (10.0)	150.7 (12.7)	123.9 (9.8)	23.8 (8.5)	-7.6 (7.8)
53-54	129.4 (8.4)	138.7 (11.8)	6.7 (18.3)	0.8 (10.0)	141.6 (7.3)	122.5 (9.3)	14.7 (3.0)	-9.0 (7.3)
54-55	132.9 (1.4)	143.3 (4.1)	10.2 (8.4)	5.5 (2.3)	137.0 (1.2)	128.9 (5.6)	10.1 (3.0)	-2.7 (3.5)
55-56	141.9 (2.1)	142.7 (2.9)	19.2 (11.9)	4.8 (1.1)	143.6 (0.8)	133.6 (2.1)	16.7 (3.5)	2.0 (0.1)
56-57	130.1 (3.3)	144.1 (0.1)	7.4 (6.5)	6.3 (1.7)	149.7 (0.8)	135.2 (1.2)	22.7 (3.5)	3.7 (3.3)
57-58	133.4 (2.1)	145.7 (5.8)	10.8 (7.7)	7.8 (4.0)	148.1 (2.8)	137.1 (0.1)	21.2 (1.5)	5.5 (1.9)
58-59	128.4 (7.7)	142.0 (0.0)	5.7 (2.1)	4.1 (1.8)	143.0 (2.3)	129.1 (1.2)	16.1 (2.0)	-2.5 (3.3)
59-60	135.0 (7.0)	137.3 (0.4)	12.3 (2.8)	-0.6 (1.4)	144.1 (2.0)	129.6 (0.2)	17.2 (6.2)	-2.0 (2.3)
60-61	137.9 (5.6)	149.1 (7.3)	15.3 (4.2)	11.2 (5.5)	145.4 (4.9)	132.8 (0.8)	18.5 (9.2)	1.2 (1.2)

Hourly Interval	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Hourly Averages (N=2)		Baseline-Adjusted Hourly Averages (N=2)		Unadjusted Hourly Averages (N=2)		Baseline-Adjusted Hourly Averages (N=2)	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
61-62	133.6 (8.9)	142.0 (0.6)	10.9 (0.9)	4.1 (1.2)	143.3 (1.4)	134.0 (1.2)	16.4 (5.7)	2.4 (0.9)
62-63	125.7 (6.5)	140.5 (0.5)	3.1 (3.3)	2.6 (2.3)	145.4 (2.4)	133.6 (2.0)	18.4 (6.7)	2.0 (4.1)
63-64	134.0 (4.3)	135.2 (0.9)	11.3 (5.5)	-2.7 (0.9)	150.2 (0.1)	130.0 (3.4)	23.3 (4.4)	-1.6 (5.4)
64-65	136.4 (8.7)	143.7 (2.0)	13.7 (1.1)	5.8 (0.3)	153.3 (7.6)	125.9 (1.1)	26.3 (11.8)	-5.7 (3.1)
65-66	133.8 (1.5)	134.3 (3.4)	11.1 (11.3)	-3.6 (1.6)	150.2 (4.6)	124.1 (3.6)	23.2 (8.9)	-7.5 (1.6)
66-67	123.0 (5.3)	138.9 (7.8)	0.3 (4.5)	1.0 (6.0)	149.0 (1.1)	136.7 (4.9)	22.1 (5.4)	5.1 (2.9)
67-68	129.8 (1.4)	138.0 (6.7)	7.2 (8.4)	0.1 (4.9)	149.8 (5.6)	126.5 (7.1)	22.9 (1.4)	-5.1 (5.1)
68-69	126.8 (0.5)	138.8 (12.4)	4.2 (9.3)	0.9 (10.6)	152.0 (10.6)	143.2 (29.5)	25.1 (6.3)	11.7 (27.4)
69-70	128.8 (3.7)	138.7 (5.5)	6.2 (13.6)	0.8 (3.7)	159.3 (8.5)	133.1 (21.7)	32.3 (4.2)	1.5 (19.6)
70-71	122.1 (2.2)	125.4 (10.5)	-0.6 (12.0)	-12.5 (8.7)	146.0 (5.2)	127.9 (19.3)	19.1 (0.9)	-3.7 (17.2)
71-72	123.9 (4.4)	129.5 (8.3)	1.2 (14.3)	-8.3 (6.5)	147.2 (1.9)	133.2 (21.4)	20.3 (6.2)	1.7 (19.3)

Table 15. Diastolic Blood Pressure (mmHg) In-Cage Means (Standard Errors) of Unadjusted and Baseline-Adjusted Hourly Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[a]

Hourly Interval	Mean (Standard Error) of Unadjusted Hourly Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Hourly Averages (N=4)		Significant Differences Between Dose Groups?[b]
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	
6-7	71.0 (6.6)	68.9 (2.9)	4.3 (9.2)	-3.2 (1.3)	
7-8	71.8 (7.7)	68.9 (3.5)	5.1 (9.1)	-3.2 (3.0)	
8-9	68.1 (6.4)	72.2 (2.9)	1.4 (5.1)	0.1 (1.9)	
9-10	69.6 (6.7)	70.0 (4.5)	2.9 (5.5)	-2.1 (2.8)	
10-11	72.5 (6.4)	72.0 (4.7)	5.8 (8.8)	-0.2 (2.9)	
11-12	66.7 (3.2)	70.8 (4.1)	-0.0 (6.8)	-1.3 (2.5)	
12-13	66.6 (4.9)	69.8 (3.1)	-0.1 (6.7)	-2.3 (1.7)	
13-14	66.8 (8.6)	70.5 (3.0)	0.1 (4.6)	-1.6 (1.8)	
14-15	63.8 (6.8)	72.0 (4.2)	-2.9 (3.5)	-0.1 (4.4)	
15-16	67.0 (7.8)	72.8 (3.7)	0.3 (5.6)	0.7 (3.3)	
16-17	70.6 (6.8)	73.9 (3.6)	3.9 (6.9)	1.7 (3.3)	
17-18	72.9 (6.8)	72.6 (4.0)	6.2 (6.1)	0.5 (3.8)	
18-19	72.9 (10.0)	71.5 (4.0)	6.2 (5.9)	-0.7 (2.6)	
19-20	68.4 (6.3)	69.8 (3.4)	1.6 (4.1)	-2.4 (2.0)	
20-21	73.5 (7.8)	65.3 (3.8)	6.8 (8.4)	-6.8 (2.1)	
21-22	71.7 (7.5)	69.6 (4.5)	5.0 (7.2)	-2.5 (2.8)	
22-23	75.4 (5.2)	71.5 (5.4)	8.7 (5.7)	-0.6 (3.9)	
23-24	73.9 (4.5)	67.4 (4.8)	7.2 (8.2)	-4.7 (3.2)	
24-25	69.5 (6.1)	73.1 (3.1)	2.8 (6.6)	0.9 (1.9)	
25-26	70.3 (4.7)	71.1 (3.3)	3.6 (7.8)	-1.0 (1.8)	
26-27	73.6 (5.6)	72.0 (4.4)	6.9 (7.5)	-0.1 (2.9)	
27-28	72.1 (3.2)	74.4 (4.0)	5.4 (7.3)	2.3 (2.3)	
28-29	72.6 (3.5)	71.0 (3.1)	5.8 (7.0)	-1.1 (1.6)	
29-30	70.4 (3.8)	72.9 (3.7)	3.7 (8.3)	0.7 (2.4)	
30-31	70.8 (4.7)	66.3 (2.2)	4.0 (8.3)	-5.8 (1.0)	
31-32	69.4 (4.9)	70.4 (3.3)	2.7 (6.1)	-1.7 (1.9)	
32-33	63.0 (5.4)	70.2 (4.0)	-3.7 (5.1)	-1.9 (3.3)	
33-34	65.2 (6.2)	72.0 (1.7)	-1.5 (5.7)	-0.2 (1.4)	
34-35	69.7 (4.9)	74.2 (3.7)	3.0 (6.6)	2.0 (3.1)	
35-36	69.7 (5.4)	71.7 (5.6)	3.0 (5.6)	-0.4 (5.1)	
36-37	68.9 (6.2)	71.7 (4.4)	2.2 (7.7)	-0.4 (4.3)	
37-38	65.1 (7.6)	75.8 (4.9)	-1.6 (5.8)	3.7 (4.7)	
38-39	66.7 (8.4)	75.7 (4.3)	-0.0 (3.1)	3.6 (3.4)	
39-40	70.9 (9.7)	75.9 (4.8)	4.2 (5.4)	3.8 (3.9)	
40-41	74.5 (8.5)	80.8 (3.7)	7.8 (5.3)	8.7 (2.5)	
41-42	75.7 (6.0)	78.6 (5.4)	9.0 (3.6)	6.5 (4.8)	
42-43	78.7 (7.9)	76.4 (3.2)	12.0 (5.5)	4.3 (2.6)	
43-44	78.4 (6.3)	69.7 (4.0)	11.7 (7.0)	-2.4 (2.4)	
44-45	75.0 (7.7)	71.3 (6.4)	8.3 (5.8)	-0.8 (4.7)	
45-46	76.2 (6.7)	69.1 (4.2)	9.5 (6.2)	-3.0 (2.4)	
46-47	74.7 (7.1)	70.3 (4.2)	8.0 (6.3)	-1.8 (2.7)	
47-48	74.6 (6.9)	71.6 (3.0)	7.9 (6.0)	-0.5 (1.3)	
48-49	72.2 (4.7)	75.4 (4.7)	5.5 (5.4)	3.2 (3.0)	
49-50	75.0 (4.4)	71.3 (3.6)	8.3 (6.1)	-0.8 (2.1)	
50-51	76.8 (5.6)	70.7 (4.1)	10.1 (7.1)	-1.4 (2.4)	
51-52	75.2 (6.3)	73.0 (5.1)	8.5 (6.1)	0.8 (3.3)	
52-53	76.6 (6.5)	67.1 (4.7)	9.9 (8.4)	-5.1 (3.0)	
53-54	71.3 (5.5)	68.5 (5.7)	4.6 (7.8)	-3.6 (4.0)	
54-55	73.1 (3.1)	74.7 (4.7)	6.4 (6.7)	2.6 (3.3)	
55-56	80.7 (3.5)	78.3 (3.7)	14.0 (7.2)	6.2 (2.7)	
56-57	79.0 (6.3)	81.3 (2.3)	12.3 (5.4)	9.1 (1.5)	
57-58	80.0 (5.3)	84.9 (3.9)	13.3 (7.7)	12.8 (2.4)	
58-59	74.5 (4.8)	80.2 (3.3)	7.8 (6.1)	8.1 (2.0)	
59-60	80.1 (4.7)	79.3 (3.6)	13.4 (6.9)	7.2 (2.7)	
60-61	80.3 (5.5)	82.5 (5.7)	13.6 (7.7)	10.4 (4.1)	
61-62	76.1 (4.9)	80.1 (1.8)	9.4 (4.7)	8.0 (0.7)	
62-63	77.6 (7.8)	81.3 (3.4)	10.9 (7.2)	9.2 (2.9)	
63-64	82.2 (5.4)	80.6 (3.6)	15.5 (6.6)	8.5 (2.8)	

Hourly Interval	Mean (Standard Error) of Unadjusted Hourly Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Hourly Averages (N=4)		Significant Differences Between Dose Groups?[b]
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	
64-65	85.3 (7.7)	77.7 (5.0)	18.6 (7.1)	5.5 (3.3)	
65-66	82.4 (7.2)	76.8 (2.7)	15.7 (8.9)	4.7 (1.3)	
66-67	77.0 (6.7)	79.6 (4.2)	10.3 (6.1)	7.4 (2.4)	
67-68	75.6 (7.8)	69.1 (3.4)	8.9 (7.6)	-3.0 (2.0)	
68-69	75.8 (9.5)	75.1 (7.2)	9.1 (7.8)	3.0 (6.7)	
69-70	77.5 (9.9)	71.7 (5.0)	10.8 (8.9)	-0.4 (4.7)	
70-71	69.8 (8.5)	65.8 (4.5)	3.1 (7.2)	-6.3 (3.6)	
71-72	72.2 (7.9)	69.7 (4.7)	5.5 (8.8)	-2.5 (4.1)	

a. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted hourly averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for diastolic blood pressure, F-tests for significant dose group effects were made across all animals, and not separately by sex.

b. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests for each interval so that the false discovery rate is no higher than 0.05 across all 66 hourly intervals simultaneously. No significant dose group effects were observed at any hourly interval.

Table 16. Diastolic Blood Pressure (mmHg) In-Cage Means (Standard Errors) of Unadjusted and Baseline-Adjusted Hourly Averages Following Dosing with CuATSM/H_2ATSM or Vehicle by Sex

Hourly Interval	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Hourly Averages (N=2)		Baseline-Adjusted Hourly Averages (N=2)		Unadjusted Hourly Averages (N=2)		Baseline-Adjusted Hourly Averages (N=2)	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
6-7	62.4 (4.7)	72.7 (4.8)	3.7 (21.1)	-1.3 (1.3)	79.6 (9.6)	65.1 (0.1)	4.9 (7.8)	-5.2 (0.5)
7-8	62.5 (2.4)	73.0 (0.9)	3.8 (18.8)	-0.9 (2.6)	81.0 (13.5)	64.8 (6.4)	6.3 (11.7)	-5.5 (6.0)
8-9	59.2 (5.4)	75.7 (2.5)	0.5 (11.0)	1.7 (1.0)	77.0 (7.6)	68.7 (4.3)	2.3 (5.8)	-1.6 (3.9)
9-10	60.5 (5.2)	75.1 (8.3)	1.9 (11.3)	1.2 (4.8)	78.7 (9.0)	64.9 (1.7)	4.0 (7.2)	-5.4 (1.3)
10-11	63.1 (4.5)	77.3 (8.5)	4.4 (20.9)	3.4 (5.0)	81.9 (6.9)	66.6 (0.3)	7.2 (5.1)	-3.7 (0.7)
11-12	63.7 (2.1)	74.7 (6.7)	5.0 (14.4)	0.7 (3.2)	69.7 (6.3)	66.9 (4.8)	-5.0 (4.5)	-3.4 (4.4)
12-13	59.5 (0.7)	70.6 (7.5)	0.8 (15.7)	-3.4 (3.9)	73.8 (6.5)	68.9 (1.1)	-0.9 (4.8)	-1.3 (0.7)
13-14	54.8 (9.3)	73.4 (4.1)	-3.9 (7.2)	-0.6 (0.6)	78.8 (8.6)	67.6 (4.6)	4.1 (6.8)	-2.7 (4.2)
14-15	55.3 (9.4)	71.3 (1.2)	-3.4 (7.0)	-2.7 (2.3)	72.4 (6.5)	72.8 (10.2)	-2.3 (4.7)	2.5 (9.8)
15-16	55.3 (5.4)	72.5 (4.7)	-3.4 (11.0)	-1.5 (1.2)	78.7 (7.9)	73.1 (7.7)	4.0 (6.1)	2.9 (7.3)
16-17	60.4 (1.0)	72.9 (4.3)	1.7 (15.4)	-1.0 (0.8)	80.8 (8.3)	74.8 (7.5)	6.1 (6.5)	4.5 (7.1)
17-18	62.8 (3.2)	72.1 (3.7)	4.1 (13.2)	-1.9 (0.2)	83.0 (8.1)	73.1 (9.0)	8.3 (6.3)	2.8 (8.6)
18-19	57.6 (8.5)	72.4 (9.3)	-1.0 (7.9)	-1.6 (5.8)	88.1 (8.3)	70.6 (2.4)	13.4 (6.6)	0.3 (2.0)
19-20	58.5 (6.8)	74.1 (4.7)	-0.2 (9.6)	0.2 (1.2)	78.2 (0.6)	65.4 (2.8)	3.5 (1.2)	-4.9 (3.2)
20-21	60.1 (2.5)	69.6 (6.7)	1.4 (18.9)	-4.4 (3.2)	86.9 (0.0)	61.1 (1.7)	12.2 (1.8)	-9.2 (2.1)
21-22	58.9 (0.1)	75.1 (7.6)	0.2 (16.3)	1.1 (4.1)	84.6 (3.3)	64.2 (1.3)	9.9 (1.5)	-6.1 (1.7)
22-23	67.1 (2.7)	76.1 (10.6)	8.4 (13.7)	2.1 (7.0)	83.8 (4.0)	67.0 (4.9)	9.1 (2.2)	-3.3 (5.3)
23-24	66.6 (3.7)	72.3 (9.2)	7.9 (20.1)	-1.7 (5.7)	81.2 (0.7)	62.6 (2.7)	6.5 (1.1)	-7.7 (3.1)
24-25	59.1 (0.5)	75.0 (6.0)	0.4 (15.9)	1.1 (2.5)	79.9 (2.6)	71.1 (3.6)	5.2 (0.9)	0.8 (4.0)
25-26	62.5 (2.7)	72.6 (7.7)	3.8 (19.1)	-1.4 (4.2)	78.2 (0.8)	69.7 (0.6)	3.5 (1.0)	-0.6 (1.0)
26-27	64.0 (1.8)	73.5 (10.0)	5.3 (18.2)	-0.5 (6.5)	83.1 (1.5)	70.5 (3.0)	8.4 (0.3)	0.2 (2.6)
27-28	67.0 (0.9)	77.7 (8.6)	8.3 (17.4)	3.7 (5.1)	77.3 (2.6)	71.1 (1.1)	2.6 (0.8)	0.8 (0.7)
28-29	66.9 (0.5)	73.7 (6.1)	8.2 (16.9)	-0.3 (2.6)	78.2 (2.6)	68.2 (2.1)	3.5 (0.8)	-2.0 (2.5)
29-30	65.8 (2.9)	73.2 (9.1)	7.1 (19.3)	-0.8 (5.6)	75.0 (5.9)	72.5 (0.3)	0.2 (4.1)	2.3 (0.1)
30-31	64.1 (3.5)	69.3 (2.6)	5.4 (19.9)	-4.7 (1.0)	77.4 (5.7)	63.3 (1.8)	2.7 (4.0)	-7.0 (1.4)
31-32	63.0 (2.7)	75.2 (4.3)	4.4 (13.7)	1.2 (0.7)	75.8 (7.6)	65.7 (1.4)	1.0 (5.8)	-4.6 (1.8)
32-33	54.7 (4.2)	72.4 (3.8)	-4.0 (12.2)	-1.6 (0.3)	71.3 (4.4)	68.1 (8.6)	-3.4 (2.6)	-2.2 (8.2)
33-34	56.8 (4.3)	72.6 (2.4)	-1.9 (12.2)	-1.4 (1.2)	73.7 (8.5)	71.3 (3.2)	-1.0 (6.7)	1.0 (2.8)
34-35	62.8 (1.2)	76.6 (2.7)	4.1 (15.2)	2.6 (0.8)	76.6 (7.0)	71.7 (7.9)	1.9 (5.2)	1.4 (7.5)
35-36	61.4 (3.3)	71.9 (6.2)	2.7 (13.1)	-2.1 (2.6)	78.0 (5.4)	71.6 (12.3)	3.3 (3.6)	1.3 (11.9)
36-37	60.8 (0.6)	72.4 (1.1)	2.1 (17.0)	-1.6 (2.4)	77.1 (10.0)	71.0 (10.6)	2.4 (8.3)	0.8 (10.2)
37-38	56.0 (6.4)	77.7 (1.0)	-2.7 (10.0)	3.7 (2.5)	74.3 (11.7)	74.0 (11.7)	-0.4 (9.9)	3.7 (11.3)
38-39	56.2 (12.3)	78.9 (3.8)	-2.5 (4.1)	4.9 (0.3)	77.2 (7.0)	72.6 (8.6)	2.5 (5.2)	2.3 (8.2)
39-40	58.7 (10.8)	79.0 (4.8)	0.0 (5.6)	5.1 (1.3)	83.1 (12.3)	72.9 (9.7)	8.3 (10.6)	2.6 (9.3)
40-41	63.1 (8.0)	83.9 (4.9)	4.4 (8.4)	9.9 (1.4)	85.9 (10.5)	77.7 (6.1)	11.1 (8.7)	7.5 (5.7)
41-42	70.0 (10.1)	82.7 (2.3)	11.3 (6.4)	8.7 (1.2)	81.4 (7.0)	74.6 (11.7)	6.7 (5.2)	4.3 (11.3)
42-43	66.5 (5.4)	80.7 (0.7)	7.8 (11.0)	6.7 (2.8)	90.9 (6.9)	72.1 (4.9)	16.2 (5.1)	1.8 (4.5)
43-44	68.1 (0.0)	73.9 (7.3)	9.5 (16.4)	-0.1 (3.8)	88.7 (5.4)	65.5 (2.8)	14.0 (3.6)	-4.8 (3.2)
44-45	62.9 (4.2)	79.4 (10.3)	4.2 (12.2)	5.4 (6.7)	87.1 (6.4)	63.3 (3.1)	12.4 (4.6)	-7.0 (3.5)
45-46	64.9 (2.0)	72.9 (8.6)	6.2 (14.4)	-1.1 (5.1)	87.5 (3.4)	65.4 (0.8)	12.8 (1.6)	-4.9 (0.4)
46-47	62.7 (2.2)	76.4 (5.3)	4.0 (14.2)	2.4 (1.8)	86.6 (3.8)	64.2 (2.5)	11.9 (2.0)	-6.1 (2.1)
47-48	63.0 (2.8)	74.6 (5.9)	4.3 (13.7)	0.6 (2.3)	86.2 (3.3)	68.6 (1.9)	11.5 (1.5)	-1.6 (1.5)
48-49	64.4 (3.2)	80.4 (8.4)	5.7 (13.2)	6.5 (4.9)	80.0 (0.2)	70.3 (3.5)	5.3 (2.0)	-0.0 (3.1)
49-50	67.5 (1.8)	75.2 (6.2)	8.8 (14.6)	1.2 (2.7)	82.4 (1.6)	67.4 (3.0)	7.7 (3.4)	-2.9 (3.4)
50-51	67.4 (0.0)	75.5 (7.2)	8.7 (16.4)	1.5 (3.7)	86.1 (3.9)	66.0 (1.7)	11.4 (5.7)	-4.3 (2.1)
51-52	64.5 (2.0)	78.3 (9.8)	5.8 (14.5)	4.3 (6.2)	86.0 (1.2)	67.6 (1.3)	11.3 (0.6)	-2.7 (1.7)
52-53	65.8 (3.0)	71.9 (8.9)	7.1 (19.4)	-2.1 (5.4)	87.4 (3.7)	62.2 (2.5)	12.6 (5.5)	-8.0 (2.9)
53-54	62.0 (2.4)	75.1 (10.2)	3.3 (18.8)	1.1 (6.6)	80.7 (0.1)	61.9 (1.9)	6.0 (1.7)	-8.4 (2.3)
54-55	68.7 (1.1)	77.9 (9.5)	10.0 (15.4)	3.9 (5.9)	77.6 (4.0)	71.5 (4.9)	2.9 (2.3)	1.2 (5.3)
55-56	75.9 (0.3)	78.6 (8.5)	17.2 (16.8)	4.6 (5.0)	85.5 (5.2)	78.1 (3.1)	10.8 (3.4)	7.8 (3.5)
56-57	68.8 (3.6)	81.8 (4.6)	10.1 (12.8)	7.9 (1.1)	89.2 (4.1)	80.7 (3.3)	14.5 (2.3)	10.4 (2.9)
57-58	71.4 (2.4)	86.8 (8.2)	12.7 (18.8)	12.8 (4.7)	88.6 (4.3)	83.0 (4.1)	13.9 (2.5)	12.8 (3.7)
58-59	66.7 (1.7)	85.3 (3.4)	8.0 (14.7)	11.3 (0.1)	82.3 (3.9)	75.2 (2.0)	7.6 (2.2)	4.9 (1.6)
59-60	75.0 (1.5)	78.9 (7.4)	16.3 (14.9)	4.9 (3.9)	85.2 (8.7)	79.8 (4.7)	10.5 (7.0)	9.5 (4.3)
60-61	75.1 (0.6)	86.4 (11.1)	16.4 (15.8)	12.5 (7.6)	85.5 (11.3)	78.6 (6.3)	10.8 (9.5)	8.3 (5.9)

Hourly Interval	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Hourly Averages (N=2)		Baseline-Adjusted Hourly Averages (N=2)		Unadjusted Hourly Averages (N=2)		Baseline-Adjusted Hourly Averages (N=2)	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
61-62	69.7 (5.7)	81.6 (3.5)	11.0 (10.7)	7.6 (0.0)	82.6 (5.4)	78.7 (2.1)	7.9 (3.6)	8.4 (1.7)
62-63	66.5 (2.0)	81.4 (4.6)	7.8 (14.4)	7.4 (1.1)	88.6 (10.8)	81.2 (7.1)	13.9 (9.0)	10.9 (6.7)
63-64	75.2 (1.8)	81.2 (6.0)	16.5 (14.6)	7.2 (2.5)	89.3 (8.6)	80.0 (6.5)	14.5 (6.9)	9.8 (6.1)
64-65	77.9 (4.8)	83.9 (7.6)	19.2 (11.6)	10.0 (4.1)	92.7 (14.9)	71.4 (3.8)	18.0 (13.1)	1.1 (3.4)
65-66	73.1 (3.0)	78.5 (5.1)	14.4 (19.4)	4.5 (1.6)	91.7 (11.5)	75.0 (3.3)	17.0 (9.7)	4.8 (2.9)
66-67	67.7 (3.5)	83.9 (7.8)	9.0 (13.0)	9.9 (4.2)	86.3 (9.2)	75.2 (2.5)	11.5 (7.4)	4.9 (2.1)
67-68	62.9 (0.2)	71.8 (6.9)	4.2 (16.6)	-2.2 (3.4)	88.3 (6.8)	66.4 (3.0)	13.6 (5.0)	-3.9 (3.4)
68-69	59.5 (1.4)	74.8 (10.9)	0.8 (15.0)	0.8 (7.4)	92.1 (2.1)	75.4 (13.9)	17.4 (0.3)	5.2 (14.3)
69-70	60.4 (1.2)	73.1 (5.1)	1.7 (17.6)	-0.9 (1.5)	94.7 (1.0)	70.3 (10.9)	20.0 (0.8)	0.0 (11.3)
70-71	55.3 (1.4)	67.2 (8.4)	-3.4 (15.1)	-6.8 (4.9)	84.3 (3.7)	64.4 (6.9)	9.6 (1.9)	-5.8 (7.3)
71-72	59.5 (3.6)	70.1 (8.0)	0.8 (20.0)	-3.9 (4.5)	85.0 (6.3)	69.2 (8.3)	10.2 (4.5)	-1.1 (8.7)

Table 17. Mean Arterial Pressure (mmHg) In-Cage Means (Standard Errors) of Unadjusted and Baseline-Adjusted Hourly Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[a]

Hourly Interval	Mean (Standard Error) of Unadjusted Hourly Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Hourly Averages (N=4)		Significant Differences Between Dose Groups?[b]
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	
6-7	92.1 (6.5)	87.8 (3.1)	7.7 (9.4)	-4.2 (1.4)	
7-8	91.9 (7.6)	87.3 (3.8)	7.5 (8.7)	-4.7 (3.3)	
8-9	85.9 (7.4)	90.6 (2.9)	1.6 (3.5)	-1.4 (2.0)	
9-10	87.8 (7.3)	88.9 (4.8)	3.5 (4.5)	-3.1 (3.0)	
10-11	91.3 (6.4)	91.2 (4.9)	6.9 (7.7)	-0.8 (3.1)	
11-12	85.8 (3.0)	89.8 (4.2)	1.4 (6.0)	-2.2 (2.8)	
12-13	85.3 (4.3)	88.7 (3.0)	1.0 (6.1)	-3.3 (1.6)	
13-14	85.3 (8.8)	88.9 (3.2)	1.0 (4.6)	-3.1 (1.8)	
14-15	82.5 (7.1)	89.4 (3.1)	-1.9 (2.8)	-2.6 (3.2)	
15-16	86.3 (7.8)	89.7 (2.9)	2.0 (5.5)	-2.3 (2.0)	
16-17	88.6 (7.5)	90.6 (2.8)	4.3 (6.9)	-1.4 (2.0)	
17-18	90.3 (6.5)	90.9 (3.3)	6.0 (6.7)	-1.1 (3.1)	
18-19	91.0 (10.2)	92.1 (3.7)	6.6 (6.4)	0.1 (2.6)	
19-20	89.2 (6.9)	91.5 (3.3)	4.9 (3.8)	-0.5 (2.0)	
20-21	97.4 (7.8)	87.1 (4.4)	13.0 (8.1)	-4.9 (2.8)	
21-22	94.5 (7.0)	91.8 (4.7)	10.2 (6.7)	-0.2 (2.9)	
22-23	99.0 (3.8)	92.8 (6.1)	14.6 (5.8)	0.8 (4.4)	
23-24	96.5 (4.0)	86.8 (6.0)	12.2 (8.2)	-5.2 (4.2)	
24-25	89.7 (6.1)	92.8 (3.3)	5.3 (5.4)	0.8 (1.6)	
25-26	90.7 (4.2)	91.1 (3.4)	6.4 (6.7)	-0.9 (1.7)	
26-27	92.8 (5.9)	90.1 (5.1)	8.4 (5.4)	-1.9 (3.3)	
27-28	90.3 (4.6)	95.1 (4.1)	5.9 (4.2)	3.1 (2.3)	
28-29	93.6 (3.1)	90.7 (3.4)	9.3 (5.8)	-1.3 (1.6)	
29-30	90.3 (3.4)	93.2 (4.1)	5.9 (6.8)	1.2 (2.6)	
30-31	89.5 (5.0)	86.1 (2.6)	5.2 (6.4)	-5.9 (1.5)	
31-32	87.6 (5.4)	89.6 (3.7)	3.3 (4.1)	-2.4 (2.2)	
32-33	81.3 (6.2)	88.6 (3.9)	-3.0 (3.9)	-3.4 (3.1)	
33-34	84.3 (6.4)	90.6 (1.2)	-0.0 (4.8)	-1.4 (0.6)	
34-35	90.0 (4.5)	92.4 (3.1)	5.7 (6.3)	0.4 (2.4)	
35-36	89.7 (5.0)	89.4 (4.9)	5.3 (4.8)	-2.6 (4.0)	
36-37	88.7 (6.1)	89.4 (3.2)	4.3 (7.4)	-2.6 (2.9)	
37-38	84.7 (7.7)	93.1 (3.9)	0.4 (5.6)	1.1 (3.5)	
38-39	85.6 (8.3)	92.6 (3.9)	1.3 (3.3)	0.6 (2.9)	
39-40	89.4 (9.1)	90.7 (3.9)	5.1 (5.6)	-1.3 (2.7)	
40-41	91.5 (8.4)	95.3 (3.2)	7.2 (5.8)	3.3 (1.5)	
41-42	93.7 (5.6)	94.3 (4.9)	9.4 (2.7)	2.3 (3.9)	
42-43	96.5 (9.1)	95.6 (2.5)	12.1 (4.0)	3.6 (1.6)	
43-44	99.7 (6.5)	91.3 (4.2)	15.3 (5.1)	-0.7 (2.8)	
44-45	98.2 (6.3)	94.0 (7.8)	13.8 (4.7)	2.0 (6.2)	
45-46	99.6 (5.4)	91.0 (5.0)	15.3 (6.0)	-1.0 (3.2)	
46-47	97.6 (5.9)	90.8 (4.9)	13.2 (6.0)	-1.2 (3.3)	
47-48	95.4 (7.4)	91.1 (4.1)	11.0 (5.2)	-0.9 (2.2)	
48-49	92.8 (4.5)	94.2 (5.0)	8.5 (4.8)	2.2 (3.2)	
49-50	95.6 (4.6)	92.0 (4.3)	11.3 (5.6)	-0.0 (2.7)	
50-51	97.5 (7.0)	93.2 (4.5)	13.2 (6.2)	1.2 (2.8)	
51-52	98.0 (5.8)	96.0 (5.6)	13.7 (5.3)	4.0 (3.8)	
52-53	100.7 (6.6)	89.3 (5.5)	16.3 (8.1)	-2.7 (3.9)	
53-54	93.7 (5.5)	88.9 (6.3)	9.3 (7.3)	-3.1 (4.5)	
54-55	92.1 (3.7)	93.6 (4.4)	7.7 (4.6)	1.6 (2.9)	
55-56	99.7 (3.5)	95.1 (3.6)	15.3 (6.1)	3.1 (2.3)	
56-57	96.3 (7.8)	96.6 (2.3)	12.0 (5.0)	4.6 (1.0)	
57-58	96.6 (6.4)	99.9 (4.0)	12.3 (6.3)	7.9 (2.4)	
58-59	90.4 (6.5)	94.3 (3.4)	6.0 (4.2)	2.3 (2.0)	
59-60	96.4 (5.5)	92.9 (2.7)	12.1 (4.4)	0.9 (1.5)	
60-61	96.8 (5.8)	97.8 (5.8)	12.5 (6.2)	5.8 (4.0)	
61-62	92.8 (5.8)	94.8 (2.2)	8.4 (3.2)	2.8 (0.4)	
62-63	92.1 (9.1)	95.9 (2.5)	7.7 (6.3)	3.9 (1.9)	
63-64	97.7 (6.5)	92.9 (3.3)	13.3 (5.3)	0.9 (2.2)	

Hourly Interval	Mean (Standard Error) of Unadjusted Hourly Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Hourly Averages (N=4)		Significant Differences Between Dose Groups?[b]
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	
64-65	100.4 (9.0)	90.9 (5.6)	16.1 (6.6)	-1.1 (3.9)	
65-66	98.3 (8.1)	89.4 (3.2)	13.9 (7.9)	-2.6 (1.6)	
66-67	91.8 (8.6)	96.1 (3.8)	7.5 (6.0)	4.1 (2.2)	
67-68	96.1 (7.8)	90.2 (3.7)	11.7 (6.0)	-1.8 (2.3)	
68-69	97.9 (9.2)	97.8 (9.1)	13.6 (7.2)	5.8 (8.6)	
69-70	101.5 (10.0)	94.5 (6.5)	17.1 (8.5)	2.5 (6.0)	
70-71	92.4 (8.1)	86.2 (5.7)	8.0 (6.4)	-5.8 (5.0)	
71-72	93.1 (8.1)	89.2 (5.6)	8.8 (7.6)	-2.8 (5.2)	

a. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted hourly averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for mean arterial pressure, F-tests for significant dose group effects were made across all animals, and not separately by sex.

b. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests for each interval so that the false discovery rate is no higher than 0.05 across all 66 hourly intervals simultaneously. No significant dose group effects were observed at any hourly interval.

Table 18. Mean Arterial Pressure (mmHg) In-Cage Means (Standard Errors) of Unadjusted and Baseline-Adjusted Hourly Averages Following Dosing with CuATSM/H_2ATSM or Vehicle by Sex

Hourly Interval	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Hourly Averages (N=2)		Baseline-Adjusted Hourly Averages (N=2)		Unadjusted Hourly Averages (N=2)		Baseline-Adjusted Hourly Averages (N=2)	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
6-7	84.8 (6.6)	91.8 (5.1)	8.1 (21.0)	-2.2 (1.6)	99.3 (10.3)	83.7 (0.2)	7.3 (9.6)	-6.3 (0.1)
7-8	83.1 (2.5)	91.9 (0.8)	6.4 (16.9)	-2.1 (2.7)	100.7 (13.6)	82.6 (6.7)	8.7 (12.9)	-7.4 (6.5)
8-9	76.3 (9.6)	94.9 (1.8)	-0.4 (4.8)	1.0 (1.7)	95.6 (7.2)	86.3 (3.2)	3.6 (6.5)	-3.8 (3.1)
9-10	78.4 (7.7)	94.0 (8.9)	1.7 (6.7)	0.1 (5.4)	97.2 (9.0)	83.7 (2.6)	5.2 (8.3)	-6.3 (2.4)
10-11	81.4 (3.4)	96.6 (9.0)	4.7 (17.7)	2.7 (5.5)	101.1 (6.5)	85.7 (0.8)	9.1 (5.8)	-4.3 (1.0)
11-12	83.1 (2.6)	93.8 (6.8)	6.4 (11.8)	-0.2 (3.4)	88.4 (5.9)	85.9 (5.5)	-3.6 (5.2)	-4.1 (5.4)
12-13	78.9 (0.3)	89.7 (7.2)	2.2 (14.0)	-4.2 (3.7)	91.8 (5.2)	87.7 (0.0)	-0.2 (4.5)	-2.3 (0.1)
13-14	73.0 (9.5)	93.3 (3.5)	-3.7 (4.8)	-0.7 (0.0)	97.6 (8.3)	84.5 (3.0)	5.6 (7.6)	-5.5 (2.9)
14-15	73.8 (10.6)	90.8 (0.8)	-2.8 (3.8)	-3.2 (2.7)	91.1 (6.2)	88.0 (7.4)	-0.9 (5.5)	-2.1 (7.3)
15-16	74.4 (4.6)	91.5 (4.4)	-2.3 (9.7)	-2.5 (0.9)	98.2 (7.7)	88.0 (5.0)	6.2 (7.0)	-2.0 (4.8)
16-17	77.0 (0.3)	91.7 (5.0)	0.3 (14.1)	-2.3 (1.5)	100.2 (8.0)	89.6 (4.6)	8.2 (7.3)	-0.5 (4.4)
17-18	80.4 (0.3)	91.7 (2.7)	3.7 (14.6)	-2.3 (0.8)	100.2 (7.5)	90.0 (7.4)	8.2 (6.8)	-0.0 (7.3)
18-19	74.7 (6.6)	91.9 (9.1)	-2.0 (7.8)	-2.1 (5.6)	107.2 (6.9)	92.3 (0.8)	15.2 (6.2)	2.3 (0.6)
19-20	78.7 (7.2)	95.3 (4.7)	2.0 (7.1)	1.3 (1.2)	99.8 (3.5)	87.8 (3.9)	7.8 (4.2)	-2.2 (4.0)
20-21	84.4 (3.2)	92.0 (7.2)	7.7 (17.5)	-2.0 (3.8)	110.3 (4.4)	82.3 (4.0)	18.3 (5.1)	-7.7 (4.1)
21-22	82.4 (0.8)	97.6 (7.7)	5.7 (15.2)	3.6 (4.2)	106.6 (0.4)	86.0 (2.1)	14.6 (0.3)	-4.0 (2.2)
22-23	92.8 (0.6)	98.5 (12.0)	16.1 (13.8)	4.5 (8.5)	105.2 (3.2)	87.1 (4.2)	13.2 (2.4)	-2.9 (4.3)
23-24	90.8 (5.5)	93.9 (10.6)	14.1 (19.8)	-0.1 (7.1)	102.3 (0.5)	79.6 (0.0)	10.3 (1.2)	-10.4 (0.1)
24-25	79.6 (1.9)	96.5 (6.0)	2.9 (12.5)	2.5 (2.5)	99.8 (3.4)	89.1 (1.5)	7.8 (2.7)	-0.9 (1.6)
25-26	83.7 (2.0)	93.5 (7.6)	7.0 (16.4)	-0.5 (4.1)	97.8 (1.3)	88.7 (0.1)	5.8 (0.6)	-1.4 (0.1)
26-27	82.7 (1.7)	94.9 (10.0)	6.0 (12.7)	0.9 (6.5)	102.9 (1.6)	85.2 (2.5)	10.9 (0.9)	-4.8 (2.4)
27-28	83.2 (4.3)	99.3 (8.2)	6.5 (10.0)	5.3 (4.7)	97.3 (2.6)	91.0 (0.4)	5.3 (1.9)	0.9 (0.2)
28-29	88.6 (0.9)	94.8 (6.0)	11.9 (13.5)	0.9 (2.5)	98.6 (2.1)	86.5 (0.1)	6.6 (1.4)	-3.5 (0.2)
29-30	85.7 (1.2)	94.7 (9.7)	9.0 (15.6)	0.7 (6.2)	94.9 (5.0)	91.7 (0.0)	2.9 (4.3)	1.7 (0.1)
30-31	81.6 (0.6)	89.8 (2.7)	4.9 (15.0)	-4.2 (0.8)	97.4 (5.1)	82.4 (2.7)	5.4 (4.4)	-7.6 (2.5)
31-32	80.3 (5.8)	95.1 (4.3)	3.6 (8.5)	1.1 (0.8)	95.0 (5.8)	84.0 (2.0)	3.0 (5.1)	-6.0 (2.1)
32-33	71.9 (5.9)	92.4 (3.1)	-4.8 (8.5)	-1.6 (0.4)	90.8 (4.2)	84.9 (7.2)	-1.2 (3.5)	-5.1 (7.1)
33-34	75.7 (5.6)	91.8 (2.5)	-1.0 (8.8)	-2.2 (1.0)	92.9 (8.3)	89.4 (0.3)	0.9 (7.5)	-0.6 (0.4)
34-35	84.1 (0.5)	96.4 (1.9)	7.4 (13.9)	2.4 (1.6)	96.0 (7.1)	88.5 (4.9)	4.0 (6.4)	-1.5 (4.8)
35-36	81.9 (3.2)	91.9 (6.1)	5.2 (11.2)	-2.0 (2.6)	97.4 (4.5)	86.8 (9.6)	5.4 (3.8)	-3.2 (9.5)
36-37	81.0 (1.2)	92.5 (0.7)	4.3 (15.6)	-1.4 (2.8)	96.4 (10.0)	86.2 (6.5)	4.4 (9.3)	-3.8 (6.3)
37-38	75.5 (6.7)	97.5 (0.3)	-1.1 (7.7)	3.5 (3.2)	93.9 (11.8)	88.7 (7.3)	1.9 (11.1)	-1.3 (7.1)
38-39	74.6 (11.4)	96.9 (3.8)	-2.1 (3.0)	3.0 (0.4)	96.6 (6.4)	88.3 (6.3)	4.6 (5.7)	-1.8 (6.2)
39-40	77.1 (8.5)	94.7 (4.9)	0.4 (5.9)	0.7 (1.4)	101.7 (11.2)	86.7 (5.9)	9.7 (10.5)	-3.3 (5.8)
40-41	80.1 (6.1)	97.7 (7.0)	3.4 (8.3)	3.7 (3.5)	103.0 (11.0)	92.9 (1.0)	11.0 (10.3)	2.9 (0.9)
41-42	87.8 (9.8)	97.3 (6.3)	11.1 (4.6)	3.3 (2.9)	99.6 (4.9)	91.2 (9.2)	7.6 (4.2)	1.2 (9.0)
42-43	83.0 (10.8)	99.1 (2.1)	6.4 (3.5)	5.1 (1.4)	109.9 (4.9)	92.1 (3.1)	17.9 (4.2)	2.1 (2.9)
43-44	88.7 (2.9)	95.4 (7.1)	12.0 (11.5)	1.4 (3.6)	110.7 (1.4)	87.3 (4.8)	18.7 (0.7)	-2.7 (4.9)
44-45	87.9 (3.9)	103.9 (12.2)	11.2 (10.5)	9.9 (8.7)	108.4 (3.6)	84.2 (5.2)	16.4 (2.9)	-5.9 (5.3)
45-46	90.2 (0.1)	95.5 (10.5)	13.5 (14.5)	1.5 (7.0)	109.0 (0.1)	86.6 (1.1)	17.0 (0.6)	-3.4 (1.3)
46-47	87.4 (0.1)	98.2 (5.6)	10.7 (14.3)	4.2 (2.1)	107.8 (1.6)	83.4 (1.4)	15.8 (0.9)	-6.6 (1.3)
47-48	82.9 (3.8)	95.7 (7.5)	6.3 (10.6)	1.7 (4.0)	107.8 (2.1)	86.5 (0.9)	15.8 (1.4)	-3.5 (0.7)
48-49	85.4 (2.7)	100.2 (8.4)	8.7 (11.7)	6.3 (4.9)	100.3 (1.0)	88.1 (2.1)	8.3 (1.7)	-1.9 (2.0)
49-50	88.1 (1.4)	96.7 (7.0)	11.4 (13.0)	2.7 (3.5)	103.2 (3.7)	87.3 (3.8)	11.2 (4.4)	-2.8 (4.0)
50-51	86.7 (2.4)	98.0 (7.9)	10.0 (11.9)	4.0 (4.4)	108.3 (7.4)	88.5 (3.5)	16.3 (8.1)	-1.6 (3.6)
51-52	88.0 (1.9)	101.8 (10.6)	11.3 (12.5)	7.8 (7.1)	108.0 (0.3)	90.2 (2.6)	16.0 (1.0)	0.2 (2.7)
52-53	90.5 (3.5)	94.9 (10.1)	13.8 (17.9)	0.9 (6.6)	110.9 (6.7)	83.7 (4.4)	18.9 (7.4)	-6.3 (4.6)
53-54	84.6 (3.2)	96.2 (10.7)	7.9 (17.6)	2.2 (7.2)	102.8 (2.0)	81.7 (3.8)	10.8 (2.7)	-8.4 (4.0)
54-55	86.5 (3.6)	97.2 (8.1)	9.8 (10.8)	3.2 (4.6)	97.7 (2.9)	90.0 (4.7)	5.7 (2.2)	-0.0 (4.8)
55-56	94.4 (0.3)	96.2 (8.1)	17.7 (14.1)	2.3 (4.6)	105.0 (4.0)	94.0 (2.8)	12.9 (3.3)	4.0 (2.9)
56-57	83.6 (4.8)	98.1 (4.7)	6.9 (9.5)	4.1 (1.2)	109.0 (3.6)	95.1 (2.1)	17.0 (2.9)	5.0 (2.0)
57-58	85.7 (0.1)	102.0 (9.3)	9.0 (14.5)	8.0 (5.8)	107.5 (3.1)	97.7 (1.4)	15.5 (2.4)	7.7 (1.3)
58-59	79.9 (5.1)	99.7 (3.5)	3.2 (9.3)	5.7 (0.0)	100.8 (2.5)	88.9 (0.1)	8.8 (1.8)	-1.2 (0.1)
59-60	89.8 (6.0)	93.4 (6.3)	13.1 (8.4)	-0.5 (2.8)	103.1 (7.5)	92.3 (1.8)	11.0 (6.8)	2.2 (1.6)
60-61	90.2 (2.6)	103.4 (11.6)	13.5 (11.7)	9.5 (8.1)	103.5 (10.3)	92.2 (2.6)	11.5 (9.6)	2.2 (2.4)

Hourly Interval	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Hourly Averages (N=2)		Baseline-Adjusted Hourly Averages (N=2)		Unadjusted Hourly Averages (N=2)		Baseline-Adjusted Hourly Averages (N=2)	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
61-62	84.9 (7.7)	97.3 (4.0)	8.2 (6.7)	3.3 (0.5)	100.6 (4.7)	92.4 (0.5)	8.6 (3.9)	2.4 (0.6)
62-63	78.1 (4.8)	97.3 (3.6)	1.4 (9.5)	3.3 (0.1)	106.0 (8.9)	94.5 (4.7)	14.0 (8.2)	4.4 (4.5)
63-64	87.9 (3.5)	93.9 (6.3)	11.2 (10.8)	-0.0 (2.8)	107.5 (7.0)	91.8 (4.7)	15.5 (6.3)	1.8 (4.6)
64-65	89.8 (7.0)	98.6 (8.0)	13.1 (7.4)	4.7 (4.5)	111.1 (14.4)	83.2 (2.8)	19.1 (13.7)	-6.8 (2.7)
65-66	86.2 (1.4)	92.3 (6.4)	9.5 (15.7)	-1.7 (2.9)	110.3 (9.9)	86.6 (2.4)	18.3 (9.2)	-3.5 (2.3)
66-67	78.6 (4.7)	98.3 (8.8)	1.9 (9.7)	4.3 (5.3)	105.1 (8.4)	93.9 (0.2)	13.1 (7.7)	3.9 (0.1)
67-68	82.8 (2.2)	93.3 (7.1)	6.1 (12.2)	-0.6 (3.6)	109.4 (2.8)	87.2 (3.8)	17.4 (2.1)	-2.9 (4.0)
68-69	82.0 (1.5)	97.3 (12.7)	5.4 (12.9)	3.3 (9.2)	113.8 (2.3)	98.4 (18.5)	21.8 (3.0)	8.4 (18.6)
69-70	84.1 (1.0)	97.1 (5.5)	7.5 (15.4)	3.2 (2.0)	118.8 (2.1)	91.9 (14.4)	26.8 (2.8)	1.9 (14.5)
70-71	78.4 (1.4)	86.6 (9.4)	1.7 (12.9)	-7.4 (6.0)	106.3 (0.9)	85.9 (10.4)	14.3 (0.2)	-4.2 (10.6)
71-72	79.6 (1.7)	88.8 (8.0)	2.9 (16.1)	-5.2 (4.5)	106.7 (5.1)	89.6 (11.2)	14.7 (4.4)	-0.5 (11.4)

Table 19. Heart Rate (BPM) In-Cage Means (Standard Errors) of Unadjusted and Baseline-Adjusted Hourly Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[a]

Hourly Interval	Mean (Standard Error) of Unadjusted Hourly Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Hourly Averages (N=4)		Significant Differences Between Dose Groups?[b]
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	
6-7	105.5 (4.9)	99.6 (6.4)	14.3 (5.5)	-1.9 (6.9)	
7-8	97.0 (7.3)	96.6 (4.1)	5.7 (5.9)	-4.9 (2.9)	
8-9	91.9 (4.1)	99.5 (6.6)	0.6 (6.3)	-1.9 (3.3)	
9-10	101.7 (6.6)	96.8 (6.4)	10.5 (4.3)	-4.6 (4.2)	
10-11	94.9 (6.4)	91.8 (7.3)	3.7 (7.9)	-9.6 (5.0)	
11-12	87.7 (4.0)	93.1 (3.6)	-3.5 (5.3)	-8.3 (3.0)	
12-13	91.0 (6.9)	89.1 (7.0)	-0.3 (5.4)	-12.4 (4.7)	
13-14	91.6 (7.4)	89.6 (4.3)	0.4 (5.2)	-11.9 (3.0)	
14-15	86.0 (5.9)	90.2 (6.7)	-5.3 (5.7)	-11.3 (1.7)	
15-16	90.0 (7.3)	94.1 (6.5)	-1.2 (5.5)	-7.4 (1.3)	
16-17	88.7 (7.5)	96.4 (5.5)	-2.5 (4.5)	-5.0 (2.3)	
17-18	93.0 (7.4)	97.3 (5.1)	1.7 (4.6)	-4.1 (2.0)	
18-19	91.2 (7.8)	103.0 (5.3)	-0.0 (3.4)	1.5 (1.0)	
19-20	101.3 (10.5)	114.3 (3.2)	10.1 (10.0)	12.8 (2.7)	
20-21	117.1 (12.4)	118.1 (3.6)	25.9 (12.6)	16.6 (2.9)	
21-22	115.6 (9.3)	118.2 (3.4)	24.4 (8.3)	16.7 (3.4)	
22-23	117.9 (2.7)	114.0 (7.3)	26.7 (6.8)	12.5 (6.3)	
23-24	110.5 (2.8)	102.9 (8.5)	19.3 (6.8)	1.5 (9.6)	
24-25	94.7 (4.1)	99.6 (6.3)	3.4 (6.1)	-1.9 (7.0)	
25-26	97.4 (3.3)	102.3 (3.9)	6.2 (5.4)	0.9 (5.4)	
26-27	101.8 (4.0)	109.3 (4.8)	10.6 (4.8)	7.9 (4.8)	
27-28	102.9 (3.6)	108.0 (3.8)	11.7 (9.9)	6.5 (4.4)	
28-29	108.2 (3.4)	102.8 (6.7)	16.9 (5.4)	1.3 (8.1)	
29-30	106.1 (6.4)	103.7 (6.3)	14.9 (4.7)	2.3 (6.7)	
30-31	102.6 (4.6)	90.5 (5.9)	11.3 (5.4)	-10.9 (6.5)	
31-32	102.3 (6.3)	92.5 (7.6)	11.1 (3.3)	-8.9 (6.1)	
32-33	94.1 (6.7)	92.3 (4.3)	2.9 (4.6)	-9.2 (3.7)	
33-34	97.5 (7.6)	95.6 (6.8)	6.3 (4.9)	-5.9 (2.4)	
34-35	93.6 (4.4)	96.2 (2.0)	2.3 (5.1)	-5.3 (3.7)	
35-36	93.7 (8.0)	96.9 (5.8)	2.5 (4.8)	-4.5 (1.1)	
36-37	93.4 (8.9)	93.3 (6.2)	2.1 (6.3)	-8.2 (1.4)	
37-38	90.8 (6.1)	92.9 (5.8)	-0.4 (5.8)	-8.6 (3.7)	
38-39	90.6 (7.4)	95.0 (5.8)	-0.6 (0.6)	-6.4 (0.7)	
39-40	87.6 (5.9)	97.0 (6.6)	-3.7 (4.4)	-4.5 (3.6)	
40-41	87.6 (8.1)	100.4 (4.5)	-3.7 (3.5)	-1.1 (3.5)	
41-42	86.9 (7.7)	97.8 (3.7)	-4.4 (2.3)	-3.7 (5.3)	
42-43	94.0 (1.6)	104.3 (2.9)	2.8 (6.8)	2.8 (3.3)	
43-44	110.1 (7.9)	113.4 (4.8)	18.8 (10.2)	11.9 (1.8)	
44-45	114.0 (5.3)	117.7 (8.9)	22.8 (6.8)	16.2 (8.7)	
45-46	113.3 (6.2)	109.0 (6.0)	22.1 (9.1)	7.6 (6.5)	
46-47	107.2 (3.5)	95.8 (3.5)	15.9 (6.8)	-5.7 (4.9)	
47-48	99.2 (4.5)	98.6 (5.0)	8.0 (7.4)	-2.9 (4.1)	
48-49	94.5 (0.7)	98.7 (5.1)	3.2 (7.5)	-2.8 (1.5)	
49-50	95.0 (2.2)	101.9 (6.7)	3.8 (6.4)	0.4 (5.4)	
50-51	113.5 (8.9)	112.9 (3.8)	22.2 (8.6)	11.4 (2.1)	
51-52	111.8 (5.9)	118.2 (3.8)	20.5 (6.5)	16.8 (2.1)	
52-53	122.2 (13.1)	115.1 (3.0)	30.9 (13.3)	13.6 (3.7)	
53-54	108.3 (7.3)	100.0 (1.7)	17.1 (6.9)	-1.5 (4.4)	
54-55	89.8 (4.8)	97.0 (7.4)	-1.4 (5.3)	-4.5 (3.8)	
55-56	95.7 (6.4)	92.4 (8.8)	4.5 (8.1)	-9.1 (6.0)	
56-57	85.8 (7.5)	90.5 (6.4)	-5.5 (8.3)	-11.0 (3.7)	
57-58	87.1 (8.4)	97.7 (7.4)	-4.1 (10.9)	-3.8 (3.8)	
58-59	81.8 (5.9)	93.2 (4.8)	-9.4 (11.7)	-8.3 (4.5)	
59-60	85.0 (6.3)	91.7 (6.1)	-6.3 (9.8)	-9.7 (1.3)	
60-61	81.6 (8.1)	91.7 (6.1)	-9.6 (12.1)	-9.8 (2.3)	
61-62	77.4 (5.3)	89.3 (4.7)	-13.9 (11.5)	-12.2 (2.2)	
62-63	84.9 (7.2)	92.0 (4.5)	-6.3 (10.7)	-9.5 (1.0)	
63-64	80.4 (7.1)	93.3 (4.2)	-10.9 (12.6)	-8.2 (2.6)	
64-65	78.9 (5.4)	85.2 (4.2)	-12.3 (10.7)	-16.3 (3.8)	

Hourly Interval	Mean (Standard Error) of Unadjusted Hourly Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Hourly Averages (N=4)		Significant Differences Between Dose Groups?[b]
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	
65-66	77.9 (2.2)	95.3 (5.3)	-13.3 (9.8)	-6.2 (4.4)	
66-67	83.4 (5.3)	102.5 (3.6)	-7.9 (12.6)	1.0 (2.0)	
67-68	98.3 (6.0)	109.2 (6.7)	7.1 (9.2)	7.7 (1.8)	
68-69	108.9 (9.7)	114.5 (8.1)	17.7 (11.9)	13.1 (5.7)	
69-70	115.1 (12.7)	123.9 (4.0)	23.8 (13.1)	22.4 (5.3)	
70-71	105.4 (6.7)	99.7 (5.6)	14.1 (6.8)	-1.8 (3.2)	
71-72	95.2 (4.4)	90.1 (4.6)	3.9 (8.8)	-11.4 (4.4)	

a. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted hourly averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for heart rate, F-tests for significant dose group effects were made across all animals, and not separately by sex.

b. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests for each interval so that the false discovery rate is no higher than 0.05 across all 66 hourly intervals simultaneously. No significant dose group effects were observed at any hourly interval.

Table 20. Heart Rate (BPM) In-Cage Means (Standard Errors) of Unadjusted and Baseline-Adjusted Hourly Averages Following Dosing with CuATSM/H_2ATSM or Vehicle by Sex

Hourly Interval	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Hourly Averages (N=2)		Baseline-Adjusted Hourly Averages (N=2)		Unadjusted Hourly Averages (N=2)		Baseline-Adjusted Hourly Averages (N=2)	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
6-7	97.2 (2.7)	100.6 (6.7)	13.4 (11.8)	6.0 (1.8)	113.9 (0.2)	98.6 (14.1)	15.2 (6.1)	-9.9 (12.5)
7-8	85.4 (1.4)	93.6 (7.0)	1.6 (13.1)	-0.9 (1.5)	108.6 (7.2)	99.6 (5.7)	9.9 (1.3)	-8.9 (4.0)
8-9	85.5 (0.8)	94.9 (12.6)	1.6 (15.3)	0.4 (4.1)	98.2 (4.4)	104.1 (7.9)	-0.4 (1.6)	-4.3 (6.2)
9-10	94.7 (5.5)	93.9 (11.7)	10.9 (9.0)	-0.6 (3.2)	108.8 (11.5)	99.8 (9.5)	10.1 (5.5)	-8.7 (7.8)
10-11	85.8 (4.5)	88.0 (11.2)	2.0 (19.1)	-6.5 (2.7)	104.0 (7.9)	95.6 (12.9)	5.3 (1.9)	-12.8 (11.2)
11-12	83.5 (2.3)	91.0 (7.2)	-0.3 (12.2)	-3.5 (1.4)	92.0 (7.4)	95.3 (4.3)	-6.7 (1.4)	-13.2 (2.7)
12-13	79.4 (2.9)	84.7 (10.0)	-4.4 (11.6)	-9.8 (1.5)	102.5 (3.7)	93.5 (12.4)	3.9 (2.3)	-14.9 (10.8)
13-14	81.8 (3.3)	86.6 (7.4)	-2.0 (11.2)	-7.9 (1.1)	101.5 (11.1)	92.6 (6.1)	2.8 (5.2)	-15.9 (4.5)
14-15	77.1 (0.7)	80.3 (8.5)	-6.8 (13.8)	-14.2 (0.0)	94.9 (7.1)	100.1 (1.2)	-3.8 (1.1)	-8.3 (0.5)
15-16	77.7 (3.2)	84.8 (9.1)	-6.1 (11.3)	-9.7 (0.5)	102.3 (3.3)	103.3 (1.7)	3.6 (2.7)	-5.1 (0.0)
16-17	77.2 (5.2)	89.1 (5.6)	-6.6 (9.3)	-5.5 (3.0)	100.2 (6.8)	103.8 (6.4)	1.5 (0.8)	-4.6 (4.7)
17-18	84.9 (5.7)	89.5 (4.2)	1.1 (8.9)	-5.0 (4.3)	101.0 (13.1)	105.2 (3.7)	2.4 (7.1)	-3.3 (2.0)
18-19	79.8 (8.4)	96.7 (8.7)	-4.0 (6.1)	2.1 (0.2)	102.7 (6.0)	109.3 (3.8)	4.0 (0.0)	0.8 (2.2)
19-20	87.5 (6.9)	109.6 (4.0)	3.7 (7.6)	15.1 (4.5)	115.1 (15.4)	118.9 (1.7)	16.5 (21.4)	10.5 (3.4)
20-21	103.3 (6.2)	116.0 (8.2)	19.5 (8.4)	21.5 (0.4)	130.9 (22.3)	120.1 (1.2)	32.3 (28.3)	11.7 (0.5)
21-22	106.4 (12.4)	117.1 (8.0)	22.6 (2.2)	22.6 (0.6)	124.8 (14.2)	119.3 (1.6)	26.1 (20.2)	10.9 (0.0)
22-23	115.3 (3.4)	115.2 (15.3)	31.4 (11.2)	20.7 (6.8)	120.6 (4.3)	112.8 (9.2)	21.9 (10.3)	4.3 (7.5)
23-24	106.6 (1.8)	109.4 (10.6)	22.8 (12.7)	14.9 (2.1)	114.4 (3.6)	96.5 (15.3)	15.7 (9.6)	-11.9 (13.6)
24-25	94.0 (3.7)	103.2 (10.6)	10.2 (10.9)	8.7 (2.1)	95.3 (9.3)	95.9 (9.8)	-3.3 (3.3)	-12.5 (8.1)
25-26	92.8 (2.1)	100.3 (0.2)	8.9 (12.5)	5.8 (8.3)	102.1 (4.3)	104.4 (9.1)	3.4 (1.7)	-4.0 (7.4)
26-27	99.2 (4.9)	106.1 (2.9)	15.4 (9.6)	11.6 (5.7)	104.5 (7.5)	112.6 (10.4)	5.8 (1.5)	4.2 (8.8)
27-28	100.3 (8.1)	106.0 (3.7)	16.5 (22.6)	11.5 (4.8)	105.5 (0.2)	109.9 (8.2)	6.9 (5.8)	1.5 (6.5)
28-29	106.4 (3.9)	101.5 (2.4)	22.5 (10.7)	7.0 (10.9)	110.0 (7.0)	104.1 (16.2)	11.4 (1.0)	-4.3 (14.5)
29-30	103.1 (7.9)	103.9 (5.6)	19.3 (6.6)	9.4 (3.0)	109.1 (13.0)	103.5 (14.3)	10.4 (7.0)	-4.9 (12.6)
30-31	95.9 (1.2)	90.5 (4.8)	12.0 (13.3)	-4.1 (3.7)	109.3 (5.7)	90.6 (13.7)	10.7 (0.3)	-17.8 (12.1)
31-32	94.3 (6.7)	91.3 (12.4)	10.4 (7.8)	-3.2 (3.9)	110.3 (7.7)	93.8 (13.8)	11.7 (1.7)	-14.6 (12.1)
32-33	85.2 (4.1)	89.7 (6.0)	1.3 (10.4)	-4.8 (2.6)	103.1 (9.6)	94.8 (7.9)	4.4 (3.6)	-13.6 (6.2)
33-34	87.4 (4.4)	87.2 (9.4)	3.6 (10.2)	-7.3 (0.9)	107.6 (11.1)	103.9 (7.0)	8.9 (5.1)	-4.6 (5.4)
34-35	89.6 (3.4)	93.4 (2.4)	5.8 (11.2)	-1.1 (6.1)	97.5 (8.6)	99.0 (1.6)	-1.2 (2.6)	-9.5 (3.2)
35-36	80.9 (5.7)	88.8 (8.3)	-2.9 (8.9)	-5.7 (0.2)	106.5 (4.8)	105.1 (0.6)	7.8 (1.2)	-3.4 (2.3)
36-37	80.4 (2.6)	84.5 (7.7)	-3.4 (12.0)	-10.0 (0.8)	106.3 (11.5)	102.1 (3.9)	7.7 (5.5)	-6.4 (2.3)
37-38	82.1 (0.6)	86.0 (7.6)	-1.7 (14.0)	-8.5 (1.0)	99.5 (8.4)	99.8 (7.3)	0.8 (2.5)	-8.7 (9.0)
38-39	82.9 (13.1)	87.6 (9.0)	-0.9 (1.4)	-6.9 (0.5)	98.4 (6.4)	102.4 (3.1)	-0.3 (0.4)	-6.0 (1.5)
39-40	80.3 (4.2)	91.3 (13.0)	-3.5 (10.3)	-3.2 (4.4)	94.8 (9.1)	102.6 (5.6)	-3.9 (3.1)	-5.8 (7.3)
40-41	76.3 (8.3)	98.3 (8.2)	-7.5 (6.2)	3.8 (0.3)	98.8 (8.4)	102.5 (6.7)	0.1 (2.5)	-5.9 (5.0)
41-42	81.8 (14.0)	100.0 (8.5)	-2.1 (0.6)	5.5 (0.0)	92.0 (10.4)	95.6 (0.6)	-6.7 (4.4)	-12.8 (1.1)
42-43	93.4 (1.2)	101.4 (3.7)	9.6 (13.4)	6.8 (4.8)	94.7 (3.7)	107.2 (4.6)	-4.0 (2.3)	-1.2 (3.0)
43-44	100.8 (0.0)	108.7 (8.8)	16.9 (14.5)	14.2 (0.2)	119.4 (14.1)	118.0 (4.4)	20.8 (20.1)	9.5 (2.8)
44-45	111.8 (9.5)	123.1 (18.6)	28.0 (5.1)	28.6 (10.1)	116.3 (8.2)	112.2 (8.2)	17.6 (14.2)	3.8 (6.5)
45-46	104.6 (2.0)	112.4 (12.3)	20.7 (16.5)	17.9 (3.8)	122.1 (8.8)	105.6 (6.2)	23.4 (14.7)	-2.8 (4.6)
46-47	102.4 (2.3)	97.1 (7.3)	18.5 (12.3)	2.6 (1.2)	112.0 (4.8)	94.4 (4.2)	13.3 (10.8)	-14.0 (2.6)
47-48	93.1 (1.8)	98.1 (11.7)	9.3 (12.8)	3.6 (3.1)	105.3 (6.8)	99.0 (3.8)	6.6 (12.8)	-9.4 (2.2)
48-49	94.4 (0.1)	93.8 (10.3)	10.6 (14.7)	-0.7 (1.8)	94.5 (1.7)	103.6 (0.6)	-4.1 (4.2)	-4.9 (1.1)
49-50	92.1 (2.8)	101.8 (13.8)	8.3 (11.8)	7.3 (5.3)	98.0 (2.1)	101.9 (8.7)	-0.7 (8.1)	-6.5 (7.1)
50-51	100.1 (4.1)	109.3 (7.0)	16.3 (10.4)	14.8 (1.5)	126.8 (10.3)	116.5 (3.2)	28.2 (16.2)	8.0 (1.6)
51-52	103.9 (5.8)	114.9 (8.0)	20.1 (8.7)	20.4 (0.5)	119.7 (7.3)	121.6 (1.0)	21.0 (13.3)	13.2 (0.7)
52-53	106.2 (3.9)	111.1 (2.8)	22.4 (10.6)	16.6 (5.7)	138.1 (22.4)	119.1 (3.8)	39.4 (28.4)	10.6 (5.4)
53-54	97.1 (4.6)	99.8 (3.9)	13.3 (9.9)	5.3 (4.7)	119.5 (6.7)	100.1 (1.4)	20.9 (12.7)	-8.3 (0.2)
54-55	85.4 (2.7)	88.0 (7.7)	1.5 (11.9)	-6.6 (0.8)	94.3 (9.5)	106.1 (10.4)	-4.4 (3.5)	-2.4 (8.7)
55-56	90.0 (3.8)	86.5 (12.3)	6.1 (18.4)	-8.0 (3.8)	101.5 (13.0)	98.3 (15.7)	2.8 (7.0)	-10.2 (14.0)
56-57	83.6 (0.1)	85.1 (9.2)	-0.2 (14.6)	-9.4 (0.6)	87.9 (18.1)	95.9 (10.3)	-10.7 (12.2)	-12.5 (8.7)
57-58	84.6 (7.9)	90.7 (10.7)	0.8 (22.4)	-3.8 (2.2)	89.6 (18.7)	104.6 (10.7)	-9.1 (12.7)	-3.8 (9.0)
58-59	85.3 (9.2)	90.2 (4.3)	1.5 (23.8)	-4.3 (4.3)	78.3 (9.9)	96.2 (10.0)	-20.4 (3.9)	-12.3 (8.3)
59-60	87.7 (2.5)	83.1 (8.7)	3.9 (17.0)	-11.4 (0.2)	82.2 (14.8)	100.4 (0.3)	-16.4 (8.9)	-8.0 (2.0)
60-61	83.0 (10.1)	86.6 (12.0)	-0.8 (24.6)	-7.9 (3.5)	80.2 (17.1)	96.7 (5.2)	-18.4 (11.1)	-11.7 (3.6)

Hourly Interval	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Hourly Averages (N=2)		Baseline-Adjusted Hourly Averages (N=2)		Unadjusted Hourly Averages (N=2)		Baseline-Adjusted Hourly Averages (N=2)	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
61-62	82.5 (7.1)	85.8 (9.7)	-1.3 (21.6)	-8.7 (1.1)	72.2 (8.0)	92.7 (3.6)	-26.5 (2.0)	-15.7 (2.0)
62-63	84.4 (7.8)	86.7 (8.1)	0.6 (22.3)	-7.8 (0.4)	85.4 (15.8)	97.3 (1.5)	-13.2 (9.8)	-11.2 (0.1)
63-64	87.3 (8.0)	90.8 (9.4)	3.5 (22.6)	-3.7 (0.9)	73.4 (11.9)	95.8 (2.4)	-25.3 (5.9)	-12.7 (0.8)
64-65	84.6 (3.4)	84.6 (10.0)	0.8 (17.9)	-9.9 (1.5)	73.2 (9.9)	85.8 (2.5)	-25.4 (3.9)	-22.7 (0.9)
65-66	81.2 (2.6)	92.5 (10.1)	-2.6 (17.1)	-2.0 (1.6)	74.6 (1.2)	98.1 (7.2)	-24.0 (7.2)	-10.3 (8.8)
66-67	91.5 (5.0)	98.1 (6.1)	7.6 (19.6)	3.6 (2.4)	75.2 (3.0)	106.9 (0.7)	-23.4 (9.0)	-1.6 (2.3)
67-68	89.6 (3.7)	99.4 (8.2)	5.7 (18.3)	4.9 (0.3)	107.1 (6.9)	119.0 (3.4)	8.4 (12.9)	10.6 (1.8)
68-69	97.7 (1.6)	112.8 (19.3)	13.9 (16.1)	18.3 (10.7)	120.1 (17.6)	116.2 (3.5)	21.4 (23.6)	7.8 (5.2)
69-70	101.5 (6.3)	124.5 (5.5)	17.6 (8.3)	30.0 (3.1)	128.6 (23.8)	123.3 (8.1)	30.0 (29.8)	14.9 (6.5)
70-71	97.8 (8.4)	93.0 (8.0)	14.0 (6.2)	-1.5 (0.5)	112.9 (9.4)	106.4 (6.1)	14.2 (15.3)	-2.1 (7.7)
71-72	91.9 (0.7)	87.6 (7.9)	8.0 (13.9)	-7.0 (0.7)	98.5 (9.6)	92.7 (7.1)	-0.2 (15.6)	-15.8 (8.7)

Table 21. In-Sling Baseline Averages for the ECG Interval Parameters, Calculated for Each Animal[a]

Sex	Animal ID	PR Interval (msec)	RR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	Corrected QT Interval[b]
Male	101	89.9	684.8	48.7	234.4	271.0
	102	111.3	968.2	40.0	244.2	248.5
	201	109.4	768.6	42.0	239.5	284.0
	202	126.8	905.9	49.3	251.8	267.6
Female	151	99.5	714.0	48.8	233.0	259.3
	152	118.8	916.6	35.8	232.3	270.3
	251	98.4	733.1	42.8	195.0	239.3
	252	93.2	563.1	43.9	196.5	243.1

a. Baseline averages were calculated for each animal by averaging the two measurements associated with 40 minutes prior to dosing and 20 minutes prior to dosing.
b. Corrected QT interval (QTc) was calculated by dividing QT interval by the cubed root of RR interval, where both intervals are expressed in seconds, and multiplying by 1000.

Table 22. In-Cage Baseline Averages for the ECG Interval Parameters, Calculated for Each Animal[a]

Sex	Animal ID	PR Interval (msec)	RR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	Corrected QT Interval[b]
Male	101	91.8	1024.6	47.1	247.7	251.5
	102	99.7	950.7	43.6	242.7	254.7
	201	105.8	673.4	48.8	237.4	270.3
	202	116.9	751.2	44.6	247.1	263.4
Female	151	96.0	670.1	54.2	228.8	263.7
	152	107.7	785.3	36.2	223.9	248.0
	251	105.7	740.3	43.3	214.1	246.4
	252	106.0	723.6	41.5	216.8	243.6

a. Baseline averages were calculated for each animal by averaging the two measurements associated with 4 hours prior to dosing and 5 hours prior to dosing for animals 101, 102, 151, and 152 (vehicle dose group), and by averaging the two measurements associated with 5 hours prior to dosing and 6 hours prior to dosing for animals 201, 202, 251, and 252 (test article dose group).
b. Corrected QT interval (QTc) was calculated by dividing QT interval by the cubed root of RR interval, where both intervals are expressed in seconds, and multiplying by 1000.

Table 23. In-Sling Means (Standard Errors), Calculated by Sex and Dose Group, of the Animals' Baseline Average Responses for the ECG Interval Parameters[a]

Sex	Dose Group	Mean (Standard Error) Across Study Animals				
		PR Interval (msec)	RR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	Corrected QT Interval[b]
Male	Vehicle (N = 2)	100.6 (10.7)	826.5 (141.7)	44.4 (4.3)	239.3 (4.9)	259.7 (11.3)
	CuATSM/H_2ATSM (0.3 mg/kg) (N = 2)	118.1 (8.7)	837.3 (68.7)	45.6 (3.6)	245.6 (6.1)	275.8 (8.2)
Female	Vehicle (N = 2)	109.1 (9.6)	815.3 (101.3)	42.3 (6.5)	232.7 (0.4)	264.8 (5.5)
	CuATSM/H_2ATSM (0.3 mg/kg) (N = 2)	95.8 (2.6)	648.1 (85.0)	43.3 (0.6)	195.8 (0.7)	241.2 (1.9)
All Animals	Vehicle (N = 4)	104.9 (6.4)	820.9 (71.2)	43.3 (3.2)	236.0 (2.8)	262.3 (5.3)
	CuATSM/H_2ATSM (0.3 mg/kg) (N = 4)	106.9 (7.4)	742.7 (70.5)	44.5 (1.6)	220.7 (14.6)	258.5 (10.6)

a. Summaries are of the baseline averages listed in Table 21. Comparisons between the two dose groups were made across all animals if the sex effect and the interaction between sex and dose group effects were not significant, and separately for each sex if the sex effect or the interaction between sex and dose group effects were significant. Significant differences between the two dose groups existed in baseline averages for QT interval in female animals.

b. Corrected QT interval (QTc) was calculated by dividing QT interval by the cubed root of RR interval, where both intervals are expressed in seconds, and multiplying by 1000.

Table 24. In-Cage Means (Standard Errors), Calculated by Sex and Dose Group, of the Animals' Baseline Average Responses for the ECG Interval Parameters[a]

Sex	Dose Group	Mean (Standard Error) Across Study Animals				
		PR Interval (msec)	RR Interval (msec)	QRS Interval (msec)	QT Interval (msec)	Corrected QT Interval[b]
Male	Vehicle (N = 2)	95.7 (3.9)	987.7 (37.0)	45.4 (1.8)	245.2 (2.5)	253.1 (1.6)
	CuATSM/H_2ATSM (0.3 mg/kg) (N = 2)	111.4 (5.6)	712.3 (38.9)	46.7 (2.1)	242.3 (4.8)	266.9 (3.5)
Female	Vehicle (N = 2)	101.8 (5.9)	727.7 (57.6)	45.2 (9.0)	226.4 (2.4)	255.9 (7.9)
	CuATSM/H_2ATSM (0.3 mg/kg) (N = 2)	105.8 (0.1)	731.9 (8.3)	42.4 (0.9)	215.5 (1.4)	245.0 (1.4)
All Animals	Vehicle (N = 4)	98.8 (3.4)	857.7 (80.1)	45.3 (3.7)	235.8 (5.6)	254.5 (3.4)
	CuATSM/H_2ATSM (0.3 mg/kg) (N = 4)	108.6 (2.8)	722.1 (17.2)	44.6 (1.6)	228.9 (8.0)	255.9 (6.5)

a. Summaries are of the baseline averages listed in Table 22. Comparisons between the two dose groups were made across all animals if the sex effect and the interaction between sex and dose group effects were not significant, and separately for each sex if the sex effect or the interaction between sex and dose group effects were significant. Significant differences between the two dose groups existed in baseline averages for RR interval in male animals.

b. Corrected QT interval (QTc) was calculated by dividing QT interval by the cubed root of RR interval, where both intervals are expressed in seconds, and multiplying by 1000.

Table 25. PR Interval (msec) In-Sling Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[a]

Hour Following Dosing	Mean (Standard Error) of Unadjusted Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Averages (N=4)		Significant Differences Between Dose Groups?[b]
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	
10 minutes	107.4 (5.9)	113.1 (8.3)	2.6 (2.5)	6.2 (1.5)	
0.5	106.0 (7.8)	109.9 (7.7)	1.2 (5.0)	3.0 (1.8)	
1	107.1 (7.4)	106.7 (7.9)	2.2 (4.5)	-0.3 (0.9)	
2	102.5 (6.3)	106.8 (7.4)	-2.3 (2.1)	-0.2 (0.8)	
4	102.3 (6.1)	101.3 (3.3)	-2.5 (1.1)	-5.6 (5.2)	

a. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for PR interval, F-tests for significant dose group effects were made across all animals, and not separately by sex.

b. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests at each time point so that the false discovery rate is no higher than 0.05 across all 5 time points simultaneously. No significant dose group effects were observed at any time point.

Table 26. PR Interval (msec) In-Sling Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle By Sex

Hour Following Dosing	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)		Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)	
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM
10 minutes	105.4 (6.3)	124.3 (12.3)	4.8 (4.4)	6.2 (3.6)	109.5 (12.7)	101.9 (3.8)	0.4 (3.0)	6.1 (1.2)
0.5	102.6 (2.2)	119.7 (12.0)	2.1 (8.5)	1.6 (3.2)	109.4 (18.3)	100.1 (5.0)	0.3 (8.7)	4.3 (2.4)
1	101.8 (2.0)	118.3 (10.4)	1.2 (8.7)	0.2 (1.6)	112.4 (16.3)	95.1 (1.3)	3.2 (6.6)	-0.7 (1.3)
2	99.7 (7.3)	117.2 (10.2)	-0.9 (3.4)	-0.9 (1.5)	105.4 (12.9)	96.4 (3.2)	-3.8 (3.2)	0.6 (0.6)
4	98.3 (8.5)	104.1 (4.5)	-2.3 (2.2)	-14.0 (4.2)	106.3 (11.1)	98.5 (5.3)	-2.8 (1.4)	2.7 (2.7)

Table 27. RR Interval (msec) In-Sling Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[a]

Hour Following Dosing	Mean (Standard Error) of Unadjusted Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Averages (N=4)		Significant Differences Between Dose Groups?[b]
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	
10 minutes	733.9 (71.7)	706.5 (102.2)	-87.0 (78.4)	-36.2 (56.5)	
0.5	790.9 (96.7)	605.5 (48.7)	-30.0 (78.1)	-137.2 (33.0)	
1	850.0 (82.7)	798.0 (100.7)	29.1 (80.2)	55.4 (31.1)	
2	800.4 (77.1)	712.9 (77.7)	-20.5 (74.1)	-29.8 (10.7)	
4	820.4 (103.3)	738.2 (109.7)	-0.5 (52.8)	-4.5 (58.5)	

a. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for RR interval, F-tests for significant dose group effects were made across all animals, and not separately by sex.

b. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests at each time point so that the false discovery rate is no higher than 0.05 across all 5 time points simultaneously. No significant dose group effects were observed at any time point.

Table 28. RR Interval (msec) In-Sling Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle By Sex

Hour Following Dosing	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)		Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
10 minutes	838.5 (10.3)	881.2 (37.4)	12.0 (131.4)	43.9 (31.2)	629.3 (94.2)	531.7 (11.8)	-186.0 (7.1)	-116.4 (73.2)
0.5	885.8 (31.0)	685.6 (6.9)	59.3 (110.7)	-151.7 (61.7)	696.1 (192.9)	525.4 (37.2)	-119.2 (91.6)	-122.6 (47.8)
1	896.2 (23.6)	923.2 (101.3)	69.7 (165.3)	86.0 (32.7)	803.8 (190.3)	672.8 (138.6)	-11.5 (89.0)	24.8 (53.6)
2	821.0 (17.7)	825.6 (65.2)	-5.5 (159.4)	-11.6 (3.4)	779.8 (185.8)	600.1 (80.8)	-35.4 (84.5)	-48.0 (4.2)
4	746.6 (205.5)	851.9 (207.0)	-80.0 (63.8)	14.7 (138.3)	894.2 (104.5)	624.4 (59.6)	79.0 (3.2)	-23.6 (25.4)

Table 29. QRS Interval (msec) In-Sling Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle [a]

Hour Following Dosing	Mean (Standard Error) of Unadjusted Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Averages (N=4)		Significant Differences Between Dose Groups?[b]
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	
10 minutes	44.2 (3.6)	46.0 (2.0)	0.9 (0.8)	1.5 (1.3)	
0.5	44.2 (3.4)	45.2 (2.0)	0.9 (0.6)	0.7 (1.1)	
1	44.7 (2.7)	47.3 (1.7)	1.3 (0.7)	2.8 (1.7)	
2	43.4 (3.4)	44.8 (1.7)	0.1 (0.6)	0.3 (0.1)	
4	42.1 (2.7)	43.8 (0.7)	-1.2 (1.2)	-0.7 (2.1)	

a. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for QRS interval, F-tests for significant dose group effects were made across all animals, and not separately by sex.

b. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests at each time point so that the false discovery rate is no higher than 0.05 across all 5 time points simultaneously. No significant dose group effects were observed at any time point.

Table 30. QRS Interval (msec) In-Sling Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle By Sex

Hour Following Dosing	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)		Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)	
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM
10 minutes	46.5 (5.0)	46.9 (4.0)	2.1 (0.6)	1.3 (0.3)	41.9 (6.4)	45.1 (2.7)	-0.4 (0.1)	1.8 (3.2)
0.5	46.3 (4.4)	47.8 (2.5)	1.9 (0.1)	2.2 (1.1)	42.2 (6.5)	42.5 (1.7)	-0.1 (0.0)	-0.8 (1.2)
1	46.2 (3.8)	50.2 (0.3)	1.8 (0.5)	4.6 (3.4)	43.2 (5.1)	44.4 (0.1)	0.9 (1.4)	1.1 (0.7)
2	45.2 (5.4)	45.8 (3.8)	0.8 (1.1)	0.2 (0.1)	41.7 (5.9)	43.7 (0.6)	-0.5 (0.6)	0.4 (0.0)
4	41.9 (1.9)	43.0 (0.5)	-2.4 (2.4)	-2.7 (4.1)	42.2 (6.2)	44.6 (1.0)	-0.0 (0.3)	1.3 (1.5)

Table 31. QT Interval (msec) In-Sling Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle [a]

Hour Following Dosing	Mean (Standard Error) of Unadjusted Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Averages (N=4)		Significant Differences Between Dose Groups?[b]
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	
10 minutes	232.2 (6.0)	227.5 (17.5)	-3.8 (6.5)	6.8 (2.9)	
0.5	237.2 (7.9)	219.9 (15.6)	1.2 (7.9)	-0.8 (5.0)	
1	243.5 (7.9)	232.6 (18.6)	7.6 (8.0)	11.9 (5.7)	
2	232.8 (8.3)	221.9 (16.4)	-3.2 (9.7)	1.2 (3.5)	
4	232.5 (6.6)	216.1 (11.3)	-3.5 (6.1)	-4.6 (4.7)	

a. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for QT interval, F-tests for significant dose group effects were made across all animals, and not separately by sex.

b. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests at each time point so that the false discovery rate is no higher than 0.05 across all 5 time points simultaneously. No significant dose group effects were observed at any time point.

Table 32. QT Interval (msec) In-Sling Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle By Sex

Hour Following Dosing	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)		Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)	
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM
10 minutes	239.3 (8.1)	257.4 (6.0)	0.0 (13.0)	11.8 (0.1)	225.1 (7.2)	197.6 (0.1)	-7.6 (7.5)	1.8 (0.8)
0.5	247.6 (8.6)	246.4 (5.2)	8.3 (13.5)	0.8 (11.4)	226.9 (9.5)	193.4 (4.6)	-5.8 (9.9)	-2.3 (3.9)
1	254.0 (9.9)	264.5 (1.0)	14.7 (14.8)	18.8 (7.2)	233.1 (7.6)	200.8 (6.3)	0.4 (7.9)	5.0 (7.0)
2	237.7 (16.1)	250.2 (0.2)	-1.6 (21.0)	4.6 (6.3)	228.0 (10.4)	193.6 (4.1)	-4.7 (10.7)	-2.2 (3.4)
4	230.1 (12.0)	234.1 (10.4)	-9.2 (7.2)	-11.6 (4.3)	234.8 (10.2)	198.1 (3.8)	2.1 (10.5)	2.3 (4.5)

Table 33. Corrected QT Interval (QTc)[a] In-Sling Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[b]

Hour Following Dosing	Mean (Standard Error) of Unadjusted Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Averages (N=4)		Significant Differences Between Dose Groups?[c]
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	
10 minutes	272.1 (5.5)	271.0 (9.2)	9.9 (2.3)	12.5 (4.6)	
0.5	276.1 (8.1)	270.2 (11.6)	13.9 (3.0)	11.7 (2.5)	
1	271.0 (4.7)	263.5 (10.1)	8.7 (4.2)	5.0 (2.8)	
2	258.8 (12.3)	263.4 (13.9)	-3.5 (11.9)	4.9 (4.2)	
4	262.1 (6.7)	252.8 (8.3)	-0.2 (6.4)	-5.7 (2.5)	

a. Corrected QT interval (QTc) was calculated by dividing QT interval by the cubed root of RR interval, where both intervals are expressed in seconds, and multiplying by 1000.

b. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for QTc interval, F-tests for significant dose group effects were made across all animals, and not separately by sex.

c. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests at each time point so that the false discovery rate is no higher than 0.05 across all 5 time points simultaneously. No significant dose group effects were observed at any time point.

Table 34. Corrected QT Interval (QTc) In-Sling Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle By Sex

Hour Following Dosing	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)		Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
10 minutes	266.1 (10.1)	286.8 (2.4)	6.4 (1.2)	11.1 (10.6)	278.2 (3.0)	255.1 (1.3)	13.4 (2.5)	13.9 (3.2)
0.5	271.1 (17.8)	290.0 (4.6)	11.4 (6.5)	14.2 (3.6)	281.1 (5.3)	250.5 (1.5)	16.3 (0.2)	9.3 (3.4)
1	275.0 (9.9)	279.2 (9.6)	15.2 (1.3)	3.4 (1.3)	267.0 (1.1)	247.7 (4.6)	2.2 (4.4)	6.5 (6.5)
2	270.0 (21.6)	287.1 (4.2)	10.2 (10.4)	11.3 (4.1)	247.6 (13.9)	239.7 (4.7)	-17.1 (19.4)	-1.5 (2.8)
4	270.4 (8.8)	265.9 (8.0)	10.6 (2.4)	-9.8 (0.2)	253.7 (7.3)	239.7 (0.7)	-11.0 (1.8)	-1.5 (1.2)

Table 35. PR Interval (msec) In-Cage Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[a]

Hour Following Dosing	Mean (Standard Error) of Unadjusted Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Averages (N=4)		Significant Differences Between Dose Groups?[b]
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	
9	103.5 (7.1)	105.7 (6.6)	4.7 (3.8)	-2.9 (4.0)	
20	92.7 (2.2)	99.0 (2.4)	-6.1 (4.5)	-9.6 (2.7)	
32	102.7 (6.6)	100.9 (3.5)	3.9 (3.5)	-7.7 (5.5)	
44	94.1 (2.7)	100.6 (2.2)	-4.7 (5.5)	-8.0 (3.0)	
56	94.4 (5.9)	105.5 (5.8)	-4.3 (6.2)	-3.1 (3.2)	

a. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for PR interval, F-tests for significant dose group effects were made across all animals, and not separately by sex.

b. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests at each time point so that the false discovery rate is no higher than 0.05 across all 5 time points simultaneously. No significant dose group effects were observed at any time point.

Table 36. PR Interval (msec) In-Cage Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle By Sex

Hour Following Dosing	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)		Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)	
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM
9	96.7 (5.2)	111.8 (12.8)	1.0 (1.3)	0.5 (7.2)	110.3 (13.4)	99.5 (4.6)	8.5 (7.6)	-6.3 (4.7)
20	96.0 (2.3)	103.0 (0.8)	0.3 (1.7)	-8.4 (6.3)	89.3 (0.4)	95.0 (1.2)	-12.5 (6.2)	-10.8 (1.3)
32	99.4 (7.6)	97.1 (1.4)	3.7 (3.7)	-14.3 (7.0)	106.0 (13.5)	104.8 (6.5)	4.1 (7.6)	-1.0 (6.6)
44	93.8 (0.2)	102.8 (0.1)	-2.0 (4.2)	-8.6 (5.6)	94.5 (6.5)	98.5 (4.3)	-7.3 (12.3)	-7.3 (4.5)
56	99.9 (12.2)	110.9 (11.8)	4.2 (8.3)	-0.5 (6.2)	89.0 (1.4)	100.2 (3.0)	-12.9 (4.5)	-5.7 (2.9)

Table 37. RR Interval (msec) In-Cage Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[a]

Hour Following Dosing	Mean (Standard Error) of Unadjusted Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Averages (N=4)		Significant Differences Between Dose Groups?[b]
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	
9	786.1 (93.1)	601.9 (22.8)	-71.5 (79.7)	-120.2 (31.9)	
20	639.7 (72.4)	532.9 (30.5)	-218.0 (31.0)	-189.2 (33.1)	
32	704.1 (133.9)	767.5 (37.5)	-153.6 (69.2)	45.4 (37.7)	
44	660.5 (97.9)	598.5 (82.9)	-197.2 (80.4)	-123.7 (70.9)	
56	861.1 (142.8)	833.7 (89.4)	3.4 (68.0)	111.6 (90.3)	

a. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for RR interval, F-tests for significant dose group effects were made across all animals, and not separately by sex.

b. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests at each time point so that the false discovery rate is no higher than 0.05 across all 5 time points simultaneously. No significant dose group effects were observed at any time point.

Table 38. RR Interval (msec) In-Cage Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle By Sex

Hour Following Dosing	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)		Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
9	841.8 (200.5)	571.0 (33.3)	-145.9 (163.5)	-141.3 (72.2)	730.5 (75.0)	632.9 (9.2)	2.8 (17.4)	-99.1 (0.9)
20	763.1 (26.6)	571.2 (19.3)	-224.6 (10.4)	-141.0 (19.6)	516.4 (17.1)	494.5 (47.7)	-211.3 (74.7)	-237.4 (39.4)
32	882.9 (188.1)	791.5 (48.7)	-104.8 (151.2)	79.2 (9.8)	525.2 (90.4)	743.6 (70.1)	-202.5 (32.8)	11.7 (78.4)
44	763.1 (174.4)	647.7 (190.8)	-224.6 (137.5)	-64.6 (151.9)	558.0 (77.8)	549.2 (1.5)	-169.7 (135.4)	-182.7 (9.8)
56	1106.8 (29.3)	972.3 (89.2)	119.1 (7.6)	260.0 (50.2)	615.5 (27.6)	695.2 (40.9)	-112.2 (30.0)	-36.7 (49.2)

Table 39. QRS Interval (msec) In-Cage Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[a]

Hour Following Dosing	Mean (Standard Error) of Unadjusted Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Averages (N=4)		Significant Differences Between Dose Groups?[b]
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	
9	46.2 (4.7)	42.9 (1.3)	0.9 (1.1)	-1.7 (2.3)	
20	44.7 (2.6)	40.1 (1.5)	-0.6 (2.7)	-4.5 (3.1)	
32	43.1 (2.8)	42.9 (1.3)	-2.2 (2.5)	-1.6 (1.0)	
44	46.1 (3.1)	41.3 (1.6)	0.8 (3.5)	-3.3 (3.0)	
56	42.6 (2.1)	43.4 (1.7)	-2.7 (2.8)	-1.2 (1.5)	

a. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for QRS interval, F-tests for significant dose group effects were made across all animals, and not separately by sex.

b. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests at each time point so that the false discovery rate is no higher than 0.05 across all 5 time points simultaneously. No significant dose group effects were observed at any time point.

Table 40. QRS Interval (msec) In-Cage Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle By Sex

Hour Following Dosing	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)		Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
9	46.6 (0.8)	43.6 (3.1)	1.2 (0.9)	-3.1 (5.2)	45.8 (11.5)	42.2 (0.6)	0.6 (2.5)	-0.2 (0.3)
20	47.1 (2.4)	37.9 (2.2)	1.7 (4.2)	-8.8 (4.3)	42.4 (5.0)	42.3 (0.3)	-2.9 (4.0)	-0.1 (1.2)
32	45.1 (4.6)	43.4 (2.9)	-0.3 (2.8)	-3.3 (0.8)	41.1 (4.4)	42.5 (0.8)	-4.2 (4.6)	0.1 (0.1)
44	49.9 (3.1)	39.1 (2.0)	4.6 (4.9)	-7.6 (4.2)	42.3 (4.4)	43.5 (1.3)	-2.9 (4.6)	1.1 (0.4)
56	43.2 (4.4)	46.1 (0.9)	-2.2 (2.6)	-0.6 (3.0)	42.0 (2.8)	40.6 (0.8)	-3.2 (6.2)	-1.8 (1.7)

Table 41. QT Interval (msec) In-Cage Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[a]

Hour Following Dosing	Mean (Standard Error) of Unadjusted Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Averages (N=4)		Significant Differences Between Dose Groups?[b]
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	
9	235.0 (7.1)	218.8 (10.2)	-0.8 (7.8)	-10.1 (4.2)	
20	216.4 (10.6)	204.4 (11.8)	-19.4 (5.3)	-24.5 (13.4)	
32	226.7 (14.6)	226.0 (6.3)	-9.1 (11.9)	-2.9 (2.3)	
44	218.7 (12.9)	199.8 (11.9)	-17.1 (8.5)	-29.0 (9.1)	
56	211.2 (7.5)	217.6 (11.5)	-24.6 (7.0)	-11.3 (4.7)	

a. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for QT interval, F-tests for significant dose group effects were made across all animals, and not separately by sex.

b. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests at each time point so that the false discovery rate is no higher than 0.05 across all 5 time points simultaneously. No significant dose group effects were observed at any time point.

Table 42. QT Interval (msec) In-Cage Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle By Sex

Hour Following Dosing	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)		Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
9	237.1 (15.5)	233.6 (13.0)	-8.1 (13.0)	-8.7 (8.2)	232.9 (7.2)	204.1 (4.6)	6.6 (9.6)	-11.4 (5.9)
20	232.9 (4.4)	207.2 (6.7)	-12.3 (1.9)	-35.1 (1.9)	199.9 (10.4)	201.6 (27.9)	-26.4 (8.0)	-13.9 (29.2)
32	243.8 (15.9)	236.1 (5.4)	-1.3 (13.4)	-6.2 (0.5)	209.6 (20.9)	215.8 (1.7)	-16.8 (23.4)	0.4 (3.0)
44	235.2 (7.1)	208.7 (25.5)	-10.0 (4.6)	-33.6 (20.7)	202.2 (20.2)	191.0 (7.1)	-24.2 (17.7)	-24.5 (5.7)
56	219.8 (6.1)	236.0 (2.9)	-25.4 (8.6)	-6.3 (1.9)	202.6 (12.5)	199.2 (10.4)	-23.8 (14.9)	-16.2 (9.0)

Table 43. Corrected QT Interval (QTc)[a] In-Cage Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[b]

Hour Following Dosing	Mean (Standard Error) of Unadjusted Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Averages (N=4)		Significant Differences Between Dose Groups?[c]
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	
9	260.8 (3.0)	256.8 (9.0)	6.3 (4.6)	0.8 (5.4)	
20	254.9 (2.2)	254.5 (11.0)	0.5 (1.3)	-1.4 (12.9)	
32	257.6 (3.3)	249.5 (6.7)	3.1 (6.2)	-6.4 (2.7)	
44	254.3 (8.2)	241.1 (5.4)	-0.2 (7.1)	-14.9 (6.9)	
56	239.2 (4.8)	236.5 (5.8)	-15.3 (6.7)	-19.4 (3.9)	

a. Corrected QT interval (QTc) was calculated by dividing QT interval by the cubed root of RR interval, where both intervals are expressed in seconds, and multiplying by 1000.

b. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for QTc interval, F-tests for significant dose group effects were made across all animals, and not separately by sex.

c. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests at each time point so that the false discovery rate is no higher than 0.05 across all 5 time points simultaneously. No significant dose group effects were observed at any time point.

Table 44. Corrected QT Interval (QTc) In-Cage Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle By Sex

Hour Following Dosing	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)		Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
9	261.9 (7.1)	271.0 (9.1)	8.8 (5.5)	4.1 (12.5)	259.6 (1.3)	242.6 (1.3)	3.8 (9.2)	-2.4 (0.2)
20	254.8 (1.6)	253.0 (4.3)	1.7 (0.0)	-13.8 (7.8)	255.1 (5.2)	256.1 (26.5)	-0.8 (2.7)	11.1 (25.1)
32	256.7 (3.4)	259.7 (1.9)	3.6 (1.8)	-7.2 (1.5)	258.5 (7.2)	239.4 (7.8)	2.6 (15.1)	-5.6 (6.4)
44	261.5 (14.1)	245.5 (2.6)	8.4 (12.5)	-21.3 (6.0)	247.1 (9.9)	236.6 (11.3)	-8.7 (2.1)	-8.4 (12.7)
56	233.4 (7.4)	245.7 (3.5)	-19.7 (9.0)	-21.1 (6.9)	245.0 (4.3)	227.3 (4.6)	-10.9 (12.2)	-17.7 (6.0)

Table 45. Baseline Averages for Pulmonary Parameters, by Animal[a]

Sex	Animal ID	Respiratory Rate (breaths/min)	Tidal Volume (mL/breath/kg)[b]	Minute Volume (mL/min/kg)[b]
Male	101	23.7	16.7	387.3
	102	14.2	14.1	185.4
	201	15.2	14.7	181.5
	202	14.7	17.2	232.9
Female	151	14.4	14.9	208.1
	152	22.6	24.2	414.9
	251	32.8	14.0	428.2
	252	20.7	17.8	352.6

a. Baseline averages were calculated for each animal by averaging data collected during the 30-minute interval from 10 to 40 minutes prior to dosing.
b. Tidal volume and minute volume data were adjusted by each animal's body weight.

Table 46. Means (and Standard Errors), by Sex and Dose Group, of Baseline Averages for Pulmonary Parameters[a]

Sex	Dose Group	Mean (Standard Error) Across Study Animals		
		Respiratory Rate (breaths/min)	Tidal Volume (mL/breath/kg)	Minute Volume (mL/min/kg)
Male	Vehicle (N=2)	18.9 (4.8)	15.4 (1.3)	286.3 (101.0)
	$CuATSM/H_2ATSM$ (N=2)	14.9 (0.2)	15.9 (1.3)	207.2 (25.7)
Female	Vehicle (N=2)	18.5 (4.1)	19.6 (4.6)	311.5 (103.4)
	$CuATSM/H_2ATSM$ (N=2)	26.7 (6.1)	15.9 (1.9)	390.4 (37.8)
All Animals	Vehicle (N=4)	18.7 (2.6)	17.5 (2.3)	298.9 (59.5)
	$CuATSM/H_2ATSM$ (N=4)	20.8 (4.2)	15.9 (0.9)	298.8 (56.1)

a Summaries are of the baseline averages listed in Table 45. Comparisons between the two dose groups were made across all animals if the sex effect and the interaction between sex and dose group effects were not significant, and separately for each sex if the sex effect or the interaction between sex and dose group effects were significant. No significant differences in baseline values were observed between the two dose groups for any parameter.

Table 47. Respiratory Rate (breaths/min) Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[a]

10-Minute Interval	Mean (Standard Error) of Unadjusted Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Averages (N=4)		Significant Differences Between Dose Groups?[b]
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	
0-10	24.8 (6.3)	18.1 (1.8)	6.1 (8.3)	-2.7 (5.4)	
10-20	15.0 (3.1)	18.8 (3.6)	-3.7 (5.0)	-2.1 (1.5)	
20-30	15.1 (0.9)	24.2 (4.9)	-3.6 (2.2)	3.4 (2.9)	
30-40	15.7 (3.6)	16.7 (0.6)	-3.1 (2.9)	-4.2 (3.9)	
40-50	15.3 (1.8)	21.0 (3.1)	-3.5 (1.0)	0.2 (2.1)	
50-60	13.2 (1.5)	20.5 (3.0)	-5.5 (3.7)	-0.3 (1.9)	
60-70	14.3 (1.7)	19.0 (4.1)	-4.4 (3.7)	-1.8 (0.6)	
70-80	18.7 (7.1)	14.1 (3.2)	-0.0 (5.7)	-6.8 (4.7)	
80-90	17.9 (4.7)	23.0 (6.4)	-0.8 (2.5)	2.1 (2.8)	
90-100	14.8 (3.6)	18.0 (5.1)	-4.0 (4.5)	-2.8 (1.3)	
100-110	10.9 (1.5)	15.7 (2.9)	-7.8 (3.3)	-5.2 (4.2)	
110-120	14.7 (3.1)	22.8 (2.1)	-4.0 (3.0)	2.0 (2.5)	
120-130	23.9 (4.3)	18.8 (2.7)	5.1 (3.6)	-2.0 (4.3)	
130-140	13.6 (2.2)	22.0 (1.1)	-5.1 (4.0)	1.2 (4.0)	
140-150	15.3 (2.1)	20.8 (4.3)	-3.5 (3.5)	-0.0 (1.1)	
150-160	14.2 (2.2)	23.4 (2.2)	-4.6 (4.7)	2.6 (5.3)	
160-170	17.5 (3.1)	17.4 (1.7)	-1.3 (1.8)	-3.4 (4.4)	
170-180	14.1 (1.9)	21.3 (6.1)	-4.7 (4.3)	0.5 (2.4)	
180-190	15.4 (2.8)	23.4 (3.1)	-3.3 (3.4)	2.5 (4.1)	
190-200	17.1 (3.6)	21.8 (3.1)	-1.6 (1.7)	1.0 (4.1)	
200-210	16.8 (3.7)	18.9 (2.4)	-2.0 (4.1)	-1.9 (3.1)	
210-220	16.0 (3.7)	15.9 (3.1)	-2.8 (5.9)	-4.9 (2.8)	
220-230	13.9 (2.2)	20.5 (3.4)	-4.8 (4.1)	-0.4 (1.4)	
230-240	18.0 (2.8)	21.9 (1.5)	-0.7 (2.9)	1.0 (3.8)	

a. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for respiratory rate, F-tests for significant dose group effects were made across all animals, and not separately by sex.

b. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests for each interval so that the false discovery rate is no higher than 0.05 across all 24 intervals simultaneously. No significant dose group effects were observed at any 10-minute interval.

Table 48. **Respiratory Rate (breaths/min) Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle by Sex**

10-Minute Interval	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)		Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)	
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM
0-10	31.6 (11.7)	19.7 (3.6)	12.6 (16.5)	4.8 (3.8)	18.1 (3.4)	16.5 (1.0)	-0.4 (7.5)	-10.2 (7.1)
10-20	19.0 (5.3)	13.2 (2.4)	0.0 (10.0)	-1.7 (2.1)	11.1 (0.5)	24.4 (3.0)	-7.4 (4.6)	-2.4 (3.1)
20-30	15.7 (2.1)	16.0 (3.1)	-3.2 (2.7)	1.1 (2.9)	14.5 (0.4)	32.4 (0.5)	-4.0 (4.5)	5.7 (5.6)
30-40	17.1 (8.5)	16.4 (1.2)	-1.8 (3.7)	1.4 (1.0)	14.3 (1.6)	17.0 (0.7)	-4.3 (5.7)	-9.8 (5.4)
40-50	15.7 (2.3)	15.7 (1.1)	-3.3 (2.4)	0.7 (0.8)	14.9 (3.8)	26.3 (1.0)	-3.6 (0.3)	-0.4 (5.0)
50-60	11.0 (2.1)	16.3 (2.8)	-7.9 (6.8)	1.4 (3.1)	15.4 (0.7)	24.7 (3.6)	-3.1 (4.8)	-2.1 (2.5)
60-70	16.9 (1.9)	12.7 (0.4)	-2.0 (6.7)	-2.2 (0.6)	11.8 (0.9)	25.3 (4.8)	-6.8 (5.0)	-1.4 (1.2)
70-80	26.6 (13.3)	10.0 (1.0)	7.6 (8.5)	-4.9 (0.8)	10.8 (1.5)	18.1 (5.3)	-7.7 (2.6)	-8.6 (11.3)
80-90	16.4 (6.0)	13.1 (4.4)	-2.5 (1.3)	-1.8 (4.2)	19.4 (9.6)	32.8 (5.6)	0.8 (5.5)	6.0 (0.4)
90-100	8.6 (0.3)	10.1 (1.1)	-10.3 (4.5)	-4.9 (0.9)	20.9 (0.2)	25.9 (5.1)	2.4 (4.3)	-0.8 (0.9)
100-110	10.9 (1.5)	11.7 (1.9)	-8.1 (3.3)	-3.2 (1.6)	11.0 (3.2)	19.6 (3.8)	-7.5 (7.3)	-7.1 (9.9)
110-120	18.9 (4.8)	20.0 (2.1)	-0.0 (0.0)	5.0 (2.4)	10.6 (0.8)	25.7 (2.4)	-8.0 (4.9)	-1.1 (3.6)
120-130	30.0 (5.9)	15.1 (0.9)	11.0 (1.1)	0.1 (1.2)	17.7 (1.2)	22.6 (3.8)	-0.8 (2.9)	-4.2 (9.9)
130-140	10.7 (0.4)	21.3 (2.6)	-8.3 (4.3)	6.3 (2.4)	16.5 (3.5)	22.8 (0.1)	-2.0 (7.6)	-4.0 (5.9)
140-150	12.8 (2.7)	14.1 (1.5)	-6.2 (7.5)	-0.9 (1.3)	17.8 (2.8)	27.6 (4.1)	-0.8 (1.3)	0.9 (2.0)
150-160	13.6 (4.8)	23.0 (3.9)	-5.3 (9.6)	8.0 (4.1)	14.7 (2.4)	23.9 (3.5)	-3.8 (6.5)	-2.8 (9.6)
160-170	18.7 (1.9)	16.3 (3.7)	-0.2 (2.9)	1.4 (3.5)	16.2 (7.2)	18.5 (1.4)	-2.3 (3.1)	-8.2 (7.5)
170-180	12.5 (3.0)	13.1 (4.6)	-6.5 (7.8)	-1.9 (4.4)	15.7 (2.6)	29.5 (8.3)	-2.9 (6.7)	2.8 (2.3)
180-190	13.8 (5.2)	19.1 (3.5)	-5.2 (0.4)	4.1 (3.8)	17.0 (3.9)	27.7 (2.9)	-1.5 (8.0)	0.9 (8.9)
190-200	19.8 (4.5)	17.5 (3.3)	0.9 (0.2)	2.6 (3.5)	14.5 (6.5)	26.1 (3.1)	-4.1 (2.4)	-0.7 (9.1)
200-210	16.5 (4.7)	14.8 (0.7)	-2.4 (9.4)	-0.2 (1.0)	17.0 (7.8)	23.0 (1.1)	-1.6 (3.7)	-3.7 (7.1)
210-220	12.1 (3.5)	10.8 (1.8)	-6.8 (8.3)	-4.1 (1.6)	19.8 (6.3)	21.0 (0.6)	1.3 (10.4)	-5.7 (6.6)
220-230	10.8 (0.4)	14.9 (0.3)	-8.2 (5.2)	-0.1 (0.5)	17.0 (3.1)	26.1 (2.6)	-1.5 (7.2)	-0.7 (3.4)
230-240	19.4 (6.0)	20.6 (3.1)	0.4 (1.2)	5.7 (2.9)	16.7 (2.6)	23.1 (0.0)	-1.9 (6.7)	-3.6 (6.1)

Table 49. Tidal Volume (mL/breath/kg) Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[a,b]

10-Minute Interval	Mean (Standard Error) of Unadjusted Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Averages (N=4)		Significant Differences Between Dose Groups?[c]
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	
0-10	16.3 (1.1)	15.7 (0.9)	-1.2 (1.7)	-0.2 (1.3)	
10-20	17.7 (2.3)	14.4 (0.8)	0.3 (0.3)	-1.6 (0.7)	
20-30	19.5 (2.4)	15.1 (1.5)	2.1 (0.5)	-0.8 (0.6)	
30-40	19.6 (2.7)	13.9 (0.9)	2.1 (0.5)	-2.0 (0.4)	
40-50	18.9 (2.2)	16.9 (2.3)	1.4 (0.3)	1.0 (1.5)	
50-60	18.7 (2.9)	16.0 (1.2)	1.2 (1.1)	0.1 (0.3)	
60-70	21.0 (2.5)	16.7 (1.0)	3.5 (0.8)	0.8 (0.5)	
70-80	23.8 (3.1)	17.3 (1.9)	6.3 (1.9)	1.4 (1.1)	
80-90	19.3 (1.5)	18.6 (2.3)	1.9 (1.9)	2.7 (1.6)	
90-100	19.9 (2.0)	18.6 (1.1)	2.5 (1.9)	2.7 (0.5)	
100-110	21.7 (2.0)	18.4 (2.5)	4.2 (0.6)	2.5 (1.7)	
110-120	23.4 (1.9)	18.5 (0.6)	5.9 (1.4)	2.6 (0.7)	
120-130	22.1 (0.4)	19.3 (1.8)	4.6 (2.0)	3.4 (0.9)	
130-140	22.3 (3.0)	17.5 (0.4)	4.8 (2.1)	1.6 (0.6)	
140-150	20.8 (1.7)	19.2 (1.7)	3.4 (1.8)	3.3 (0.9)	
150-160	21.5 (2.1)	18.3 (2.5)	4.0 (1.4)	2.3 (1.7)	
160-170	22.6 (1.5)	15.1 (1.7)	5.1 (2.2)	-0.8 (1.5)	
170-180	23.5 (1.3)	18.6 (1.0)	6.0 (1.4)	2.7 (0.7)	
180-190	24.5 (1.3)	20.4 (1.6)	7.0 (1.2)	4.5 (1.9)	
190-200	22.2 (1.3)	20.2 (1.5)	4.7 (1.5)	4.3 (2.1)	
200-210	21.9 (1.4)	20.9 (0.7)	4.4 (2.1)	4.9 (1.3)	
210-220	22.5 (2.2)	21.3 (0.6)	5.0 (0.8)	5.4 (1.4)	
220-230	23.0 (1.6)	20.9 (0.8)	5.6 (0.8)	4.9 (1.4)	
230-240	23.7 (1.7)	20.1 (1.6)	6.2 (1.3)	4.2 (2.4)	

a. Tidal volume data were adjusted by each animal's body weight.

b. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for tidal volume, F-tests for significant dose group effects were made across all animals, and not separately by sex.

c. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests for each interval so that the false discovery rate is no higher than 0.05 across all 24 intervals simultaneously. No significant dose group effects were observed at any 10-minute interval.

Table 50. Tidal Volume (mL/breath/kg) Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle by Sex[a]

10-Minute Interval	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)		Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)	
	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM	Vehicle	CuATSM/ H_2ATSM
0-10	15.1 (2.0)	15.0 (1.6)	-0.3 (0.7)	-1.0 (2.9)	17.4 (0.8)	16.5 (1.1)	-2.2 (3.9)	0.6 (0.8)
10-20	15.4 (1.7)	15.2 (0.1)	0.0 (0.4)	-0.8 (1.2)	20.1 (4.2)	13.6 (1.6)	0.5 (0.5)	-2.3 (0.2)
20-30	17.5 (2.5)	15.5 (1.3)	2.1 (1.2)	-0.4 (0.0)	21.6 (4.4)	14.7 (3.3)	2.1 (0.3)	-1.2 (1.4)
30-40	17.3 (2.4)	14.5 (0.7)	2.0 (1.1)	-1.4 (0.6)	21.9 (5.2)	13.3 (1.9)	2.3 (0.5)	-2.6 (0.0)
40-50	16.5 (1.1)	15.1 (2.1)	1.1 (0.2)	-0.8 (0.8)	21.3 (4.0)	18.7 (4.5)	1.7 (0.6)	2.8 (2.7)
50-60	15.2 (0.3)	16.0 (2.0)	-0.2 (1.6)	0.1 (0.7)	22.2 (5.0)	16.0 (2.0)	2.6 (0.3)	0.1 (0.1)
60-70	18.6 (3.2)	15.9 (1.7)	3.2 (1.9)	-0.0 (0.4)	23.4 (3.9)	17.5 (1.5)	3.8 (0.8)	1.6 (0.4)
70-80	23.3 (5.2)	17.5 (1.2)	7.9 (3.9)	1.5 (0.1)	24.3 (5.6)	17.2 (4.6)	4.7 (1.0)	1.3 (2.7)
80-90	17.8 (2.3)	16.7 (2.1)	2.5 (3.6)	0.7 (0.8)	20.8 (1.9)	20.6 (4.4)	1.3 (2.8)	4.7 (2.5)
90-100	18.0 (2.9)	19.2 (2.0)	2.6 (4.2)	3.3 (0.7)	21.9 (2.8)	18.0 (1.8)	2.3 (1.9)	2.1 (0.1)
100-110	19.9 (0.0)	19.3 (1.7)	4.5 (1.3)	3.3 (0.4)	23.5 (4.1)	17.6 (5.8)	3.9 (0.5)	1.7 (3.9)
110-120	22.2 (3.6)	18.0 (1.2)	6.8 (2.3)	2.1 (0.1)	24.6 (2.4)	19.1 (0.4)	5.0 (2.3)	3.2 (1.4)
120-130	22.0 (0.6)	20.1 (1.6)	6.6 (0.7)	4.2 (0.3)	22.1 (0.7)	18.5 (3.9)	2.6 (4.0)	2.6 (2.0)
130-140	19.0 (3.6)	17.9 (0.6)	3.7 (4.9)	1.9 (0.7)	25.5 (4.3)	17.2 (0.7)	5.9 (0.3)	1.3 (1.2)
140-150	19.5 (2.6)	19.9 (1.1)	4.1 (3.9)	3.9 (0.2)	22.2 (2.6)	18.5 (3.9)	2.6 (2.0)	2.6 (2.0)
150-160	20.9 (1.5)	17.5 (1.7)	5.5 (2.8)	1.6 (0.5)	22.1 (4.9)	19.0 (5.8)	2.5 (0.3)	3.1 (3.9)
160-170	23.1 (3.3)	17.7 (0.9)	7.7 (2.0)	1.8 (0.4)	22.1 (1.2)	12.4 (1.8)	2.5 (3.4)	-3.5 (0.1)
170-180	22.3 (1.0)	19.6 (0.5)	6.9 (2.3)	3.7 (0.8)	24.6 (2.5)	17.5 (1.8)	5.1 (2.1)	1.6 (0.0)
180-190	24.0 (0.4)	18.6 (2.3)	8.6 (0.9)	2.6 (1.1)	24.9 (3.0)	22.3 (1.9)	5.3 (1.7)	6.4 (3.8)
190-200	22.3 (1.4)	17.8 (0.0)	6.9 (0.1)	1.8 (1.3)	22.1 (2.8)	22.6 (1.7)	2.5 (1.8)	6.7 (3.5)
200-210	19.4 (0.5)	21.0 (0.9)	4.1 (1.8)	5.0 (0.4)	24.3 (0.0)	20.7 (1.4)	4.7 (4.7)	4.8 (3.3)
210-220	20.5 (0.6)	21.7 (0.3)	5.2 (1.9)	5.8 (1.0)	24.5 (4.5)	21.0 (1.2)	4.9 (0.1)	5.1 (3.1)
220-230	21.9 (0.4)	21.5 (1.1)	6.5 (0.9)	5.5 (0.2)	24.2 (3.5)	20.3 (1.4)	4.6 (1.1)	4.4 (3.3)
230-240	23.5 (2.0)	20.2 (0.2)	8.1 (0.7)	4.3 (1.1)	23.8 (3.5)	20.0 (3.9)	4.2 (1.1)	4.1 (5.8)

a. Tidal volume data were adjusted by each animal's body weight.

Table 51. Minute Volume (mL/min/kg) Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle[a,b]

10-Minute Interval	Mean (Standard Error) of Unadjusted Averages (N=4)		Mean (Standard Error) of Baseline-Adjusted Averages (N=4)		Significant Differences Between Dose Groups?[c]
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	
0-10	322.0 (51.4)	255.8 (10.6)	23.1 (106.3)	-43.0 (52.9)	
10-20	229.6 (22.3)	249.1 (40.8)	-69.3 (64.5)	-49.7 (23.7)	
20-30	277.0 (30.6)	347.9 (94.4)	-21.9 (29.3)	49.0 (68.2)	
30-40	286.1 (67.8)	224.6 (9.0)	-12.8 (40.2)	-74.2 (59.5)	
40-50	259.9 (47.5)	358.6 (90.4)	-39.0 (29.1)	59.7 (58.8)	
50-60	231.1 (50.1)	318.8 (48.4)	-67.8 (65.4)	20.0 (22.2)	
60-70	263.9 (23.9)	313.7 (80.3)	-35.0 (39.8)	14.8 (28.6)	
70-80	415.3 (190.1)	245.1 (75.1)	116.4 (161.0)	-53.7 (79.6)	
80-90	302.3 (75.3)	413.5 (134.8)	3.3 (29.2)	114.7 (86.3)	
90-100	255.0 (62.7)	311.7 (77.8)	-43.9 (77.4)	12.9 (26.5)	
100-110	213.7 (21.1)	277.7 (84.1)	-85.2 (56.0)	-21.1 (82.6)	
110-120	311.3 (80.1)	376.0 (64.0)	12.4 (67.7)	77.1 (14.0)	
120-130	445.2 (117.5)	331.0 (80.8)	146.3 (104.4)	32.1 (76.1)	
130-140	259.7 (43.5)	344.4 (38.9)	-39.3 (78.3)	45.6 (31.0)	
140-150	266.2 (43.0)	353.8 (73.1)	-32.8 (65.5)	55.0 (33.9)	
150-160	254.3 (30.3)	410.0 (99.2)	-44.6 (77.9)	111.2 (94.3)	
160-170	345.2 (75.5)	234.8 (18.1)	46.3 (31.6)	-64.1 (49.7)	
170-180	284.0 (29.0)	350.1 (90.8)	-14.9 (78.3)	51.3 (51.0)	
180-190	311.9 (56.2)	411.6 (90.1)	13.0 (59.9)	112.7 (45.8)	
190-200	341.5 (94.1)	395.9 (91.0)	42.6 (55.1)	97.1 (46.1)	
200-210	286.4 (49.5)	347.7 (64.4)	-12.5 (53.9)	48.9 (13.7)	
210-220	291.9 (54.5)	316.1 (62.1)	-7.0 (96.8)	17.2 (22.4)	
220-230	281.3 (42.3)	363.6 (79.9)	-17.6 (70.1)	64.8 (27.4)	
230-240	374.5 (71.7)	357.7 (58.8)	75.6 (54.6)	58.9 (33.1)	

a. Minute volume data were adjusted by each animal's body weight.

b. A single fit of the repeated measures ANOVA model was made to the baseline-adjusted averages for all animals. Because neither the sex effect nor the interaction of sex and dose group was significant at the 0.05 level in this model for minute volume, F-tests for significant dose group effects were made across all animals, and not separately by sex.

c. "Yes" indicates that dose group effects were significant at the given interval, after using a Benjamini and Hochberg approach to adjusting the p-values of these tests for each interval so that the false discovery rate is no higher than 0.05 across all 24 intervals simultaneously. No significant dose group effects were observed at any 10-minute interval.

Table 52. Minute Volume (mL/min/kg) Means (Standard Errors) of Unadjusted and Baseline-Adjusted Averages Following Dosing with CuATSM/H_2ATSM or Vehicle by Sex[a]

10-Minute Interval	Mean (Standard Error) for Male Animals				Mean (Standard Error) for Female Animals			
	Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)		Unadjusted Averages (N=2)		Baseline-Adjusted Averages (N=2)	
	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM	Vehicle	CuATSM/H_2ATSM
0-10	370.2 (96.6)	245.8 (10.6)	83.9 (197.6)	38.6 (15.1)	273.7 (42.9)	265.9 (19.1)	-37.7 (146.3)	-124.5 (56.8)
10-20	243.8 (36.5)	183.8 (18.6)	-42.5 (137.5)	-23.4 (44.3)	215.5 (35.2)	314.3 (33.8)	-96.0 (68.2)	-76.1 (4.0)
20-30	264.8 (47.8)	203.1 (10.2)	-21.6 (53.2)	-4.1 (35.9)	289.2 (55.1)	492.6 (107.1)	-22.2 (48.3)	102.2 (144.8)
30-40	291.1 (163.1)	225.1 (1.7)	4.7 (62.1)	17.9 (27.4)	281.1 (31.1)	224.1 (21.9)	-30.3 (72.3)	-166.3 (59.7)
40-50	226.3 (36.2)	214.3 (14.3)	-60.1 (64.8)	7.1 (11.4)	293.5 (99.7)	502.8 (85.0)	-18.0 (3.7)	112.4 (122.8)
50-60	152.1 (16.1)	252.6 (65.9)	-134.3 (117.1)	45.3 (40.2)	310.1 (47.8)	385.1 (30.6)	-1.3 (55.6)	-5.4 (7.2)
60-70	272.7 (51.5)	192.6 (22.8)	-13.6 (49.5)	-14.7 (2.9)	255.2 (25.1)	434.8 (93.9)	-56.3 (78.3)	44.4 (56.1)
70-80	593.9 (385.5)	172.6 (7.8)	307.6 (284.5)	-34.6 (33.5)	236.6 (65.1)	317.6 (152.5)	-74.9 (38.3)	-72.8 (190.3)
80-90	263.4 (75.7)	180.8 (24.4)	-22.9 (25.3)	-26.4 (50.1)	341.1 (159.1)	646.2 (10.3)	29.6 (55.7)	255.8 (48.1)
90-100	149.0 (14.0)	179.0 (2.5)	-137.3 (115.0)	-28.3 (28.2)	360.9 (30.7)	444.4 (32.9)	49.5 (72.7)	54.0 (4.9)
100-110	201.6 (43.9)	186.8 (17.3)	-84.7 (57.1)	-20.4 (43.0)	225.8 (21.4)	368.6 (160.0)	-85.7 (124.8)	-21.8 (197.8)
110-120	378.8 (171.4)	280.2 (38.4)	92.4 (70.4)	73.0 (12.7)	243.8 (4.9)	471.7 (69.0)	-67.7 (98.5)	81.3 (31.2)
120-130	580.7 (214.7)	240.1 (24.3)	294.3 (113.7)	32.8 (1.4)	309.8 (10.1)	421.9 (148.6)	-1.7 (93.3)	31.4 (186.4)
130-140	186.9 (15.2)	281.1 (31.5)	-99.4 (116.2)	73.8 (57.2)	332.4 (23.4)	407.7 (7.7)	20.9 (126.9)	17.3 (30.1)
140-150	210.7 (40.4)	228.3 (7.9)	-75.6 (141.4)	21.1 (33.6)	321.6 (57.5)	479.4 (21.1)	10.1 (45.9)	88.9 (58.9)
150-160	234.5 (67.3)	318.4 (93.2)	-51.9 (168.2)	111.1 (67.5)	274.2 (14.0)	501.6 (183.2)	-37.3 (89.4)	111.2 (220.9)
160-170	382.1 (126.3)	211.2 (18.8)	95.7 (25.3)	3.9 (44.5)	308.4 (124.7)	258.4 (22.2)	-3.1 (21.3)	-132.0 (60.0)
170-180	245.0 (39.2)	222.7 (56.0)	-41.3 (140.2)	15.5 (81.7)	323.0 (22.0)	477.6 (117.7)	11.5 (125.4)	87.1 (79.9)
180-190	279.2 (123.7)	270.0 (90.5)	-7.2 (22.8)	62.8 (64.8)	344.6 (38.8)	553.2 (20.2)	33.1 (142.2)	162.7 (58.0)
190-200	409.6 (170.7)	240.7 (24.5)	123.3 (69.7)	33.5 (1.2)	273.3 (121.1)	551.2 (30.3)	-38.1 (17.7)	160.8 (68.1)
200-210	247.0 (25.5)	238.3 (26.4)	-39.3 (126.5)	31.1 (0.7)	325.8 (104.7)	457.1 (15.6)	14.3 (1.3)	66.7 (22.2)
210-220	213.3 (43.6)	211.2 (23.8)	-73.1 (144.6)	3.9 (49.5)	370.6 (59.4)	421.0 (23.0)	59.1 (162.8)	30.6 (14.8)
220-230	208.5 (5.9)	241.6 (23.7)	-77.8 (95.1)	34.4 (2.0)	354.1 (11.3)	485.5 (89.2)	42.6 (114.7)	95.1 (51.4)
230-240	407.8 (169.1)	290.2 (2.5)	121.4 (68.1)	83.0 (23.2)	341.2 (8.3)	425.3 (107.7)	29.7 (95.1)	34.9 (69.9)

a. Minute volume data were adjusted by each animal's body weight.

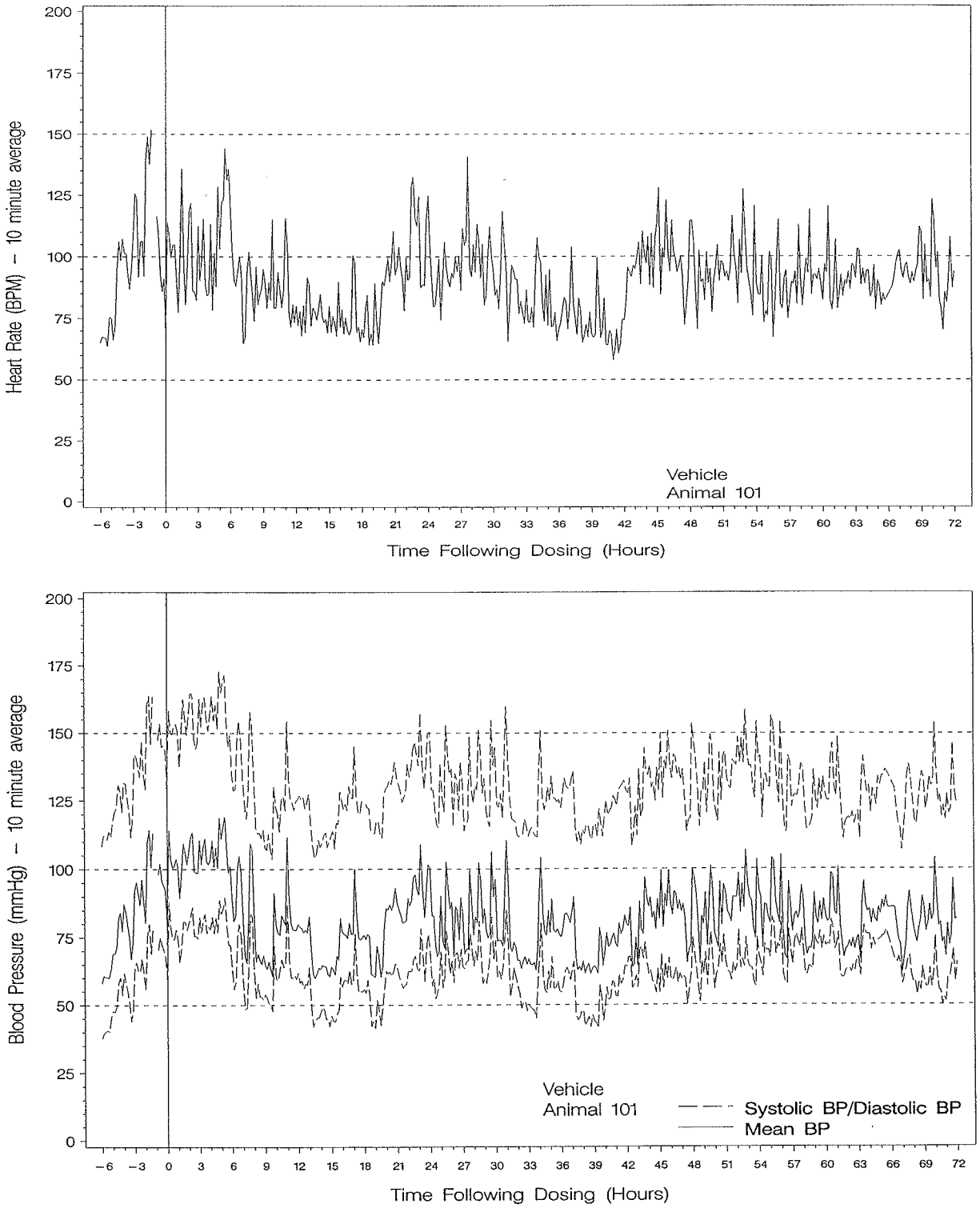


Figure 0-1a. 10-Minute Averages for Blood Pressure Parameters and Heart Rate for Animal 101

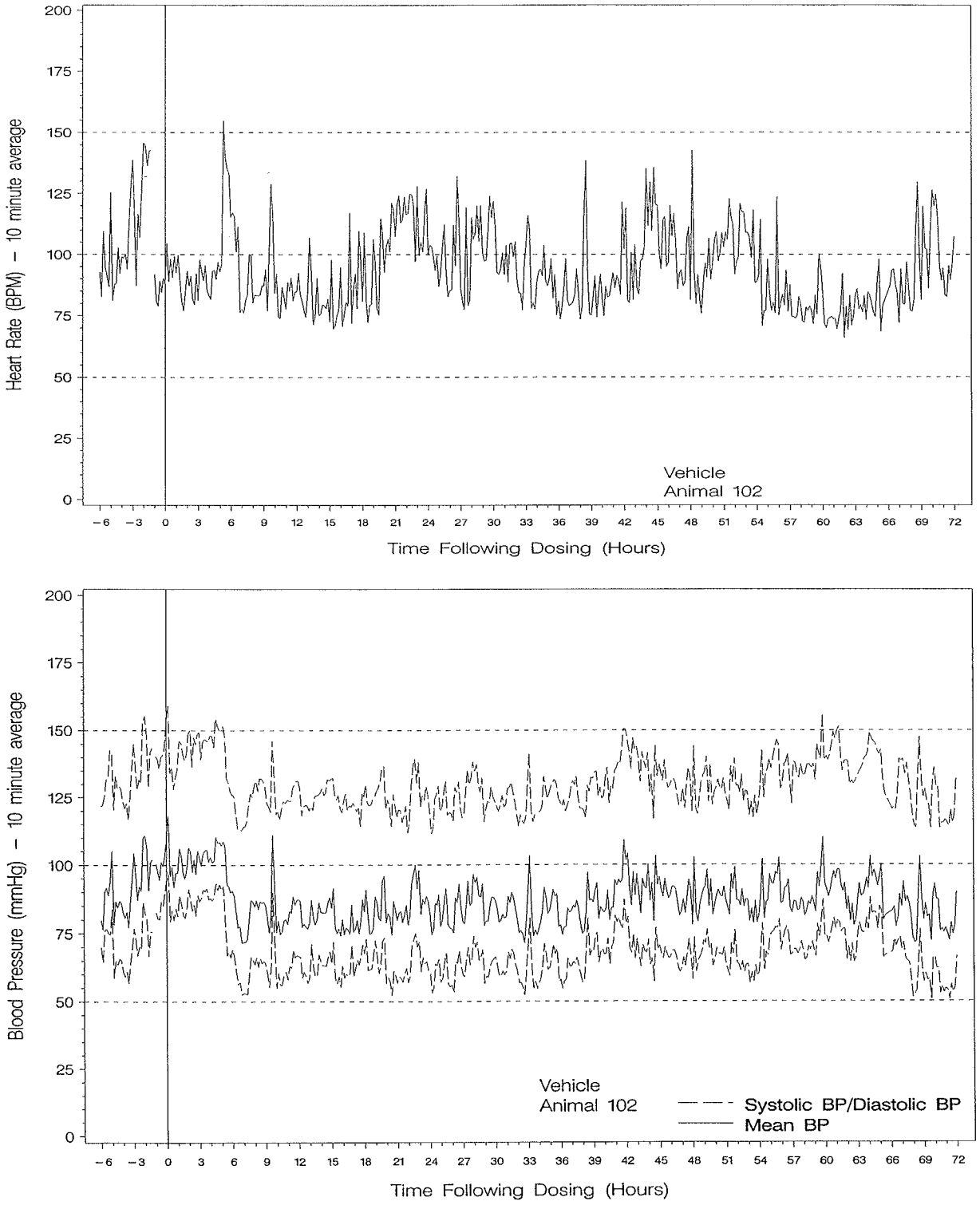


Figure 0-1b. 10-Minute Averages for Blood Pressure Parameters and Heart Rate for Animal 102

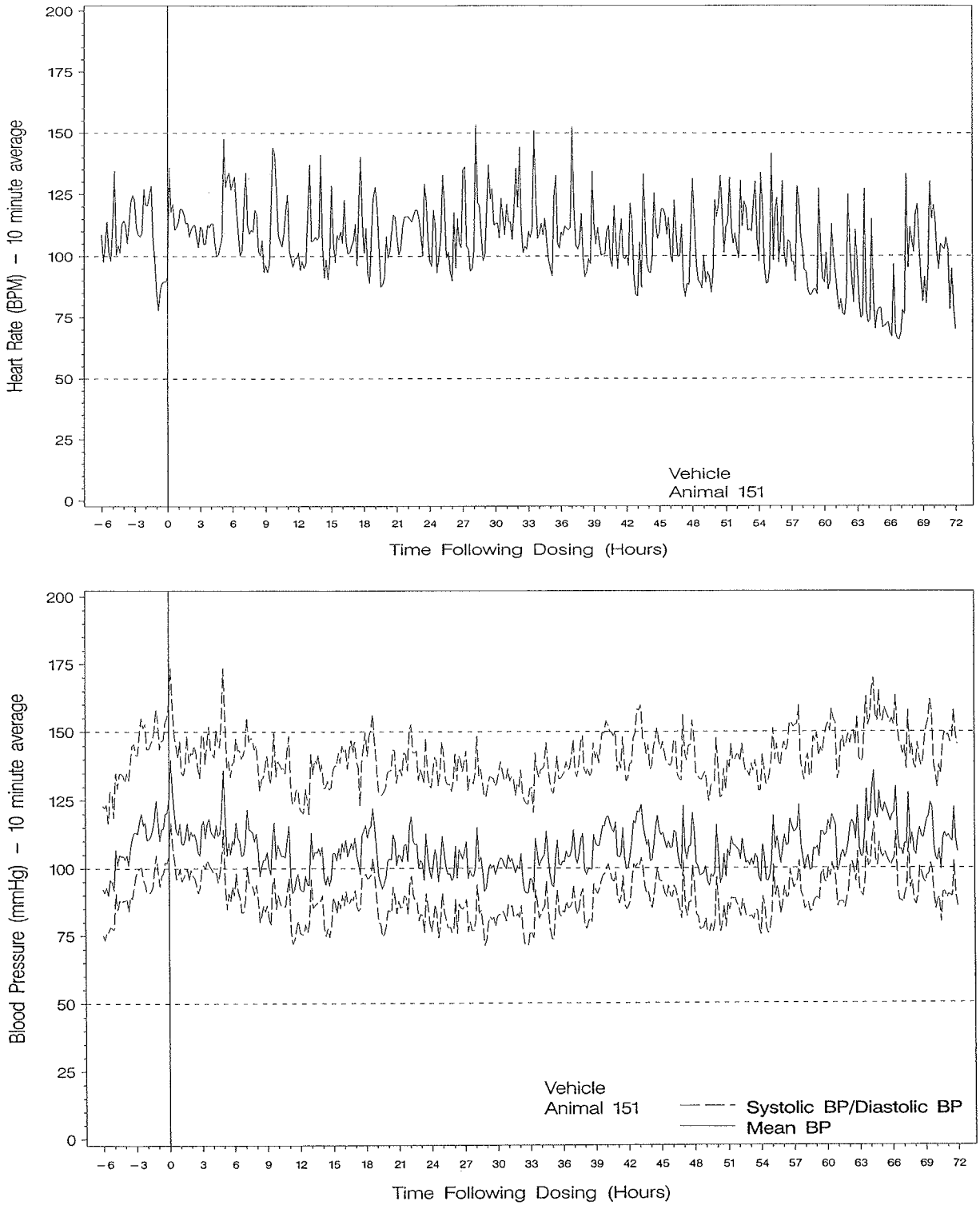


Figure 0-1c. 10-Minute Averages for Blood Pressure Parameters and Heart Rate for Animal 151.

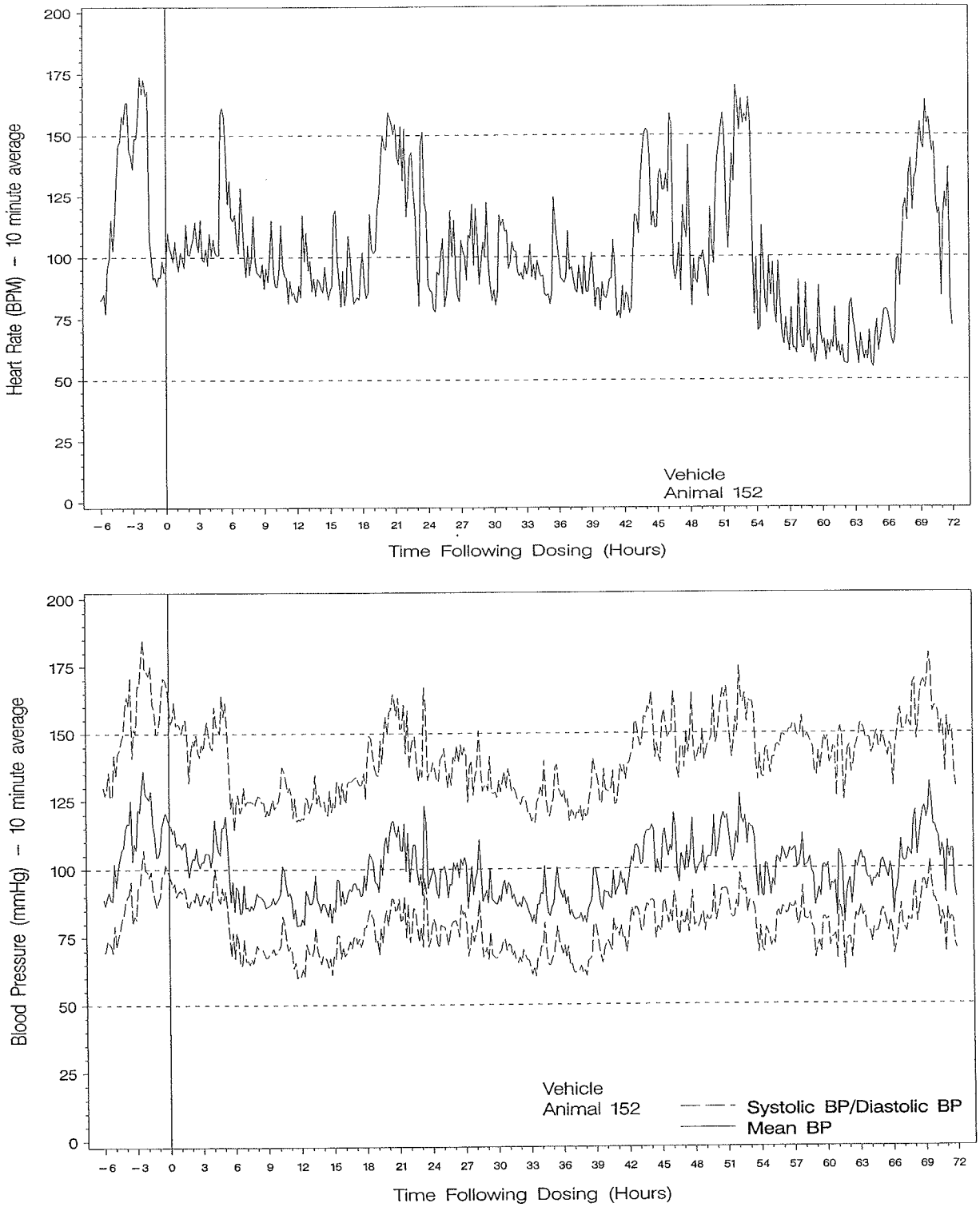
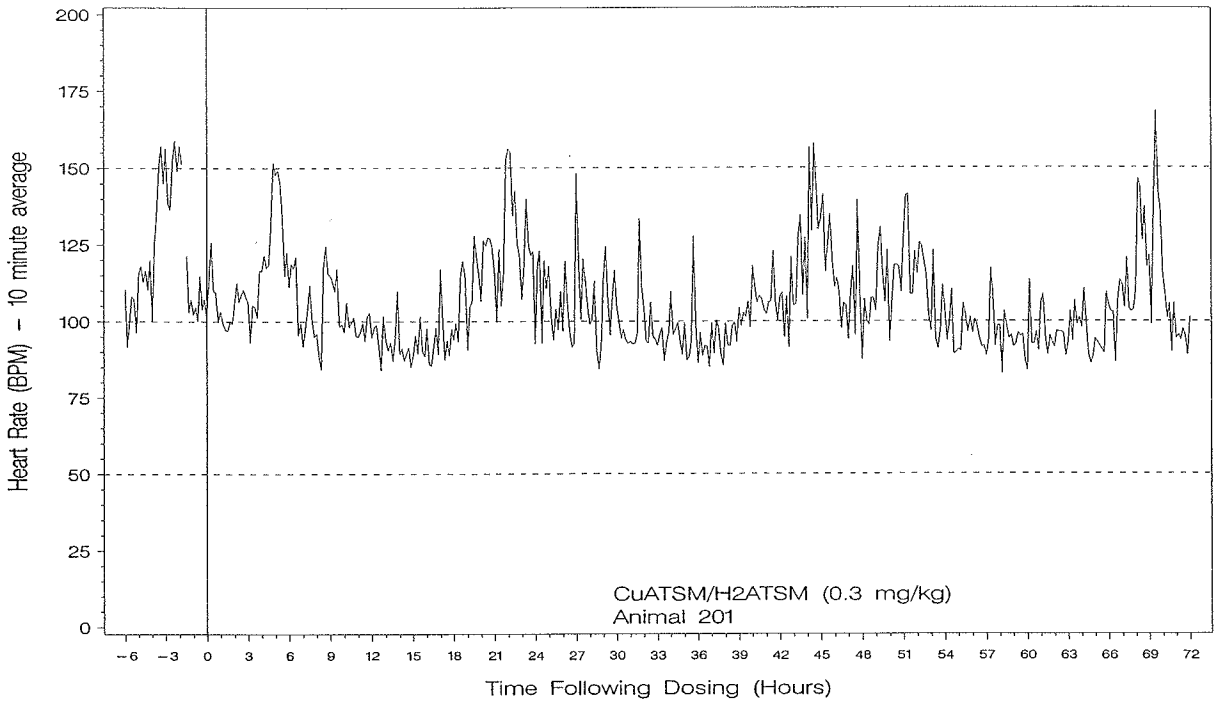


Figure 0-1d. 10-Minute Averages for Blood Pressure Parameters and Heart Rate for Animal 152



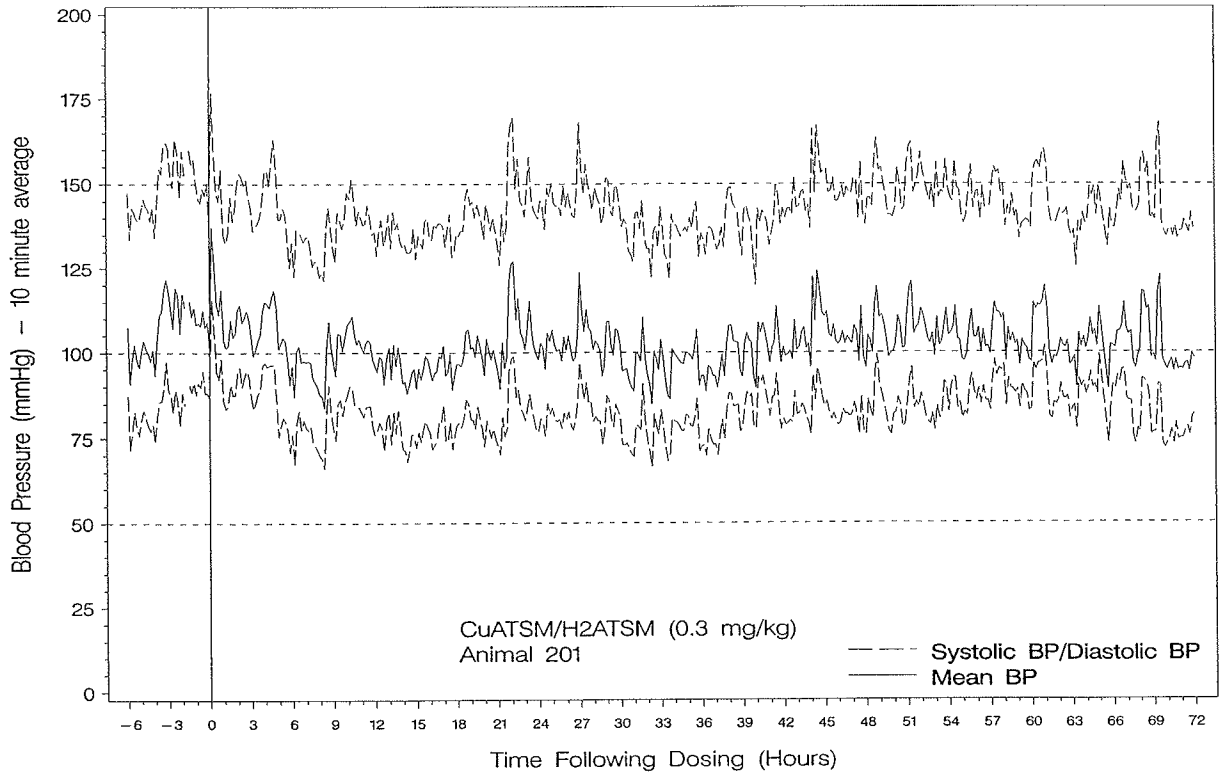


Figure 0-1e. 10-Minute Averages for Blood Pressure Parameters and Heart Rate for Animal 201

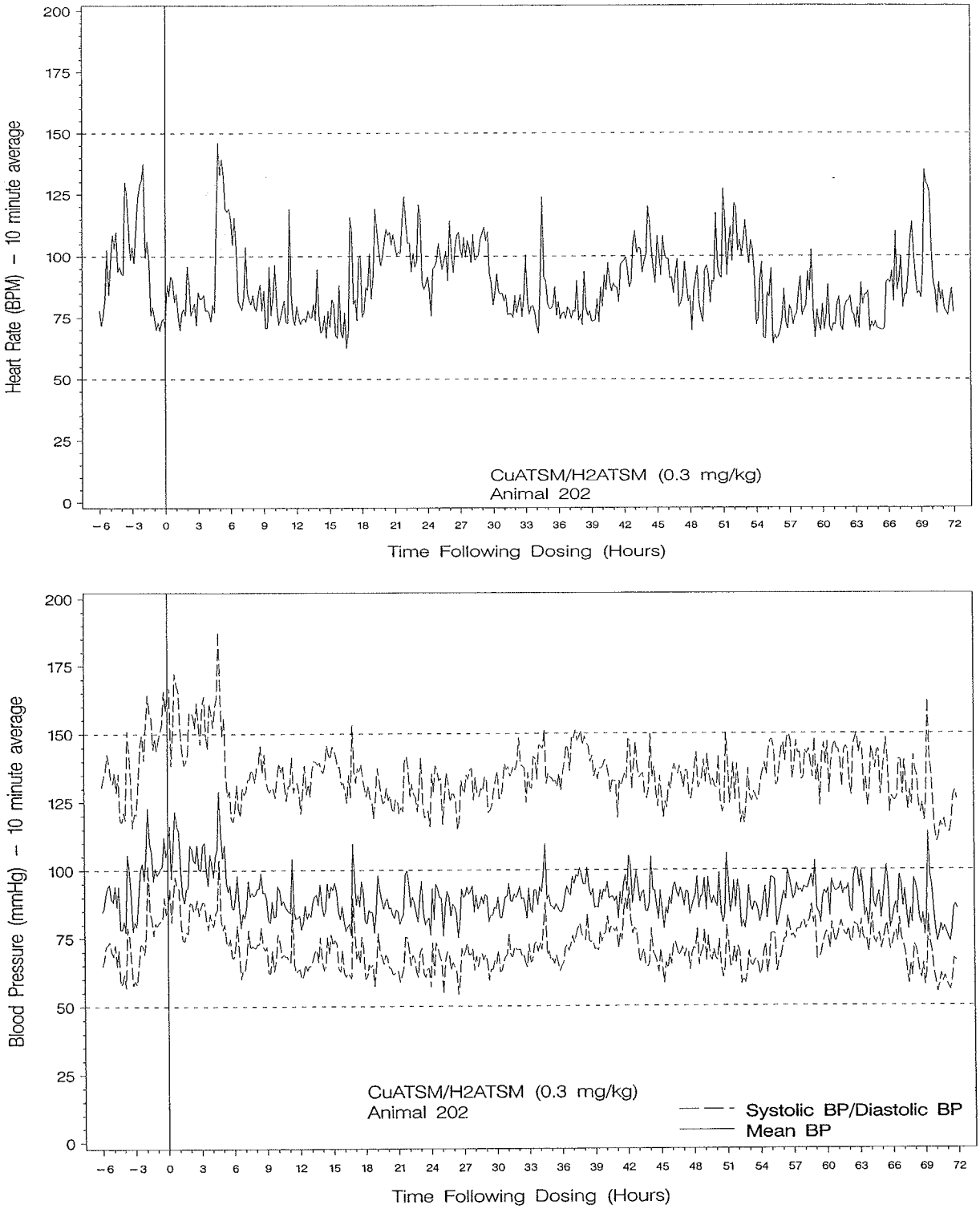


Figure 0-1f. 10-Minute Averages for Blood Pressure Parameters and Heart Rate for Animal 202

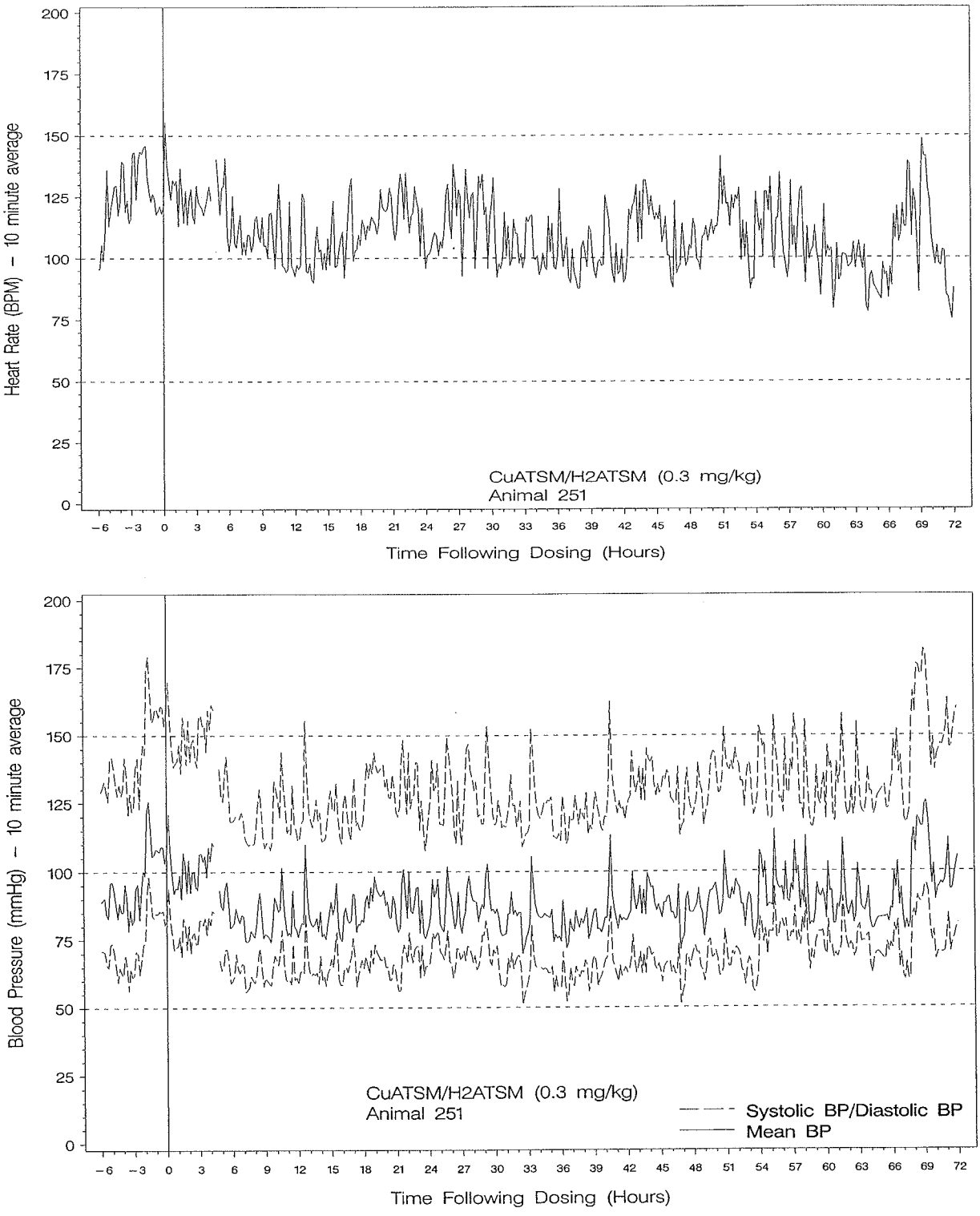


Figure 0-1g. 10-Minute Averages for Blood Pressure Parameters and Heart Rate for Animal 251

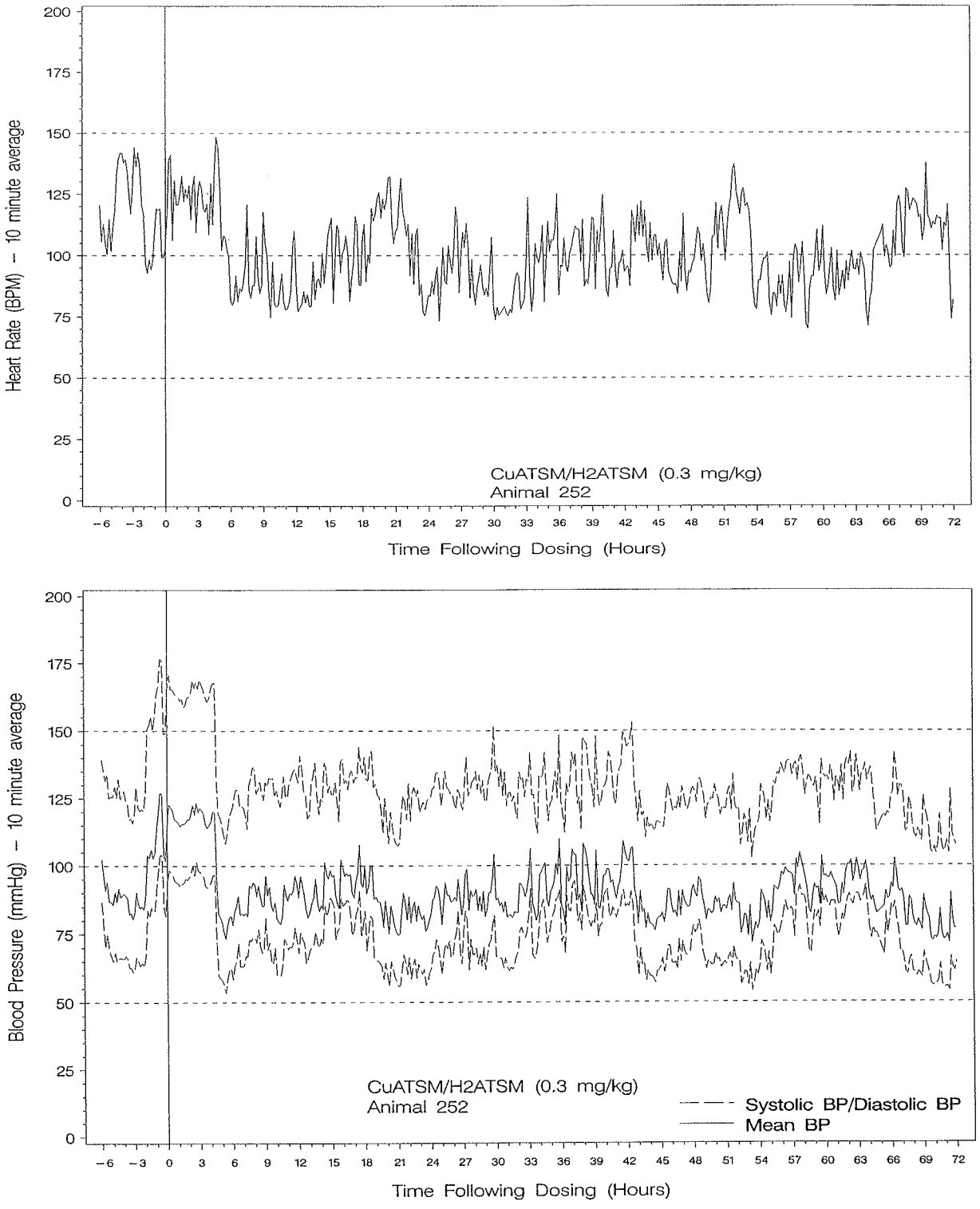


Figure 0-1h. 10-Minute Averages for Blood Pressure Parameters and Heart Rate for Animal 252

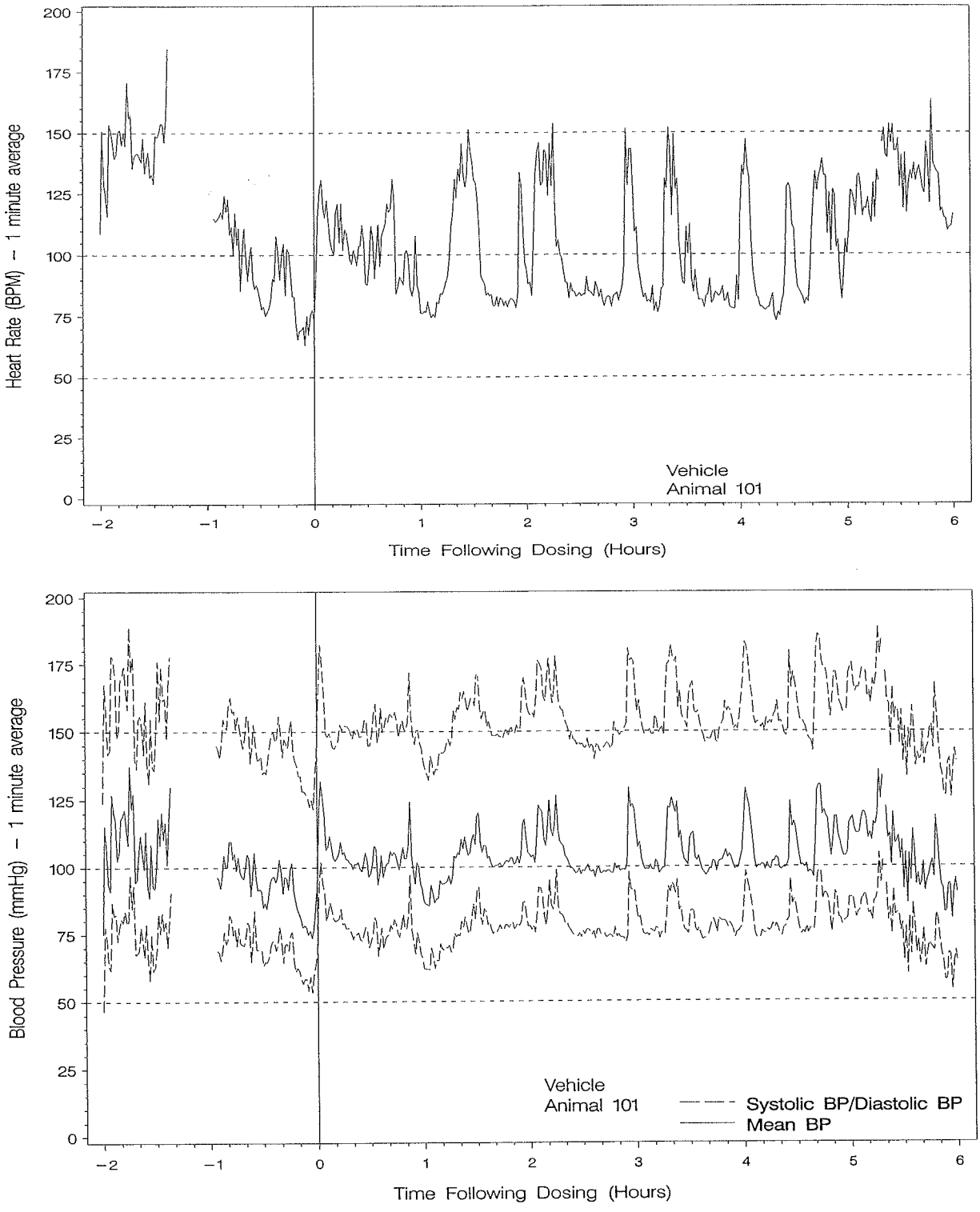


Figure 0-2a. 1-Minute Averages for Blood Pressure Parameters and Heart Rate for Animal 101

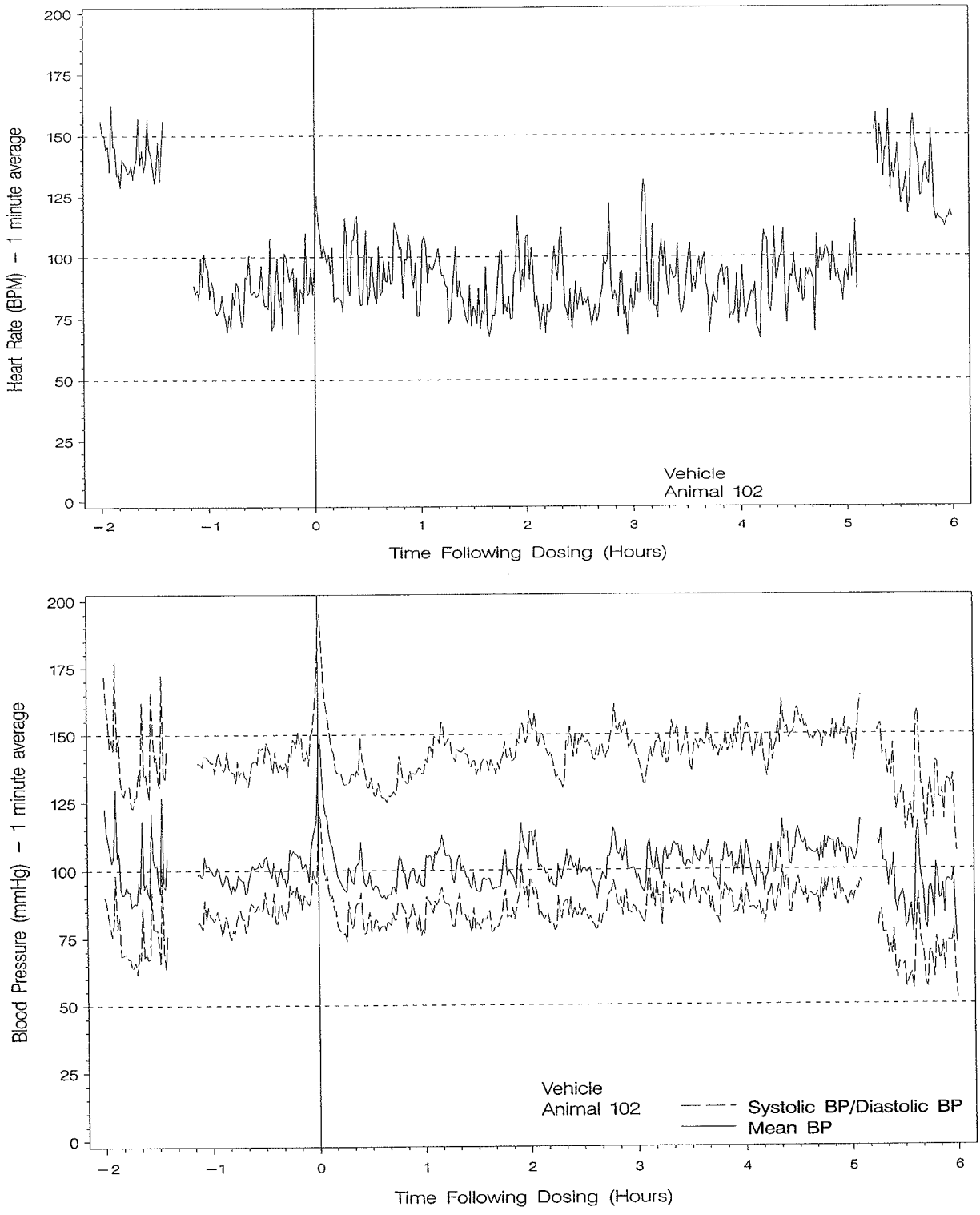


Figure 0-2b. 1-Minute Averages for Blood Pressure Parameters and Heart Rate for Animal 102

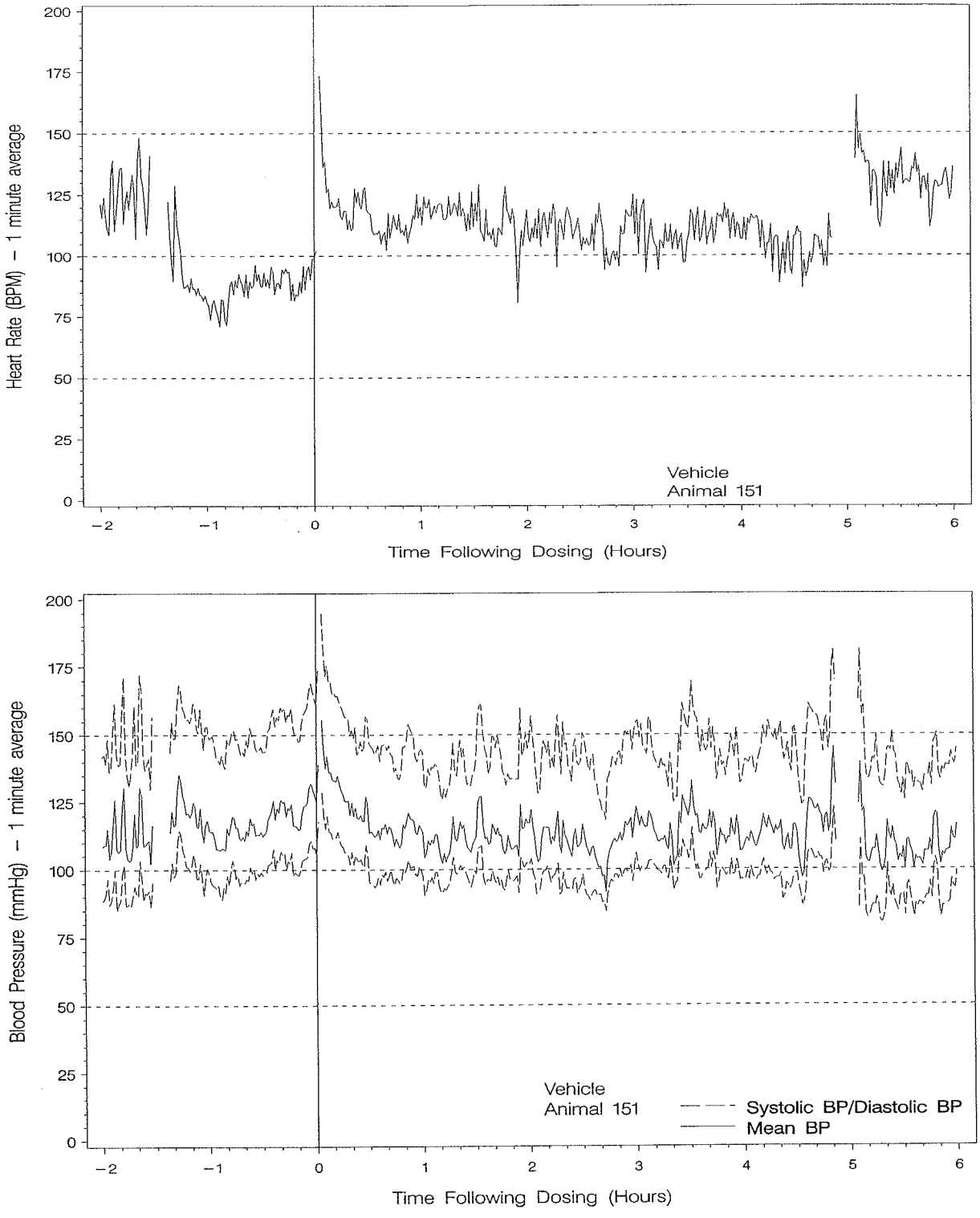


Figure 0-2c. 1-Minute Averages for Blood Pressure Parameters and Heart Rate for Animal 151

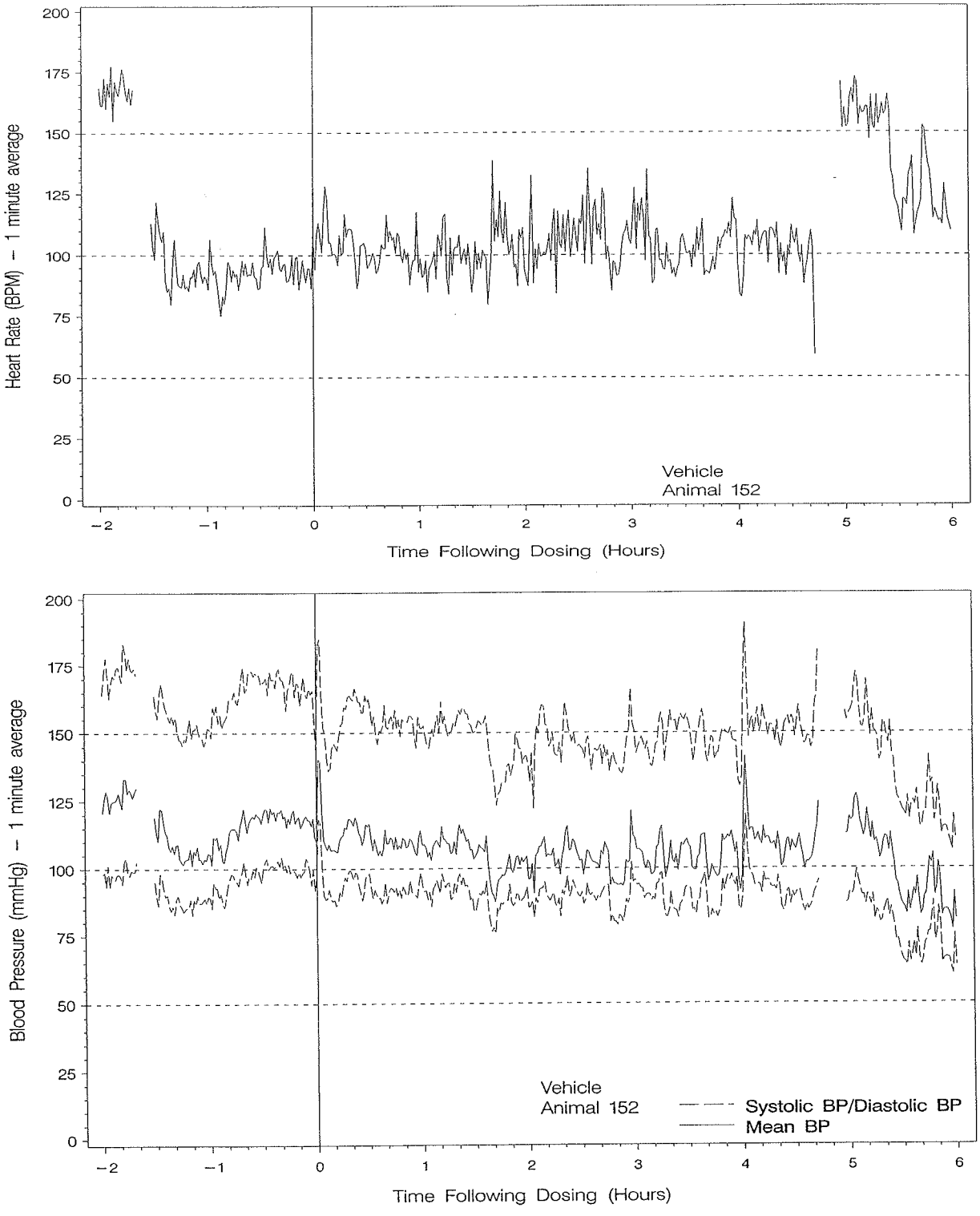


Figure 0-2d. 1-Minute Averages for Blood Pressure Parameters and Heart Rate for Animal 152

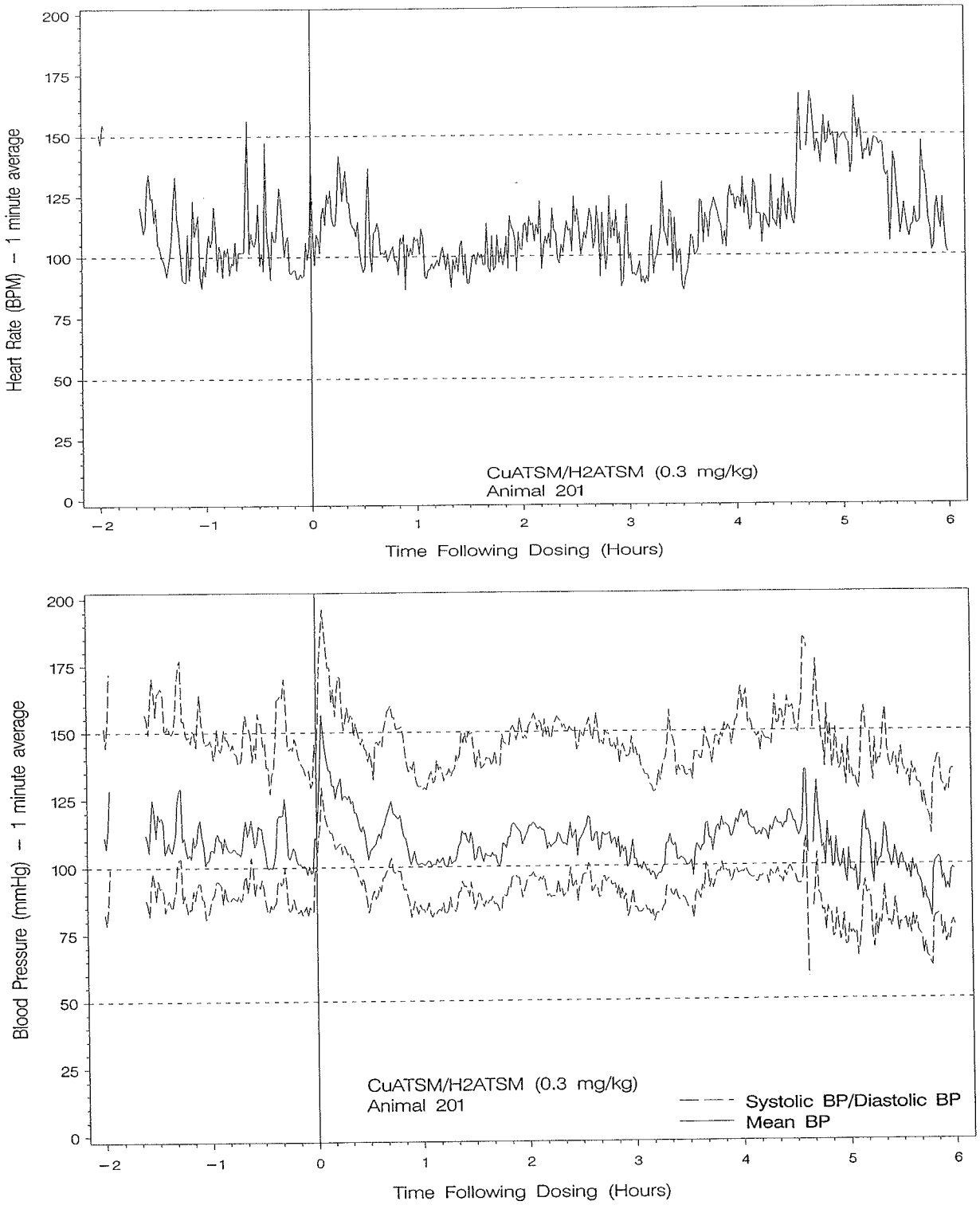


Figure 0-2e. 1-Minute Averages for Blood Pressure Parameters and Heart Rate for Animal 201

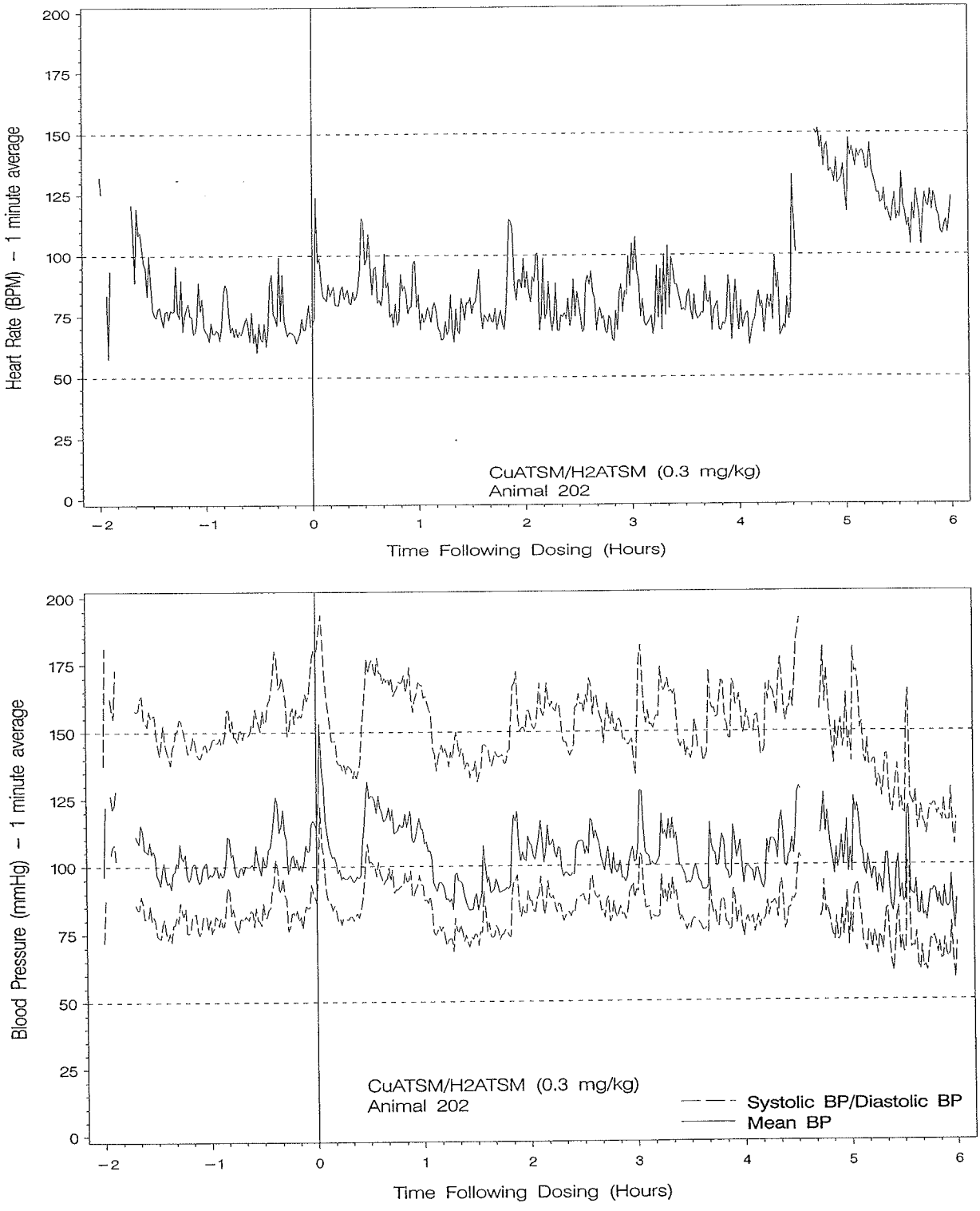


Figure 0-2f. 1-Minute Averages for Blood Pressure Parameters and Heart Rate for Animal 202

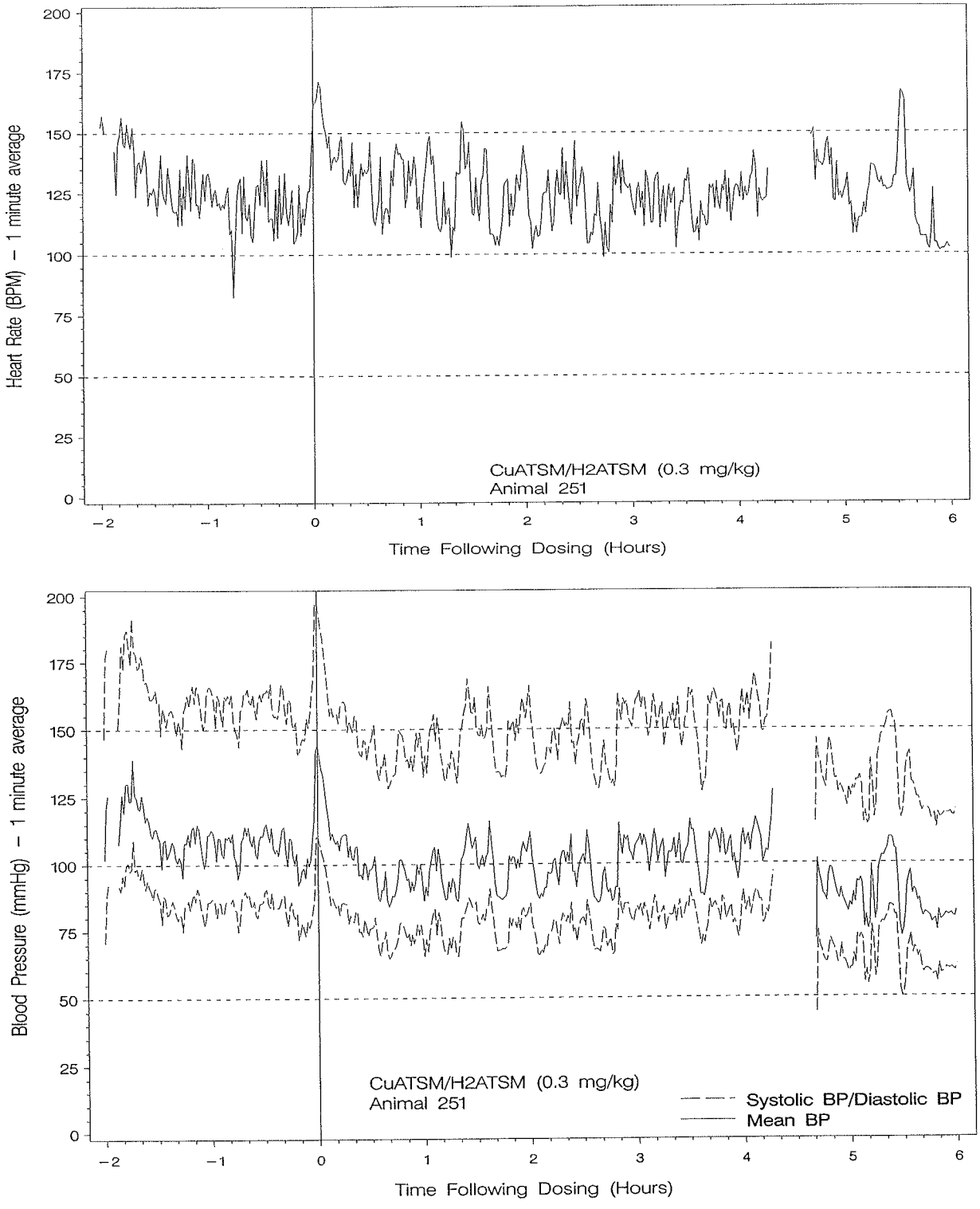


Figure 0-2g. 1-Minute Averages for Blood Pressure Parameters and Heart Rate for Animal 251

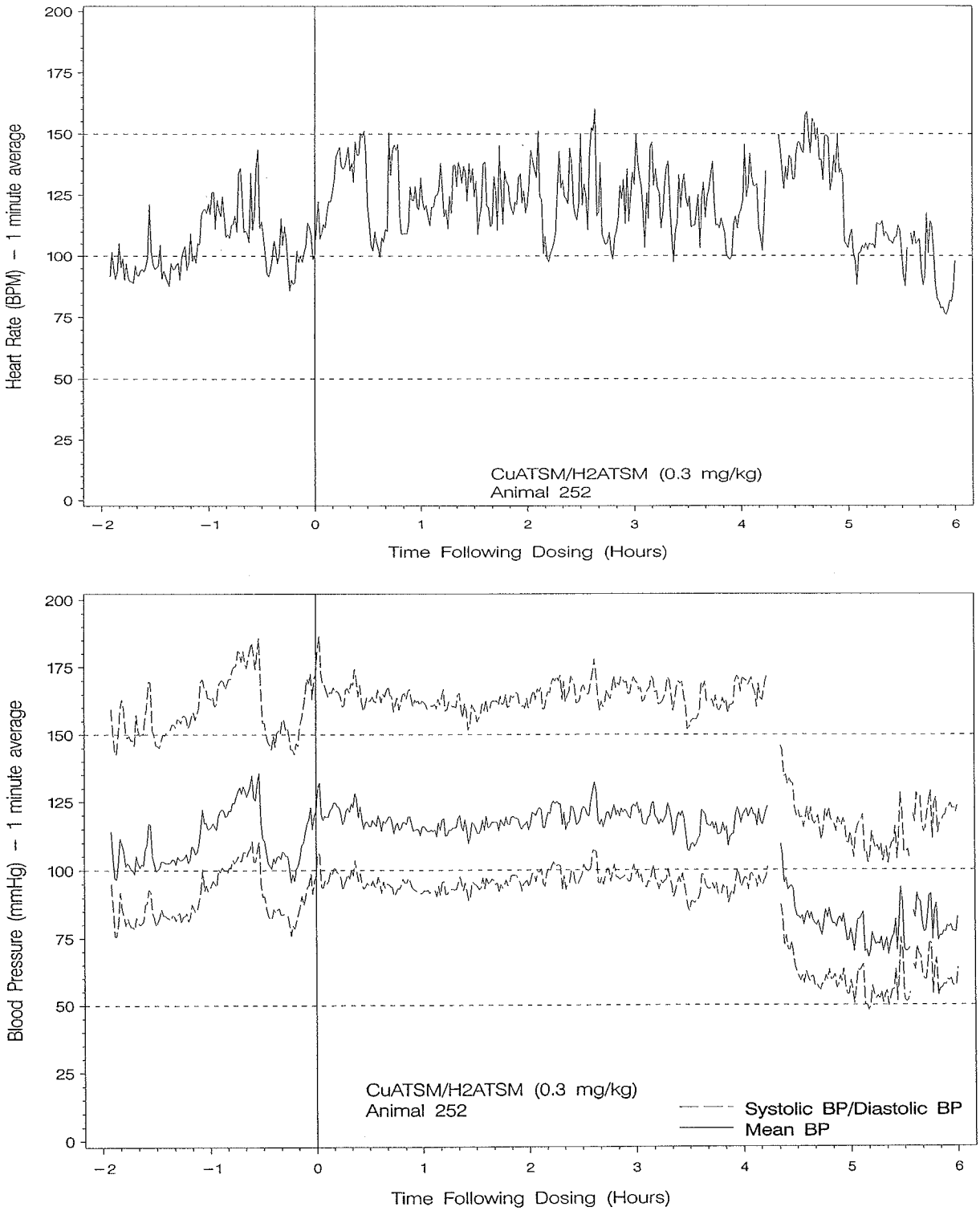


Figure 0-2h. 1-Minute Averages for Blood Pressure Parameters and Heart Rate for Animal 252

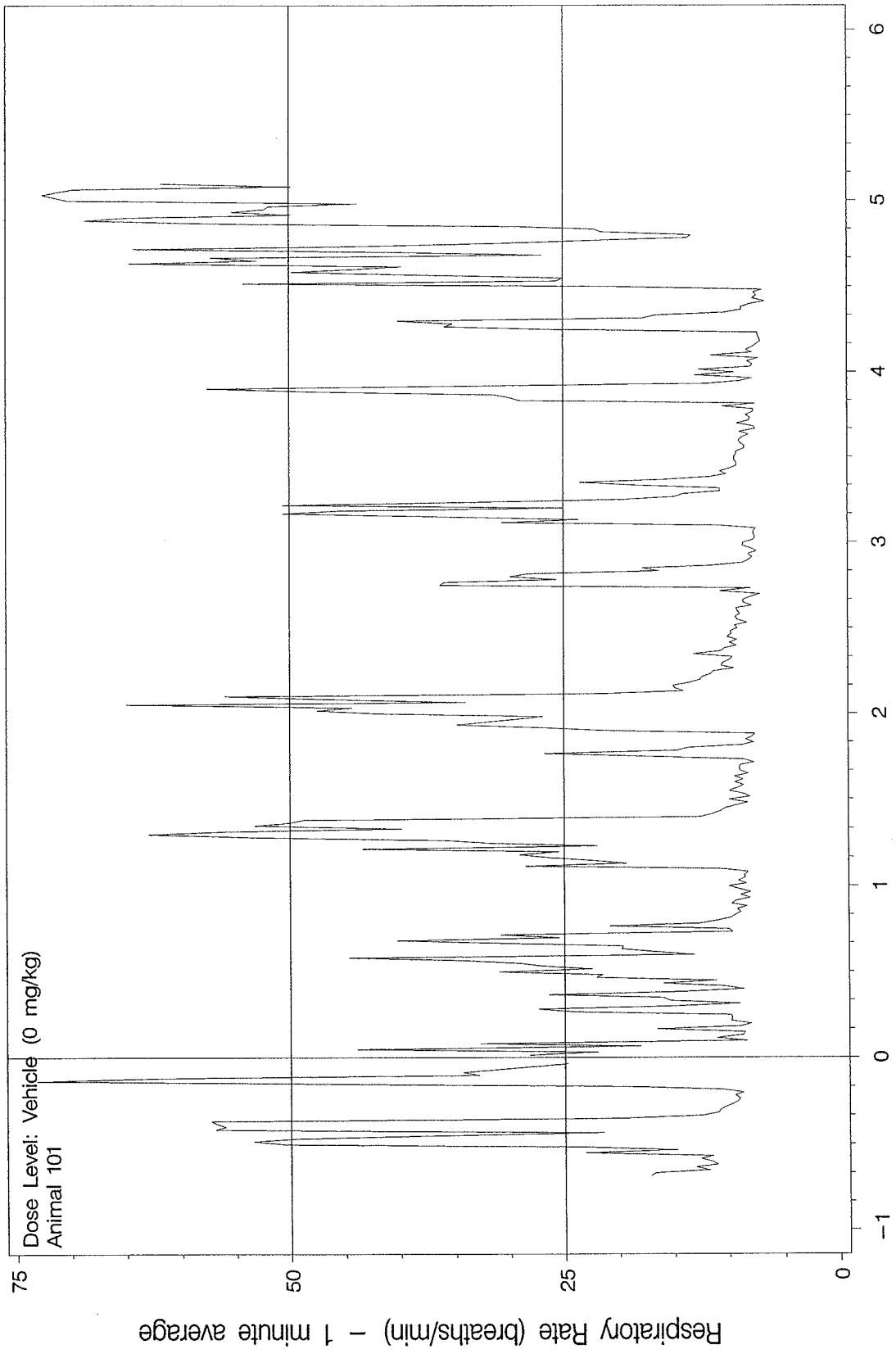


Figure 0-3a. Respiratory Rate (breaths/min): 1-Minute Averages for Animal No. 101

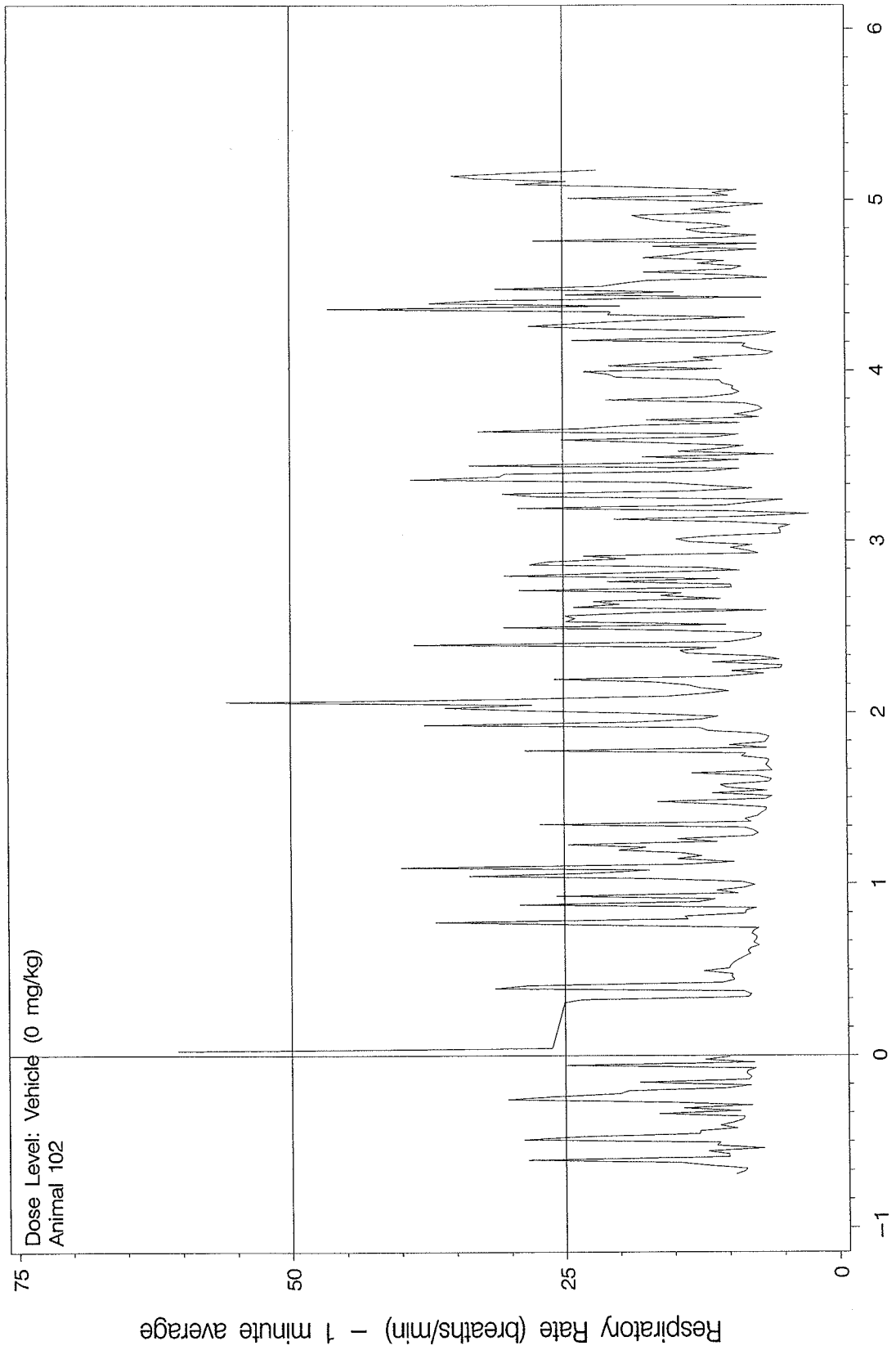


Figure 0-3b. Respiratory Rate (breaths/min): 1-Minute Averages for Animal No. 102

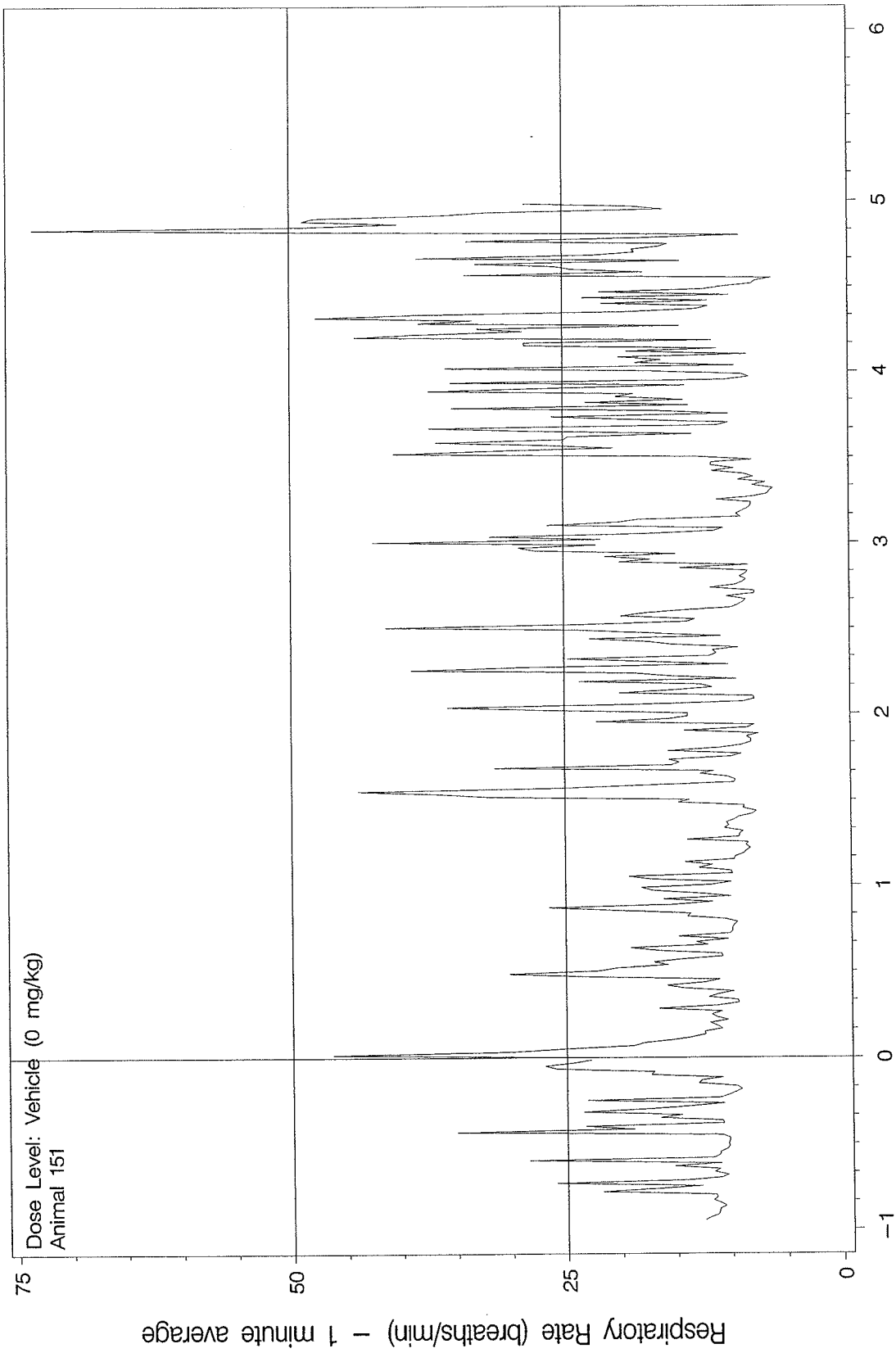


Figure 0-3c. Respiratory Rate (breaths/min): 1-Minute Averages for Animal No. 151

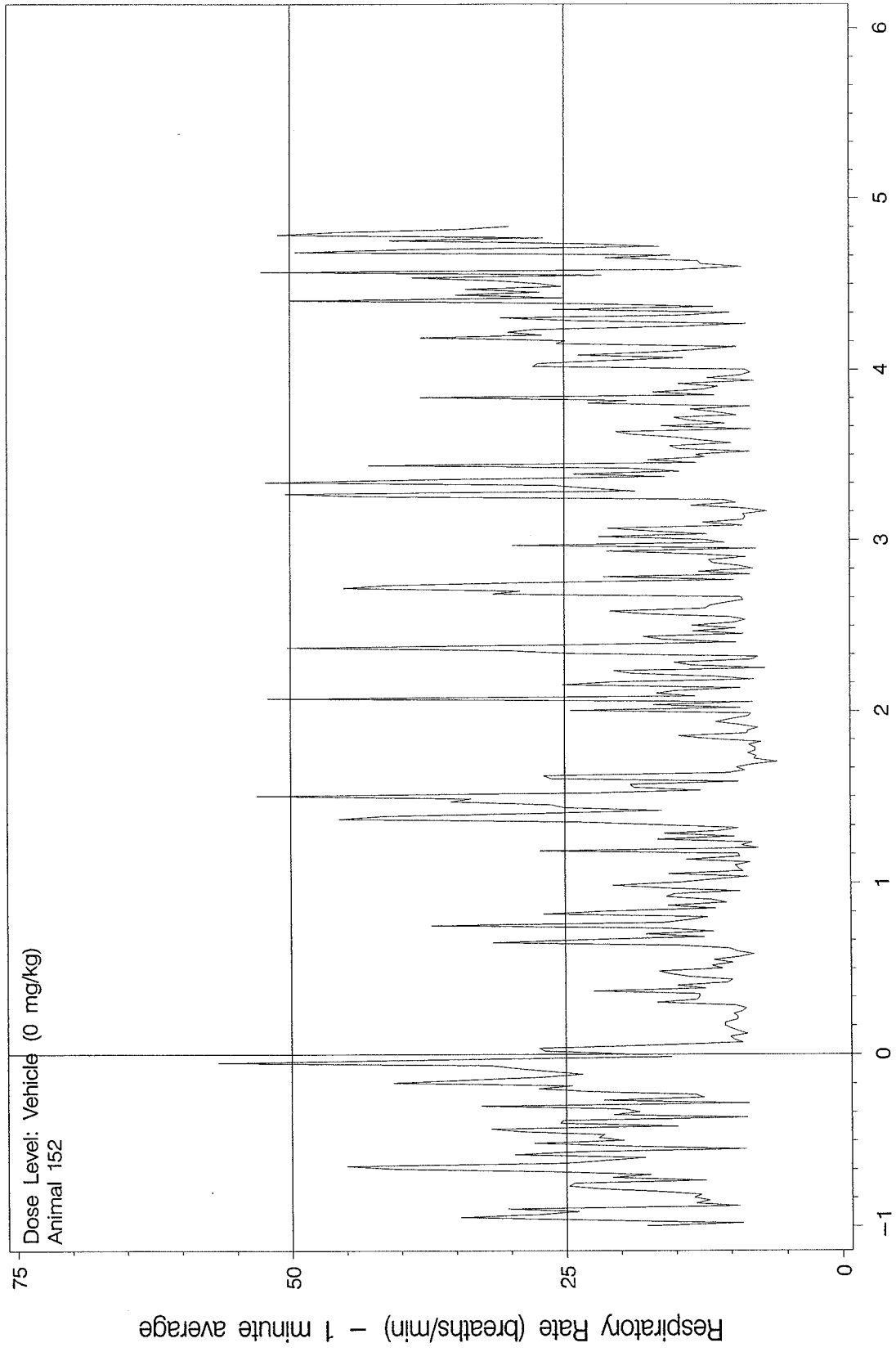


Figure 0-3d. Respiratory Rate (breaths/min): 1-Minute Averages for Animal No. 152

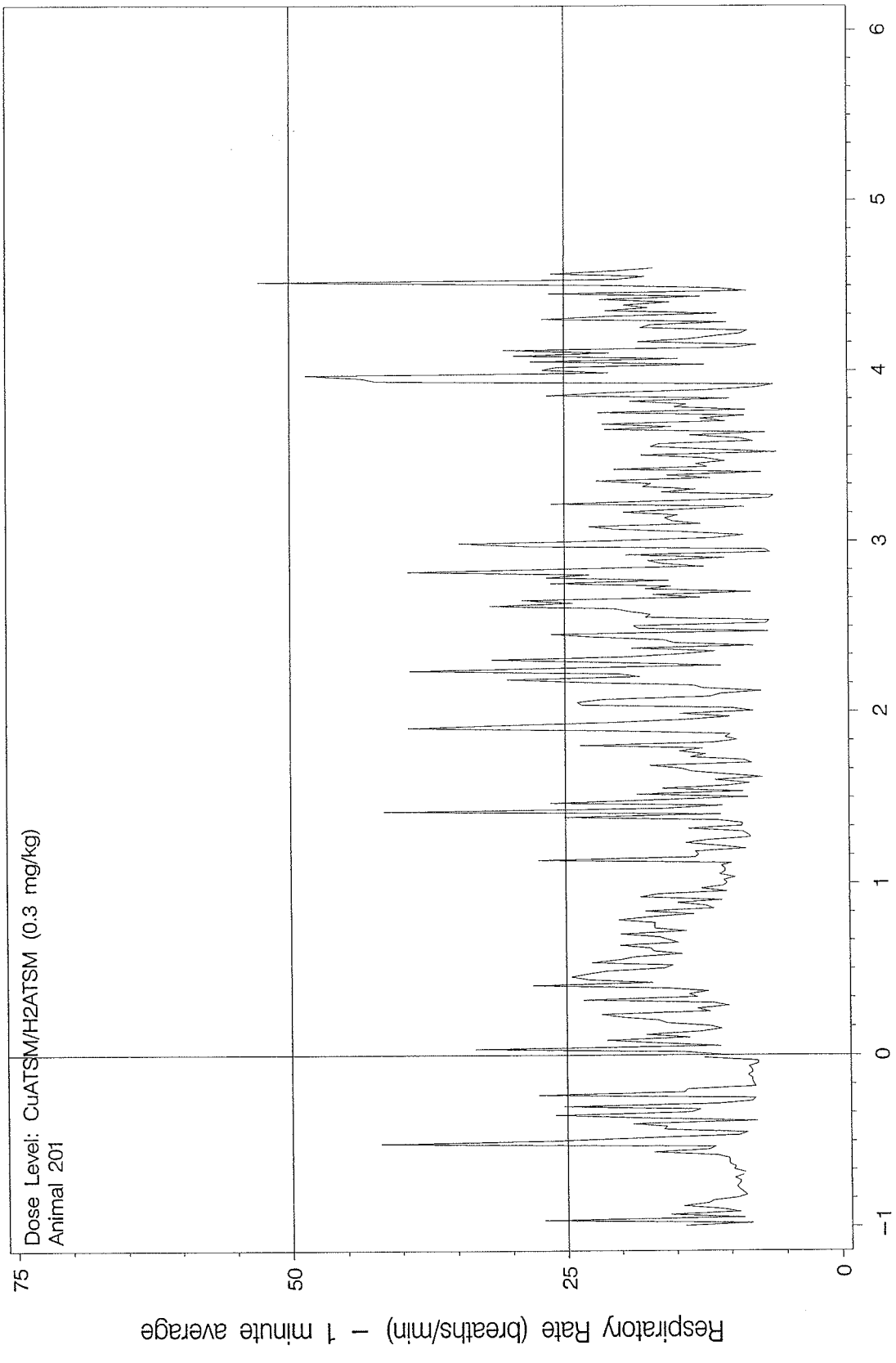


Figure 0-3e. Respiratory Rate (breaths/min): 1-Minute Averages for Animal No. 201

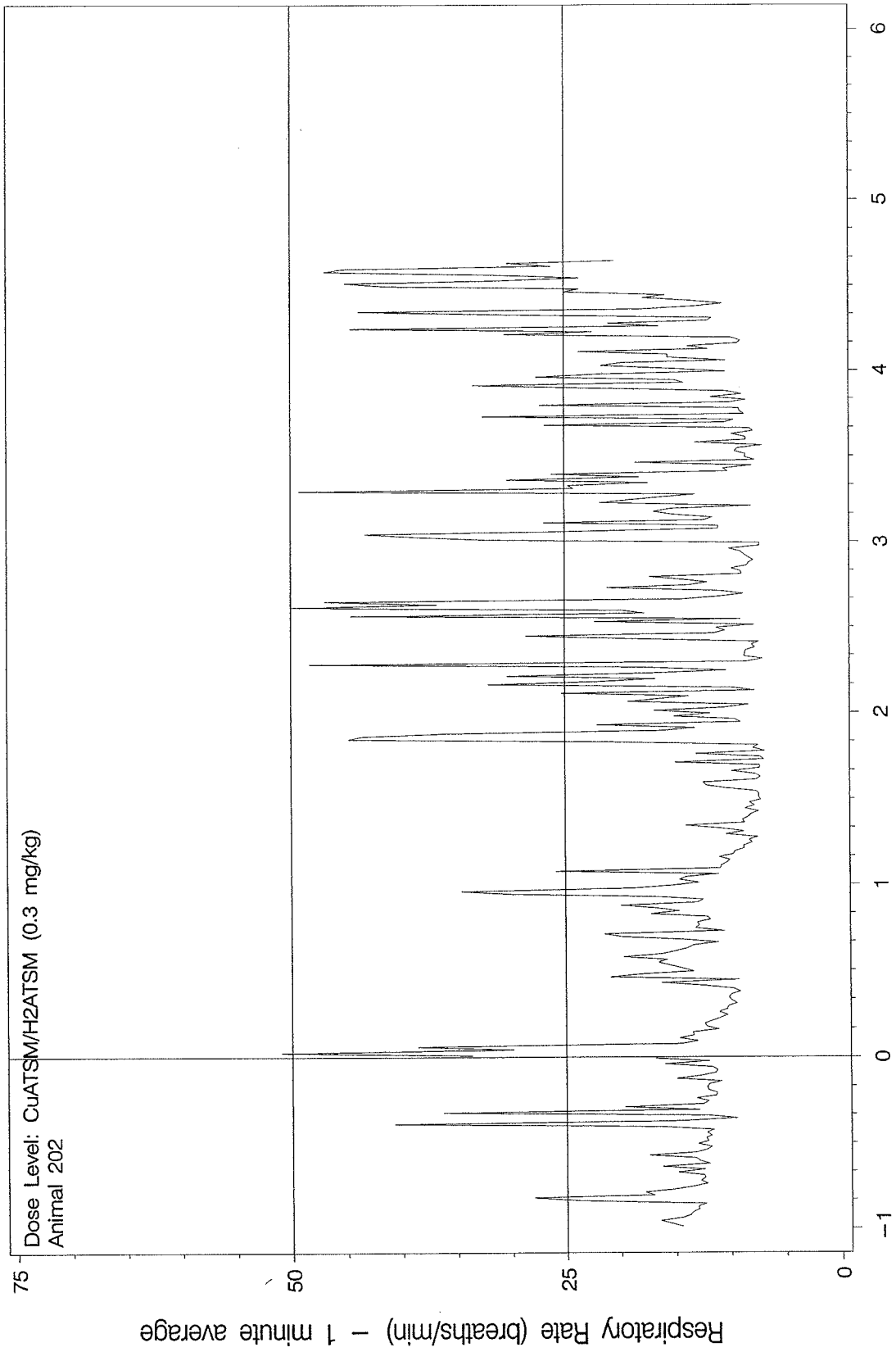


Figure 0-3f. Respiratory Rate (breaths/min): 1-Minute Averages for Animal No. 202

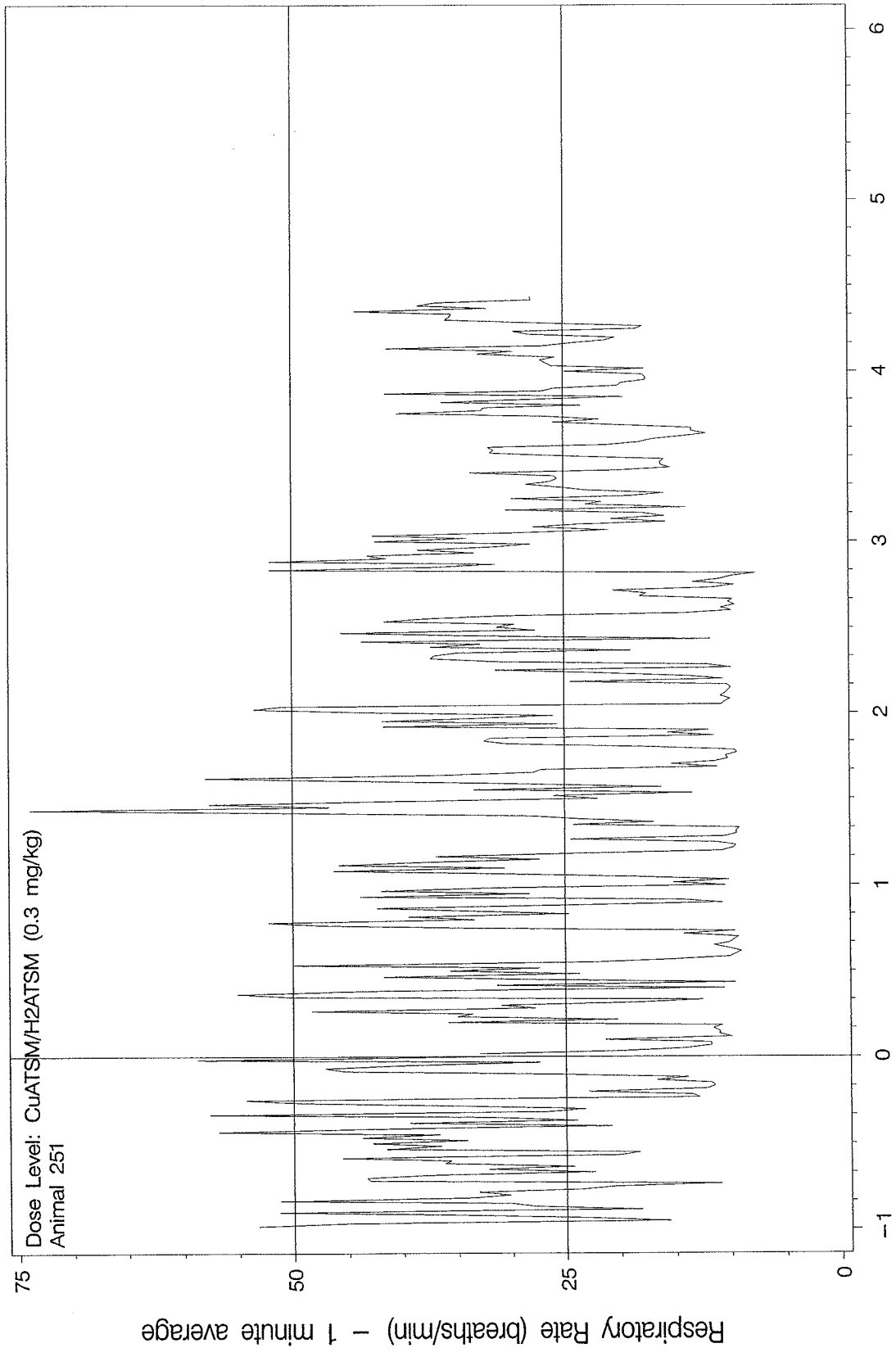


Figure 0-3g. Respiratory Rate (breaths/min): 1-Minute Averages for Animal No. 251

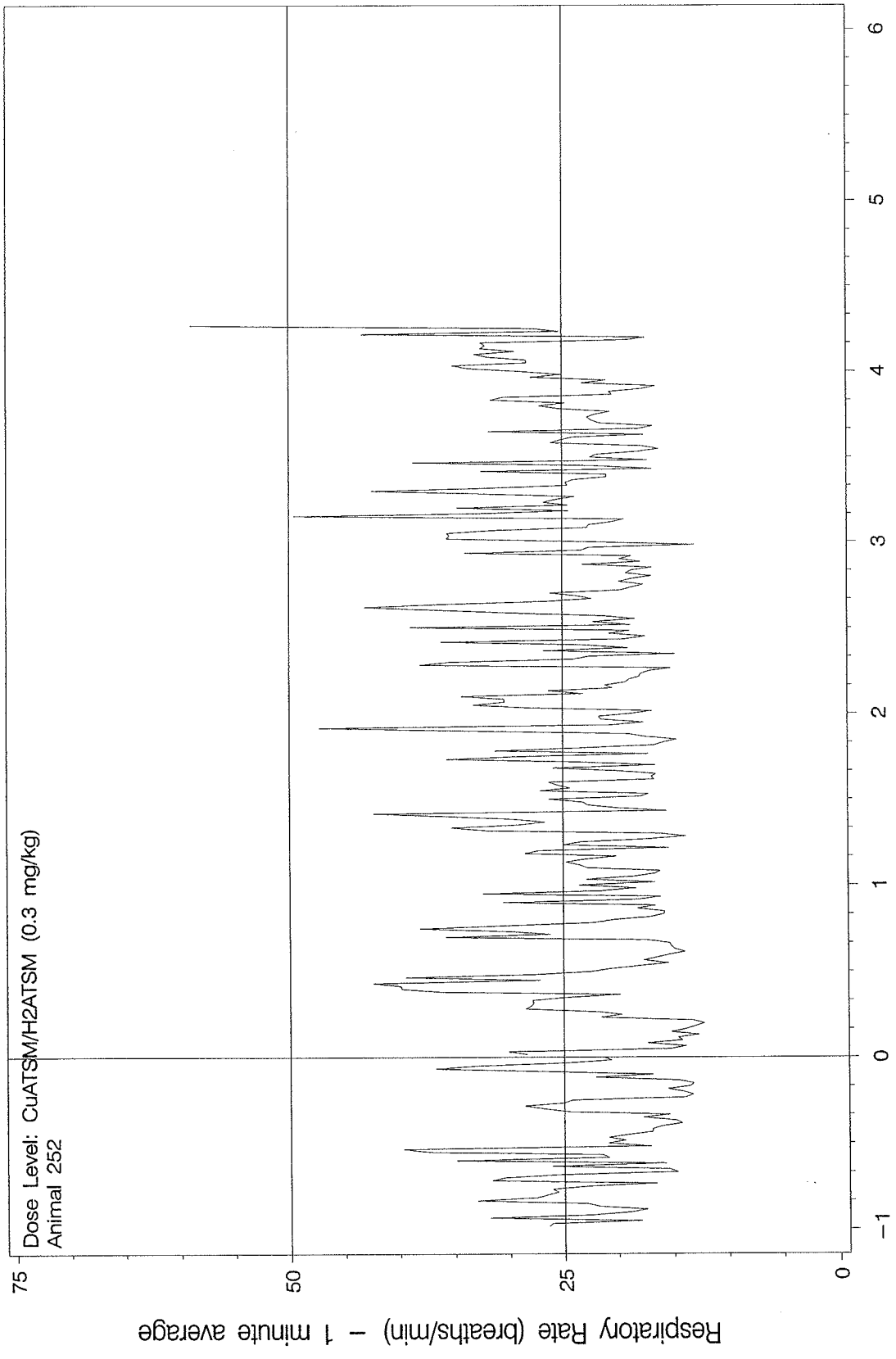


Figure 0-3h. Respiratory Rate (breaths/min): 1-Minute Averages for Animal No. 252

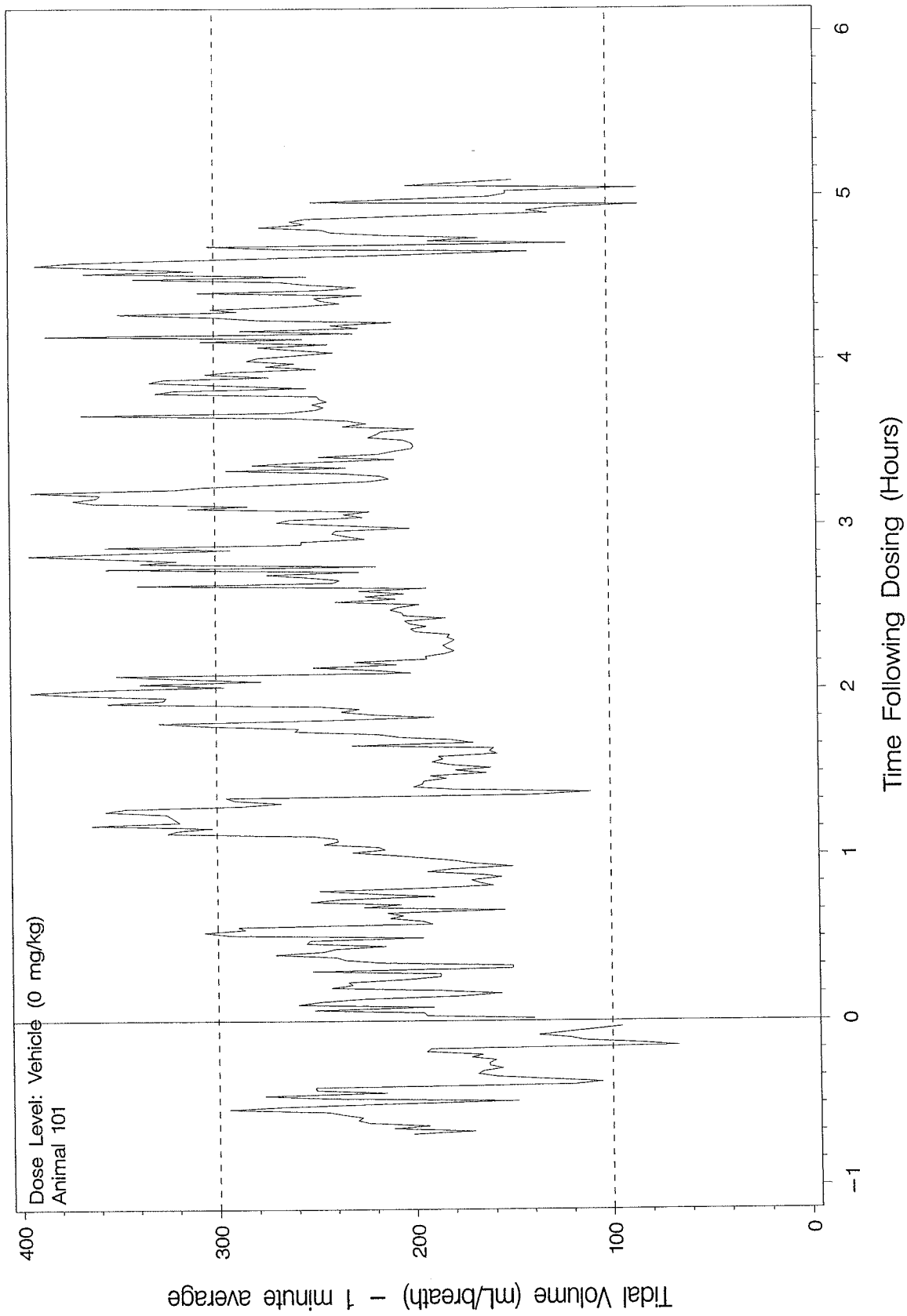


Figure 0-4a. Tidal Volume (mL/breath): 1-Minute Averages for Animal No. 101

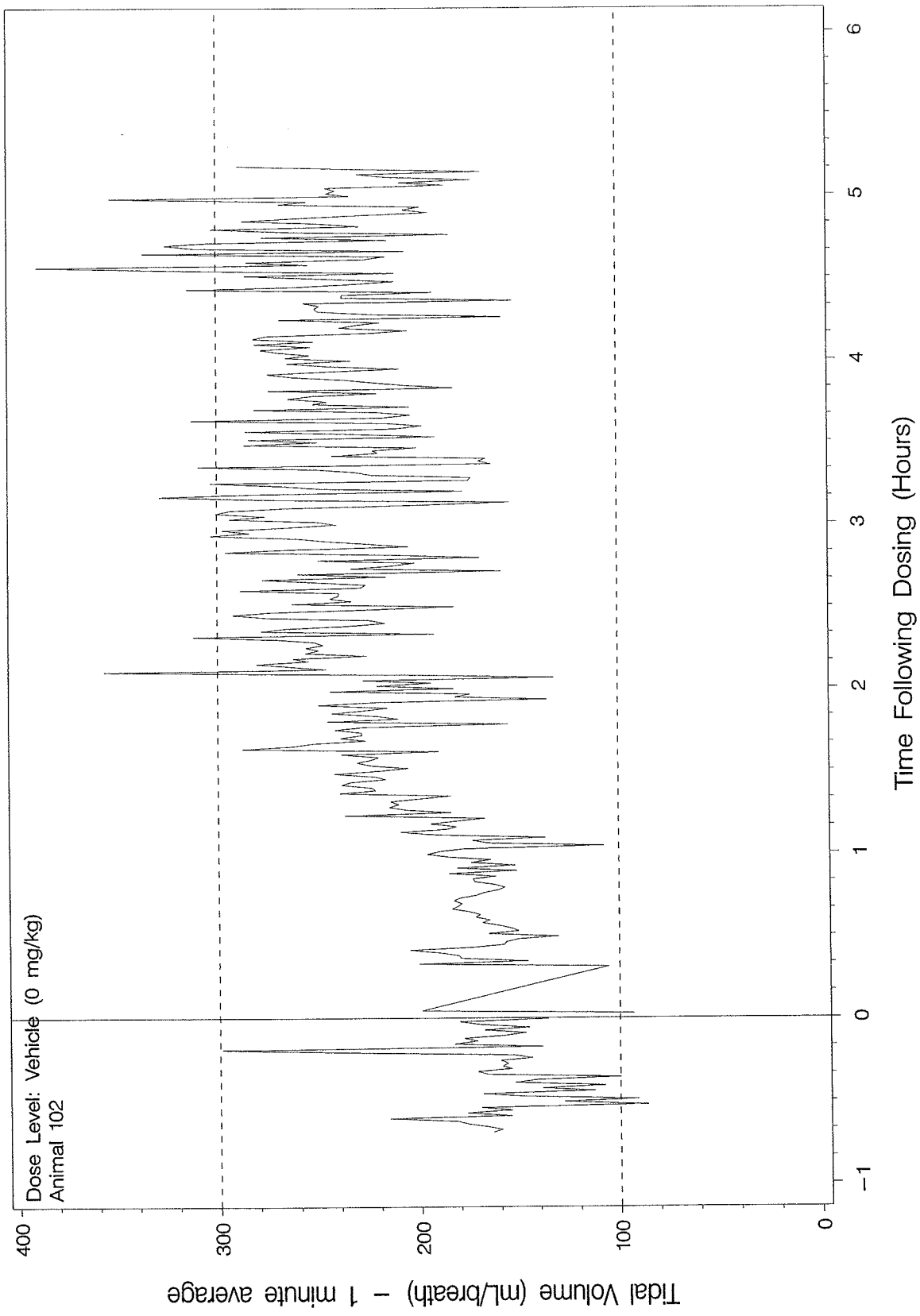


Figure 0-4b. Tidal Volume (mL/breath): 1-Minute Averages for Animal No. 102

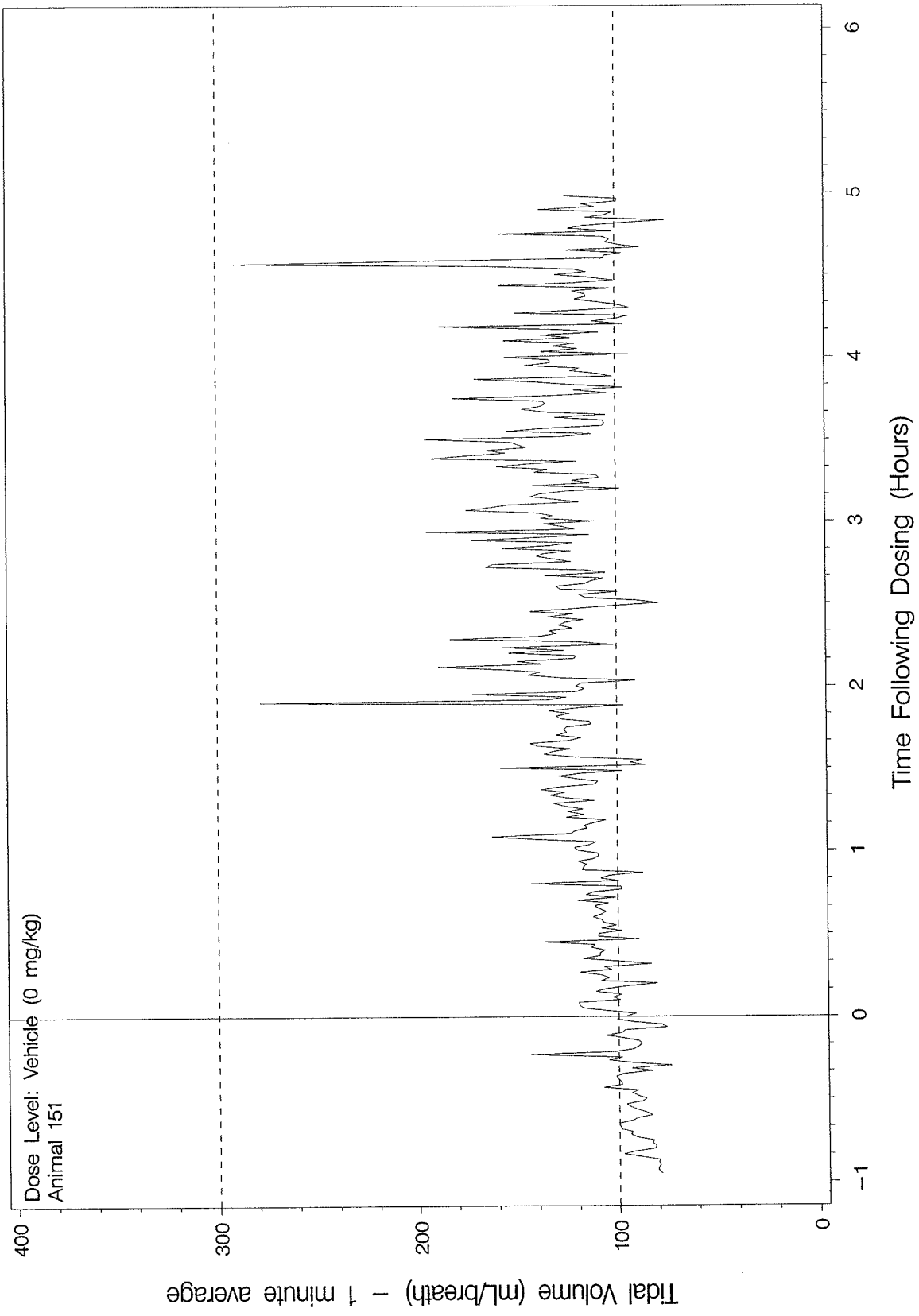


Figure 0-4c. Tidal Volume (mL/breath): 1-Minute Averages for Animal No. 151

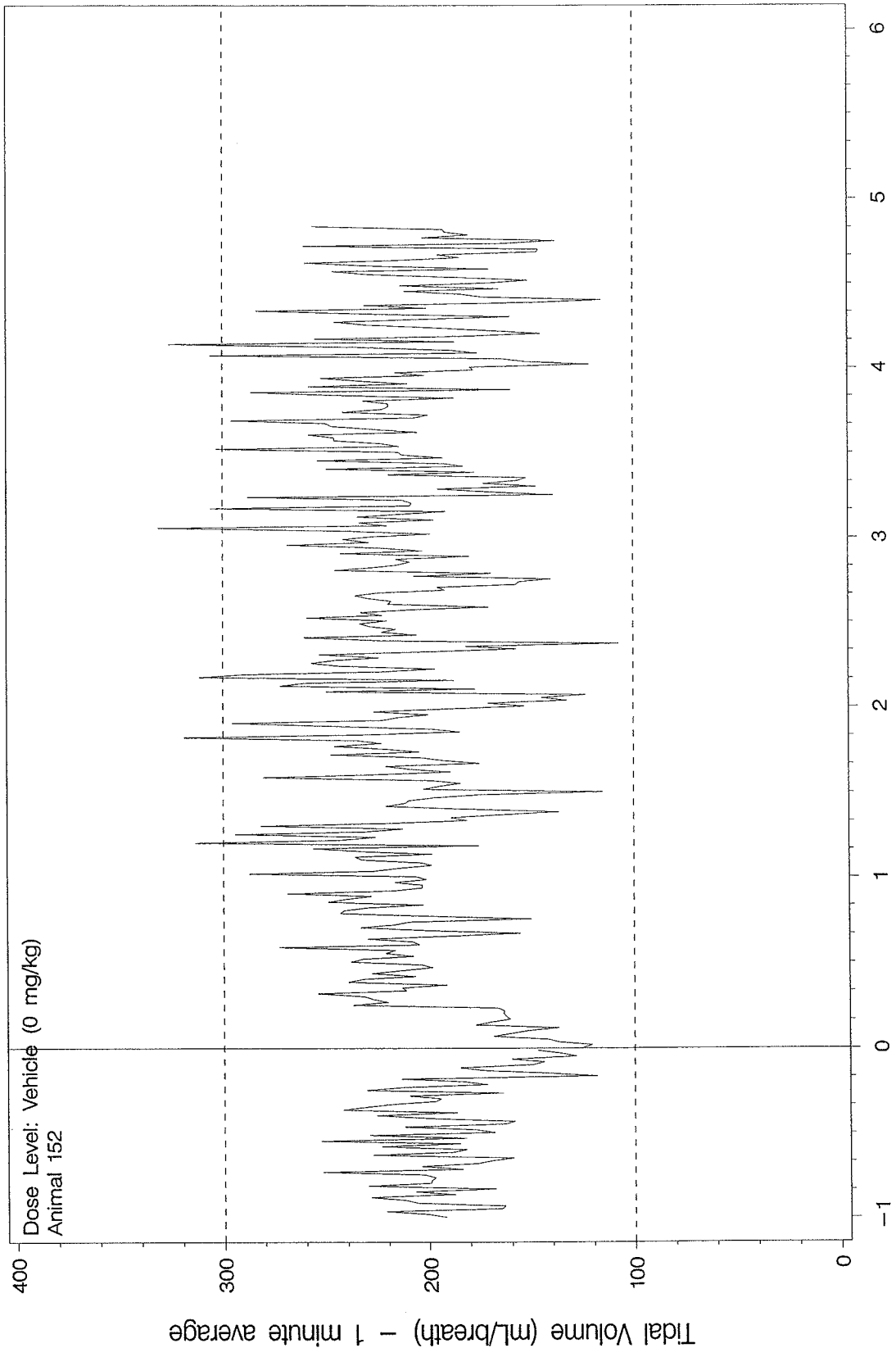


Figure 0-4d. Tidal Volume (mL/breath): 1-Minute Averages for Animal No. 152

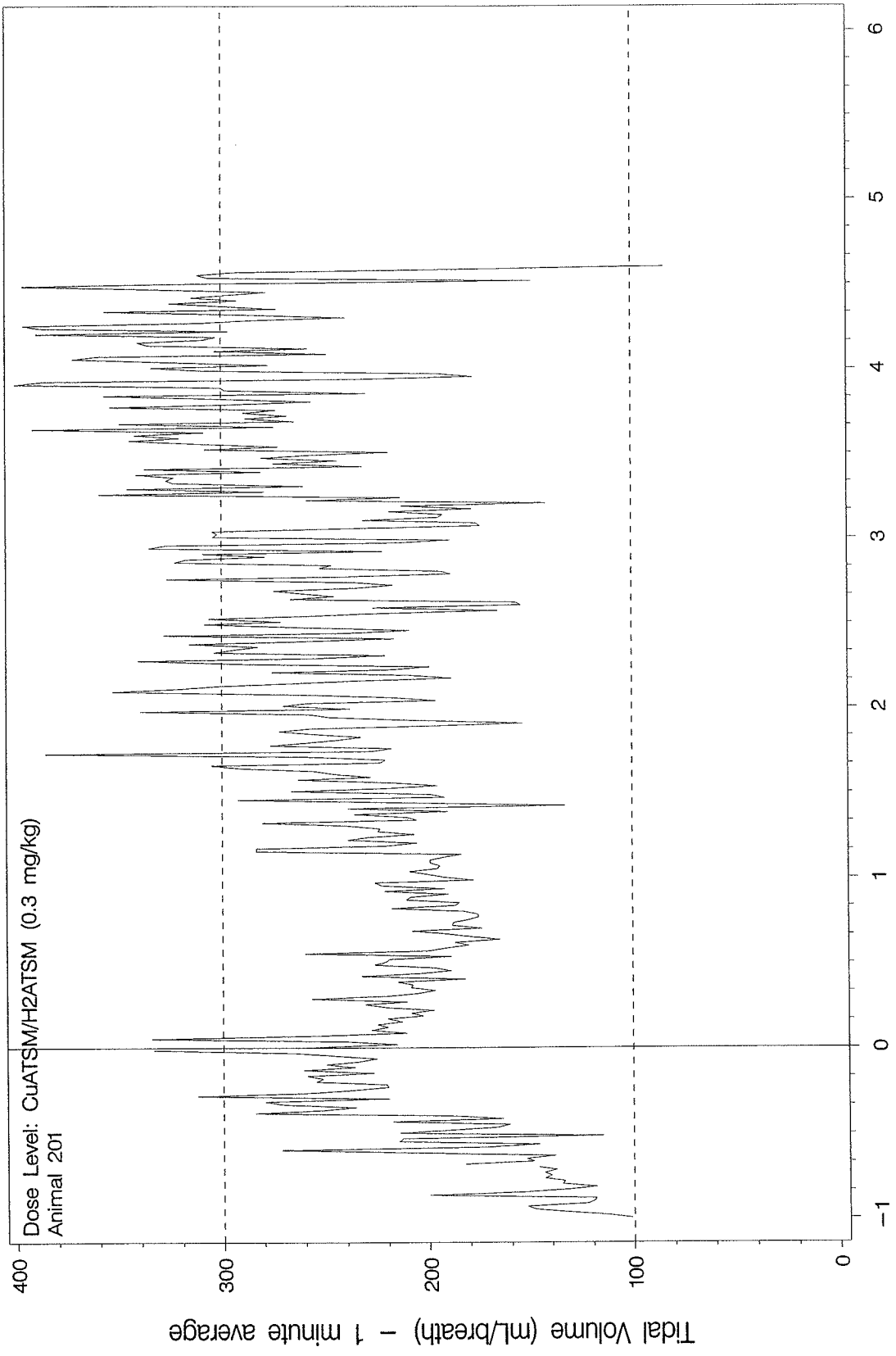


Figure 0-4e. Tidal Volume (mL/breath): 1-Minute Averages for Animal No. 201

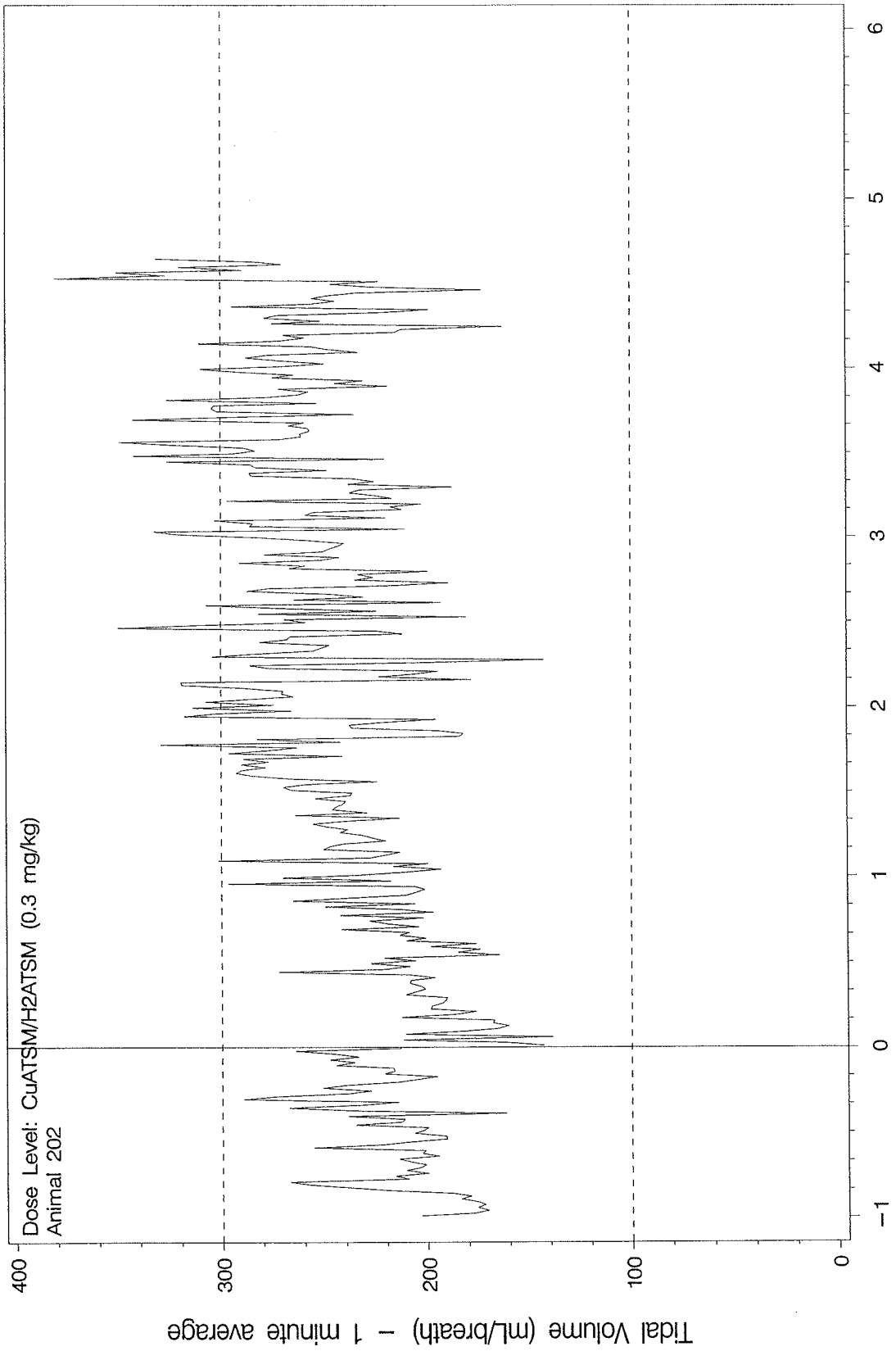


Figure 0-4f. Tidal Volume (mL/breath): 1-Minute Averages for Animal No. 202

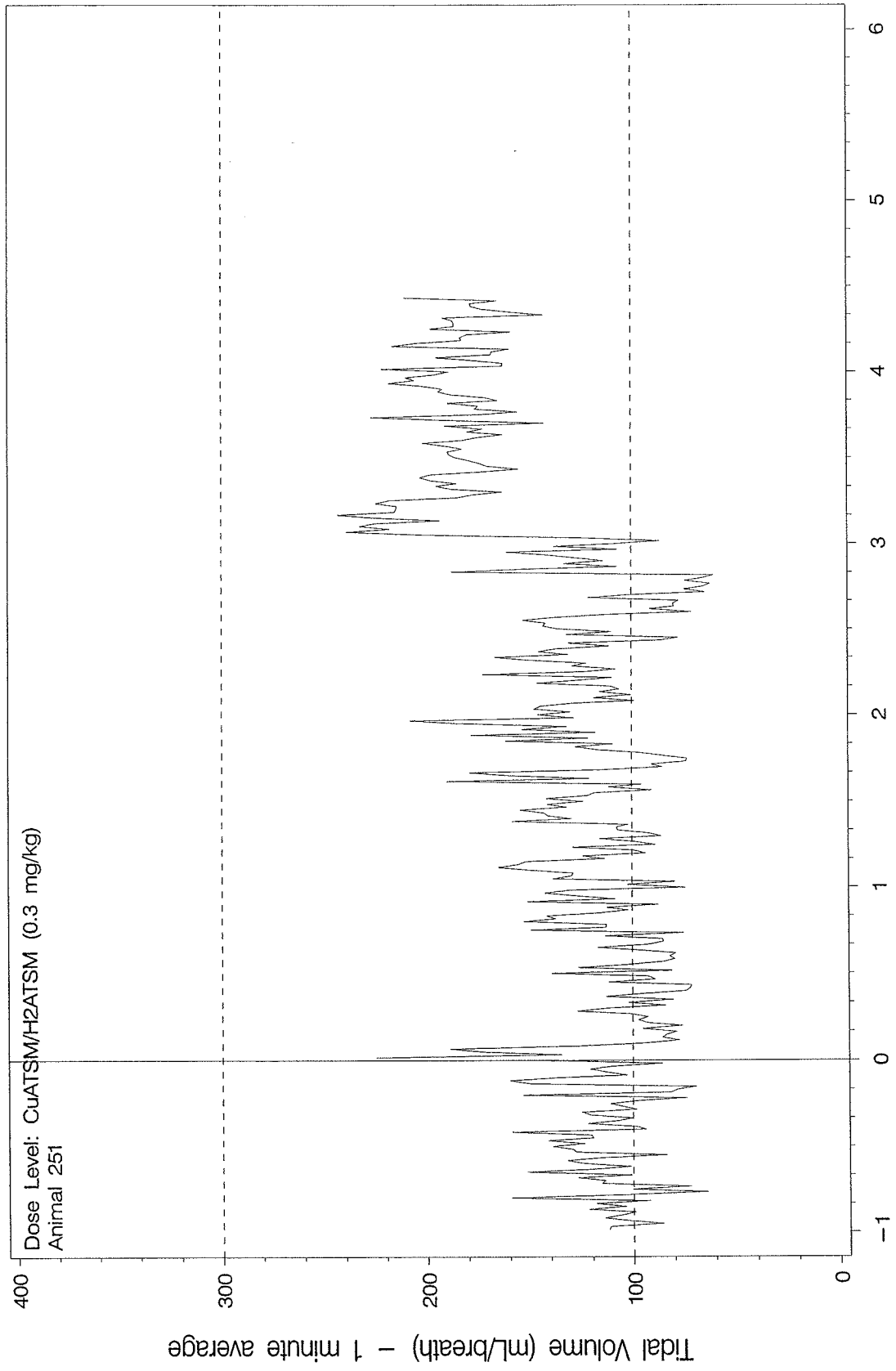


Figure 0-4g. Tidal Volume (mL/breath): 1-Minute Averages for Animal No. 251

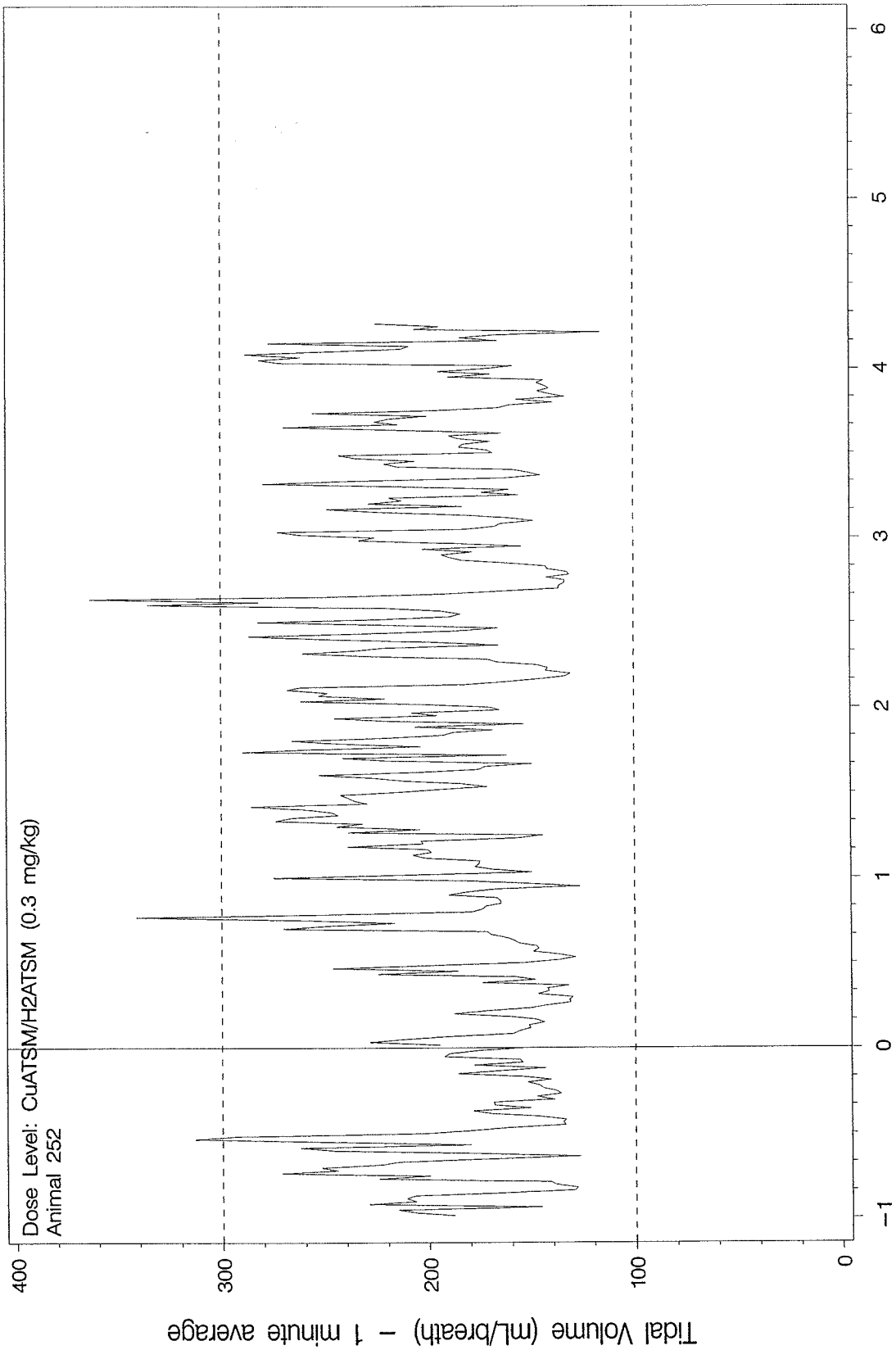


Figure 0-4h. Tidal Volume (mL/breath): 1-Minute Averages for Animal No. 252

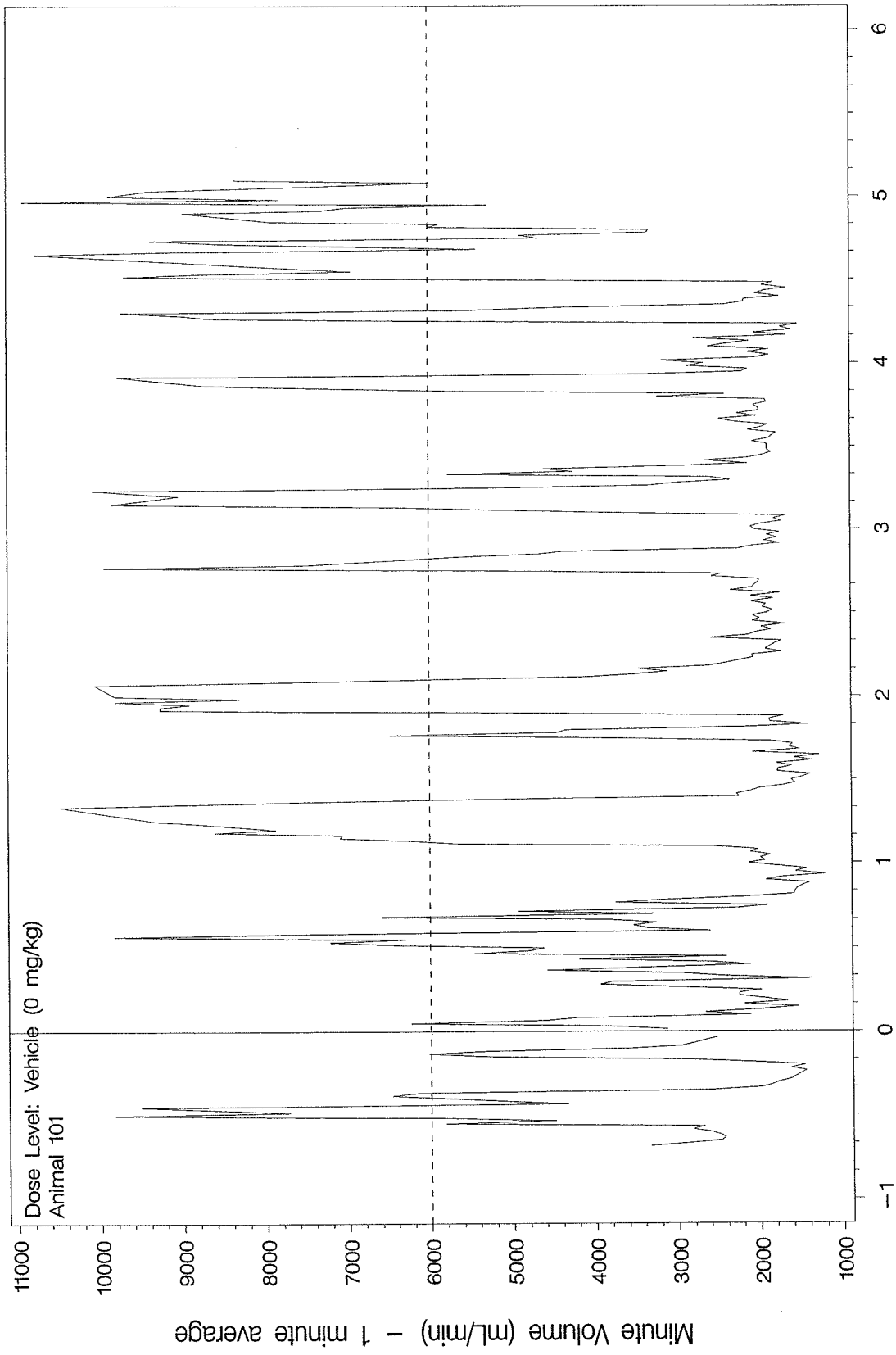


Figure 0-5a. Minute Volume (mL/min): 1-Minute Averages for Animal No. 101

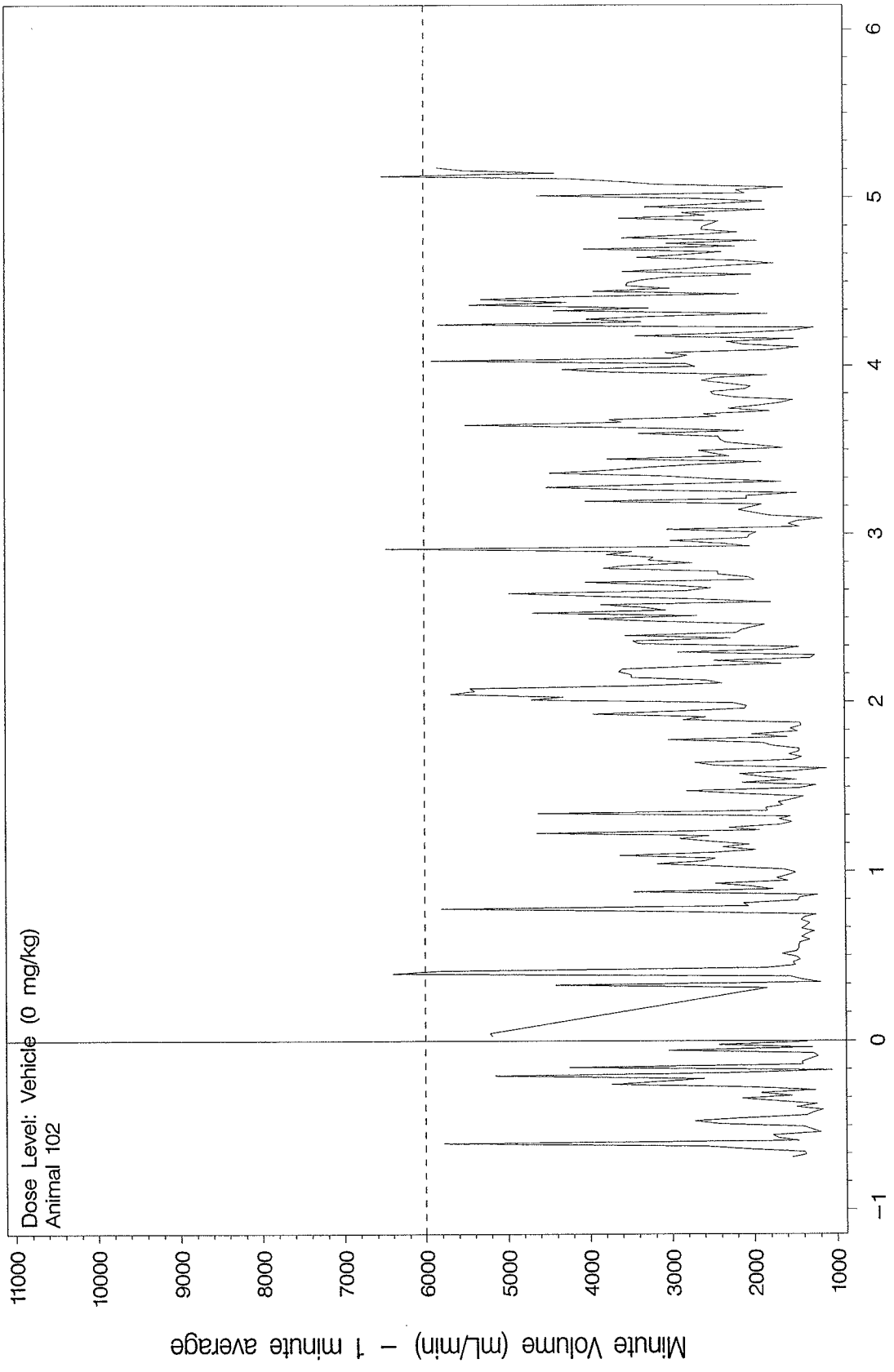


Figure 0-5b. Minute Volume (mL/min): 1-Minute Averages for Animal No. 102

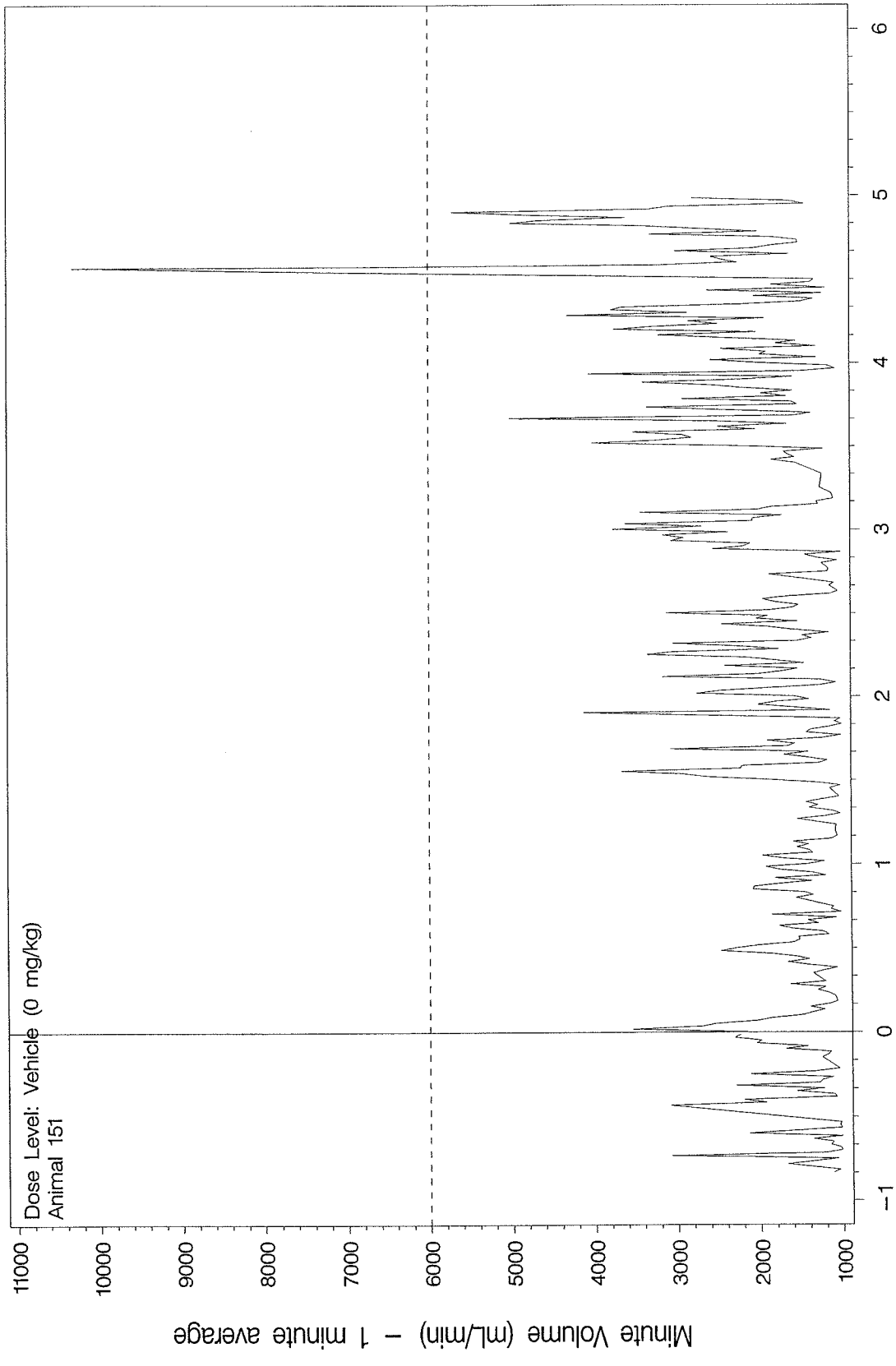


Figure 0-5c. Minute Volume (mL/min): 1-Minute Averages for Animal No. 151

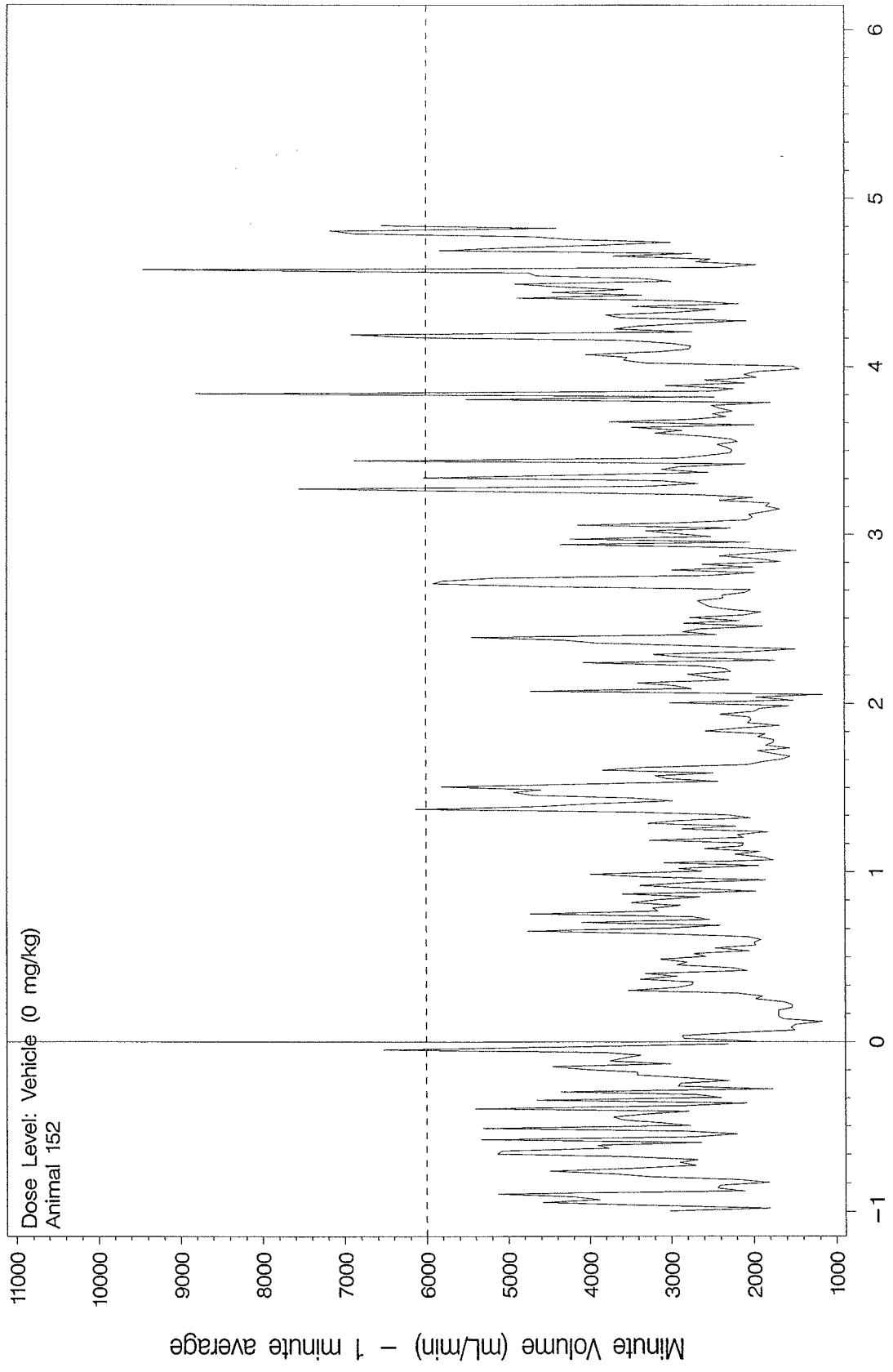


Figure 0-5d. Minute Volume (mL/min): 1-Minute Averages for Animal No. 152

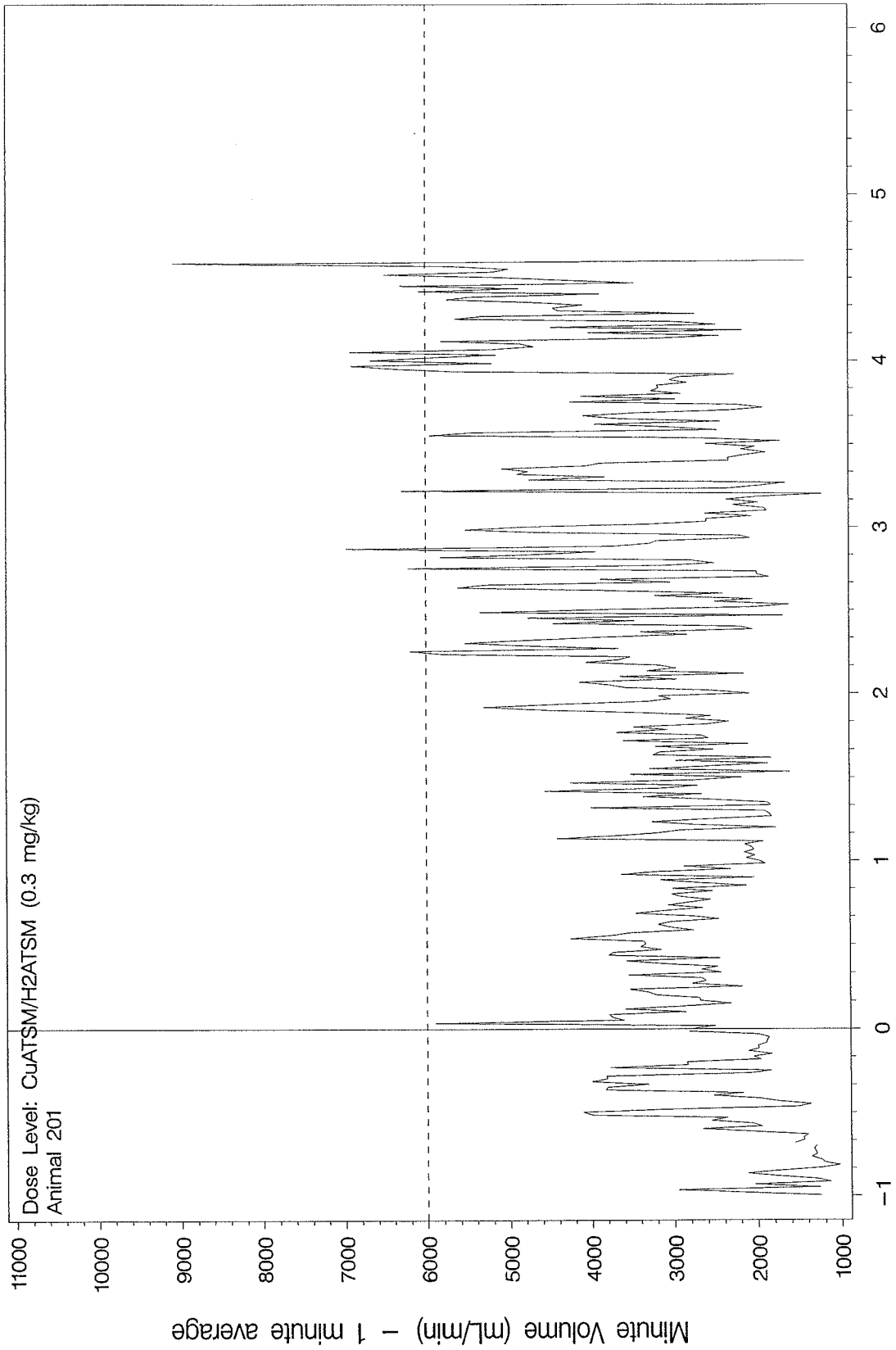


Figure 0-5e. Minute Volume (mL/min): 1-Minute Averages for Animal No. 201

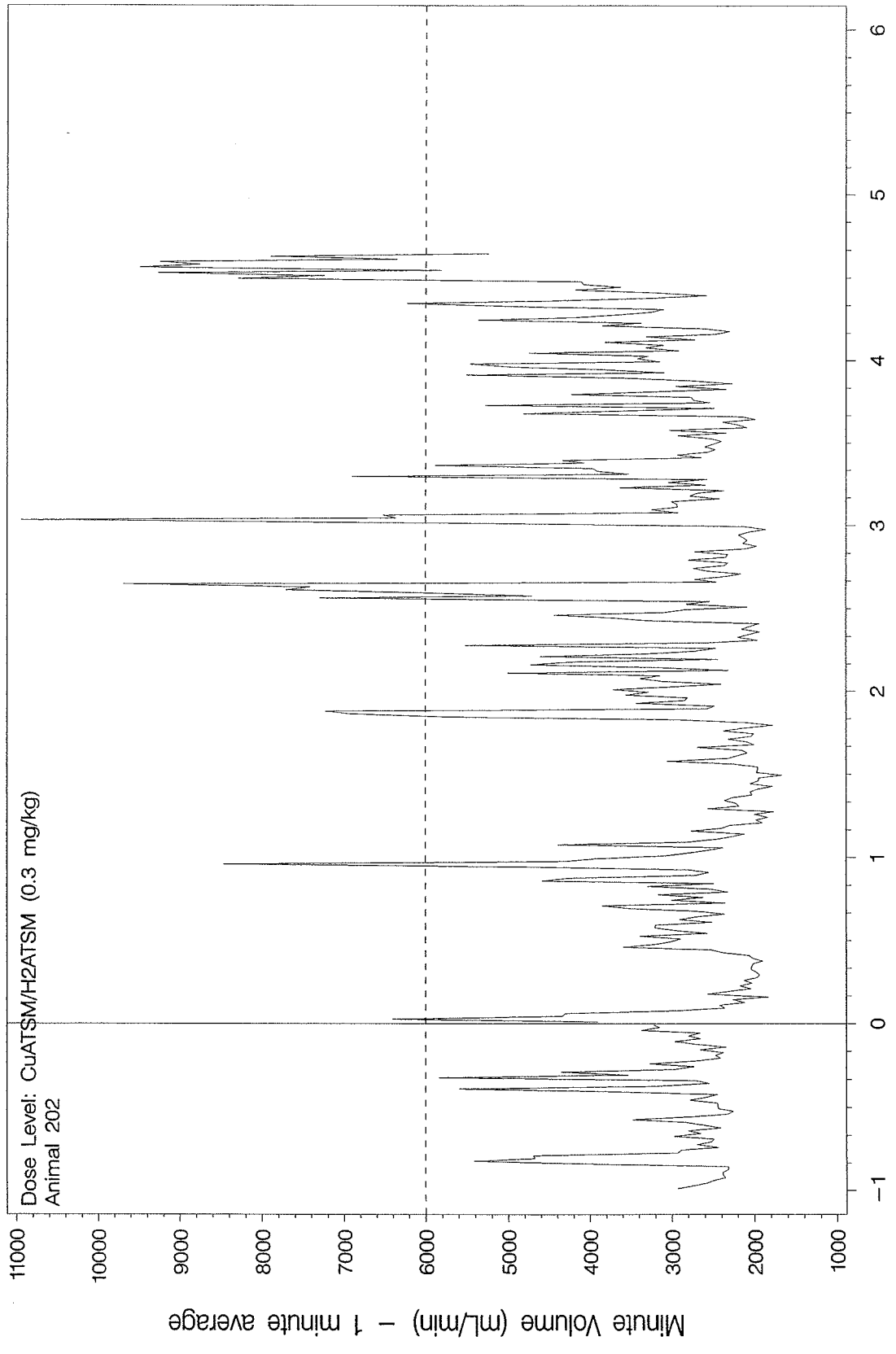


Figure 0-5f. Minute Volume (mL/min): 1-Minute Averages for Animal No. 202

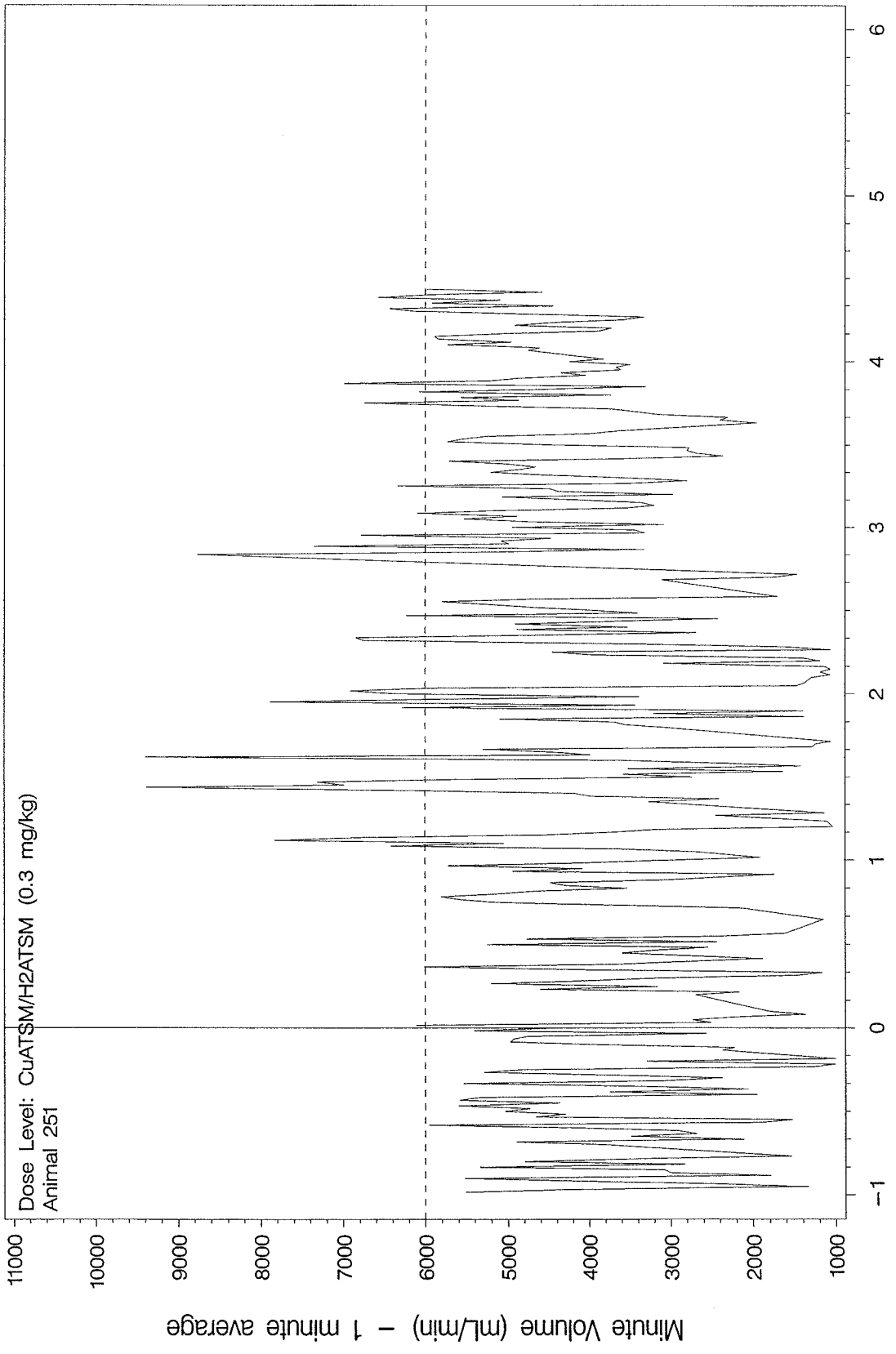


Figure 0-5g. Minute Volume (mL/min): 1-Minute Averages for Animal No. 251

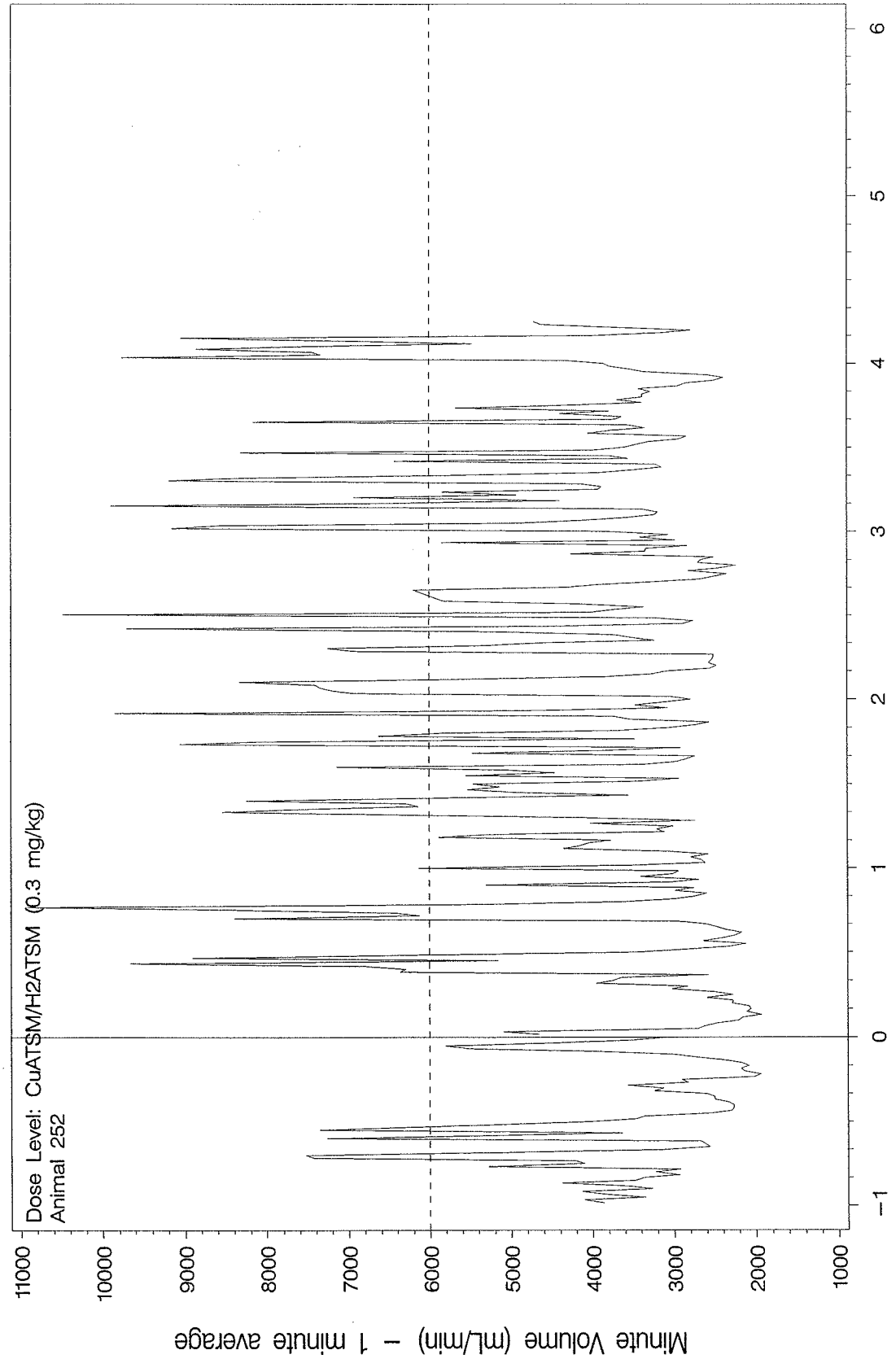


Figure 0-5h. Minute Volume (mL/min): 1-Minute Averages for Animal No. 252

APPENDIX E

QUALITATIVE ECG EVALUATION

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March 30, 2004

Dr. Craig R. Hassler
Battelle Memorial Institute
505 King Avenue
Columbus, Ohio 43201

RE: Qualitative ECG Evaluation for Dogs on Battelle Study Number G465535A

All ECG waveforms are within normal limits. A number of traces show changes in heart rates or in configurations of components deflections. These changes did not appear to be test-article related. Additionally, several traces contained high frequency artifacts but these did not interfere with their interpretations.

There appeared to be no electrocardiographic changes that could be attributed to the test article.

Sincerely,

Robert L. Hamlin, D.V.M., Ph.D., D.A.C.V.I.M.
(Cardiology/Internal Medicine)

3-30-04
Date