Defense Centers for Public Health - Aberdeen

8300 Ricketts Point Road, Aberdeen Proving Ground, Maryland 21010-5403

Toxicology Study No. S.0082641-21, May 2024

Subchronic Oral Toxicity of 1,1-Diamino-2,2-Dinitroethene (FOX-7) in Rats

Prepared by: Lee C.B. Crouse, Meredith E. Bohannon, Blas A. Guigni, Matthew A. Bazar, and Taryn K. Brown

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the support of David Kurk of the Laboratory Sciences Directorate, Defense Centers for Public Health–Aberdeen, as well as Benedict Arrey and Sylvestre Dossou, formerly of the Laboratory Sciences Directorate, for their efforts in analyzing the dosing suspensions used for this study. We would also like to thank Alicia Shiflett and Shannon Rodriguez, Office of Toxicologic Pathology, for their efforts in necropsy and tissue processing.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
08-05-2024	Technical Report	August 2019 - November 2021

4. TITLE AND SUBTITLE

Subchronic Oral Toxicity of 1,1-Diamino-2,2-Dinitroethene (FOX-7) in Rats

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Lee C.B. Crouse, Meredith E. Bohannon, Blas A. Guigni, Matthew A. Bazar, and Taryn K. Brown

5d. PROJECT NUMBER

S.0082641-21

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Defense Centers for Public Health-Aberdeen
Toxicology Directorate (DCPH-ATS-TOX)
8988 Willoughby Road (E2100)
Aberdeen Proving Ground, MD 21010-5403

8. PERFORMING ORGANIZATION REPORT NUMBER

S.0082641-21

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

Director, Safer Alternatives for Readiness Program (SAFR/Kimberly Watts)
U.S. Army Combat Capabilities Development Command
3072 Aberdeen Blvd.
Aberdeen Proving Ground, MD 21005-5201

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT

Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The acute oral median lethal dose of 1,1-diamino-2,2-dinitroethene (FOX-7) was 875 mg/kg in male rats and 805 mg/kg in female rats. Subacute administration of FOX-7 resulted in 100% mortality at doses ≥200 mg/kg-d within 1 week of initiation. Gross pathology indicated mortality was primarily induced by severe gastrointestinal irritation. Male and female rats in the highest dose group (70 mg/kg-d) of the subchronic study experienced excitability/irritability, seizures, lethargy, rough haircoat, disorientation, squinting, and occasional reductions in body mass. Increased urine volume and nitrite concentration, increased spleen and thyroid mass with associated increased TSH and decreased T4 (female rats only), thrombocytopenia, leukocytosis, and anemia were observed at the highest dose. Decreased epididymal mass and atrophy and degeneration of the testicular spermatogonia were observed in the high-dose male rats. Benchmark dose (BMD) analysis was conducted using dose-dependent reductions in hemoglobin concentration in female rats as the critical effect. The BMD was 12 mg/kg-d and the standard deviation BMDL was 10 mg/kg-d.

15. SUBJECT TERMS

oral toxicity, explosives, insensitive munitions, 1,1-diamino-2,2-dinitroethene, FOX-7, DADNE, thyroid, thrombocytopenia, leukocytosis, anemia

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Lee C.B. Crouse
U	U	U	SAR	295	19b. TELEPHONE NUMBER *(Include area code)* 410-436-3980

Study Title

Toxicology Study No. S.0082641-21
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of 1,1-Diamino-2,2-Dinitroethene (FOX-7) in Rats

Data Requirement

Organisation for Economic Cooperation and Development
Guideline for the Testing of Chemicals 408

Authors

Lee C.B. Crouse
Meredith E. Bohannon
Blas A. Guigni
Matthew A. Bazar
Taryn K. Brown

Study Completed On

May 2024

Performing Laboratory

Defense Centers for Public Health–Aberdeen
Toxicology Directorate (DCPH-ATS-TOX)
8988 Willoughby Road (E2100)
Aberdeen Proving Ground, MD 21010-5403

Laboratory Project ID

Protocol No. 38-18-12-01

Good Laboratory Practice Compliance Statement

The study described in this report was conducted in compliance with Title 40, Code of Federal Regulations (CFR), Part 792, Good Laboratory Practice Standards, except for the following:

1. The statistical analyses of the data were conducted by several technical report authors and were not audited by the DCPH-A Quality Assurance Unit. It is not known if these analyses were conducted in accordance with Good Laboratory Practice Standards.

2. The concentrations of the test article dosing suspensions for the acute portion of the study were not verified analytically in accordance with Good Laboratory Practice Standards. The accuracy of the data reported is considered sufficient for the purposes of the study.

3. The test article characterization (purity) was conducted by the manufacturer, and it is not known whether the testing was done in compliance with the above regulation.

CROUSE.LEE.1239523265 Digitally signed by CROUSE.LEE.1239523265 Date: 2024.05.08 14:09:20 -04'00'

LEE C.B. CROUSE
Biologist
Toxicity Evaluation Division

Date

EXECUTIVE SUMMARY
TOXICOLOGY STUDY NO. S.0082641-21
SUBCHRONIC ORAL TOXICITY OF 1,1-DIAMINO-2,2-DINITROETHENE (FOX-7) IN RATS
AUGUST 2019 – NOVEMBER 2021

1 PURPOSE

The objectives of this study were to determine the oral median lethal dose (LD_{50}), slope, and 95% confidence intervals resulting from the acute oral administration of 1,1-diamino-2,2,-dinitroethene (FOX-7). Additionally, this study sought to determine if adverse effects occurred from a subacute (14-day) and subchronic (90-day) repetitive oral exposure regimens of FOX-7 to the laboratory rat.

2 CONCLUSIONS

The estimated FOX-7 LD_{50} from the acute study was 875 milligrams per kilogram (mg/kg) for male rats and 805 mg/kg for female rats with a combined-sexes LD_{50} of 839 mg/kg. Subacute administration of FOX-7 resulted in 100% mortality at doses ≥200 milligrams per kilogram per day (mg/kg-d) within 1 week of initiation. Clinical and gross pathological signs of gastrointestinal irritation were observed at doses ≥100 mg/kg-d. The rat peripheral blood micronucleus assay, run concurrently with the subacute study, was negative for genotoxicity.

In the subchronic repetitive oral exposure study, FOX-7-induced mortality only occurred in one male rat in the highest dose group (70 mg/kg-d) on day 74. Gross pathology indicated that this was most likely the result of direct gastrointestinal irritation, but histopathology was not informative. Male and female rats in the 70-mg/kg-d group experienced excitability/irritability, seizures, lethargy, rough haircoat, disorientation, and squinting. Excitability/irritability was also occasionally observed throughout all FOX-7 dose groups. Weekly neurotoxicity assessments or analysis of motor activity at week 11 did not indicate any significant neurological differences from controls, except for some sporadic, open-arena observations.

Weekly body mass was reduced in the 70 mg/kg-d group compared to controls starting at week 3 (male rats) and week 5 (female rats), while paired food consumption was only reduced in male rats during week 12. Paired food efficiency was reduced during week 3 for both sexes. Timed urine collection yielded increased volume and nitrite concentration with reduced specific gravity in both sexes at 70 mg/kg-d. Male rats in this group additionally had increased leukocytes, and female rats had increased urine pH.

Thyroid and spleen mass was increased in both sexes at 70 mg/kg-d. The increased thyroid mass was associated with increased thyroid-stimulating hormone (TSH), decreased T_4 (female rats only), and microscopic findings of follicular cell hypertrophy. Although thrombocytopenia was observed at the highest dose, histopathology did not indicate increased incidence of splenic

findings. Anemia, in the form of reduced red blood cell count, hematocrit, and hemoglobin (HGB), was apparent in the 70-mg/kg-d male and female rats. Male rats at 17.5 mg/kg-d also exhibited reduced HGB. Leukocytosis was observed in both sexes at 70 mg/kg-d; however, this effect was only significant in male rats. Decreased mass of the epididymides and atrophy and degeneration of the testicular spermatogonia with hypospermia were observed in the 70-mg/kg-d group.

The critical effect selected for benchmark dose (BMD) analysis was a dose-dependent reduction in hemoglobin concentration in female rats. The best fitting viable model resulted in a BMD of 12 mg/kg-d and a standard deviation (BMDL) of 10 mg/kg-d.

Table of Contents

TABLES

FIGURES

TOXICOLOGY STUDY NO. S.0082641-21
SUBCHRONIC ORAL TOXICITY OF 1,1-DIAMINO-2,2-DINITROETHENE (FOX-7) IN RATS
AUGUST 2019 – NOVEMBER 2021

1 PURPOSE

The objectives of this study were to determine the oral median lethal dose (LD_{50}), slope, and 95% confidence intervals resulting from the acute oral administration of 1,1-diamino-2,2,-dinitroethene (FOX-7). Additionally, this study sought to determine if adverse effects occurred from a subacute (14-day) and subchronic (90-day) repetitive oral exposure regimens of FOX-7 to the laboratory rat.

2 REFERENCES

See Appendix A for a listing of references.

3 AUTHORITY

This study was conducted with funding from the Army Safer Alternatives for Readiness (SAFR) Program (AFCC-PPP-E) via Military Interdepartmental Purchase Request (MIPR) No. 11651265. This toxicology study addresses, in part, the environmental safety and occupational health requirements outlined in the following:

- Army Regulation (AR) 200–1, *Environmental Protection and Enhancement,* 2007 (reference 1).
- AR 40–5*, Preventive Medicine,* 2007 (reference 2).
- AR 70–1, *Army Acquisition Policy,* 2003 (reference 3).
- Department of Defense Directive (DoDD) 4715.1E, *Environment, Safety, and Occupational Health (ESOH)*, 2005, Change 1, 2018 (reference 4).
- Army Environmental Requirements and Technology Assessments (AERTA). Requirement PP-3-02-05, *Compliant Ordnance Lifecycle for Readiness of the Transformation and Objective Forces*, 2012 (reference 5).

It was performed as part of an on-going effort by the U.S. Army Combat Capabilities Command (CCDC), SAFR Program, to produce munitions that are less hazardous to human health and the environment.

4 BACKGROUND

FOX-7 is an insensitive energetic compound developed by the Swedish Defence Research Agency in the late 1990s. The U.S. Military is currently evaluating it as a potential replacement for cyclotrimethylenetrinitramine (RDX) in conventional munitions. FOX-7 shows significant improvements in sensitivity compared with RDX, particularly in its response to impact and friction stimuli (reference 6). Experimental data indicate that the performance of FOX-7 is slightly superior to that of the benchmark nitramine explosive RDX (reference 7). Historically,

military munitions and propellants have been developed and fielded based solely on their effectiveness on the battlefield. Any potential toxicity associated with the manufacture and use of these munitions was not investigated until after the material had been fielded and the contamination had already occurred. RDX has been reported in sediment and groundwater samples taken near military munition depots and test ranges in the United States. The health effects associated with environmental and occupational RDX exposure are well documented. RDX-induced epileptiform seizure neurotoxicity has been reported in rodent toxicity studies as well as from incidental human exposure. The Centers for Disease Control and Prevention (CDC) Agency for Toxic Substances and Disease Registry (ATSDR) have developed a Minimum Risk Level (MRL) of 0.2 milligrams per kilogram per day (mg/kg-d) for acute-duration oral exposure to RDX and an MRL of 0.1 mg/kg-d for intermediate- and chronic-duration oral exposure. RDX is also classified as a possible carcinogen (reference 8). The U.S. Environmental Protection Agency (EPA) established a chronic oral reference dose (RfD) of 0.004 mg/kg-d based on nervous system effects (seizures/convulsions) in rodents (reference 9).

Before this series of toxicity studies, data on FOX-7 were limited to several acute studies, a teratogenicity study in rodents, *in vitro* testing, and *in silico* predictions. These studies reported acute oral toxicity in the low-moderate range with an *in vivo* estimate of >500 mg/kg, a TOPKAT estimated $LD_{50\text{-rat}}$ of 1,200 mg/kg, and an *in vitro* LD_{50} prediction of 1,764 mg/kg using the neutral red uptake assay (references 10 and 11). TOPKAT modeling has also predicted FOX-7 to likely be a developmental or reproductive toxicant, mutagenic, and moderate skin sensitizer, but not a skin irritant (reference 11). *In vivo* testing with guinea pigs confirmed that FOX-7 was not a skin irritant up to the highest concentration of 460 milligrams per liter (mg/L) and was a mild sensitizer at 230 mg/L (reference 10). Liu et al. evaluated the teratogenicity of FOX-7 in rats at dosages of 0, 5, 15, and 45 mg/kg-d. Fetal body weight, body length, and mortality were increased in the 15- and 45-mg/kg-d groups, and fetal tail length was decreased in the 45-mg/kg-d group. Increased fetal skeletal and internal organ malformations were also observed in the 45-mg/kg-d group (reference 12).

Research, development, testing, and training with explosives and pyrotechnics potentially less hazardous to human health and the environment are vital to the readiness of the U.S. Army. The Army SAFR Program is dedicated to finding replacements for substances causing environmental and/or occupational risks to health. Toxicity assessments such as this study are necessary for safeguarding the health of Soldiers, civilians, and the environment and, if begun early in the research, development, testing, and evaluation process, can save significant time and effort by identifying unacceptable replacement compounds (reference 13).

Table 1 identifies the critical dates of this study.

Table 1. Critical Study Events

Critical Event	Date of Event
Animal Use Protocol Approved	December 6, 2018
Acute Study Initiation	August 7, 2019
Acute Study In-Life Completion	September 10, 2019
14-Day Study Initiation	February 17, 2021
14-Day Study Scheduled Necropsies	March 9–12, 2021
90-Day Study Initiation	July 14, 2021
90-Day Study Scheduled Necropsies	October 27–29 and November 3–5, 2021
90-Day In-Life Completion	November 5, 2021
Study Completion	May 2024

5 Materials

5.1 Test Substance

FOX-7 (CASRN 145250-81-3) is a bright yellow crystalline, odorless, insensitive energetic material. The chemical formula is $C_2H_4N_4O_4$, with a density of 1.885 grams per milliliter (g/mL) (reference 7). The chemical structure is shown below in Figure 1. The material was supplied by EURENCO Bofors, Karlskoga, Sweden and identified as lot number 20119001 with a 30-micron particle size. The manufacturer performed the compound purity and reported it as 100% by High Performance Liquid Chromatography (HPLC) Ultraviolet Detection. The material was shipped to the CCDC, Chemical Biological Center (CBC), Pyrotechnics Team, Aberdeen Proving Ground - Edgewood Area, Maryland, for storage before use. The FOX-7 manufacturer indicated that the entire lot was wetted with not less than 15% water or alcohol by mass. The moisture content and uniformity of the shipment used for this study could not be confirmed; therefore, the FOX-7 received was treated as 100% pure.

For the acute study, fresh dosing suspensions were prepared the day before use for each round of dosing. For the subacute and subchronic studies, separate dosing suspensions were prepared for each dose group in volumes sufficient for approximately 2–3 weeks of dosing. Targeted suspension concentrations were 1.25, 2.5, 5, 10, 20, 40, and 80 milligrams per milliliter (mg/mL) for the subacute study and 0.218, 0.875, 3.5, and 14 mg/mL for the subchronic study. All concentrations/batches of dosing suspensions for the subacute and subchronic studies were sampled, extracted, and analyzed by the DCPH-A Laboratory Sciences Directorate via HPLC with a Triple Quad mass spectrometric system to verify the concentration. In addition, the homogeneity of the subacute and subchronic suspensions was verified by determining the concentration of samples taken from the top, middle, and bottom of the most concentrated (80 and 14 mg/mL) suspension. Before subacute study initiation, samples were collected from a representative suspension (1 mg/mL) at weekly intervals for 4 weeks to determine the stability of FOX-7 in corn oil.

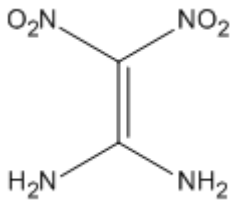


Figure 1. FOX-7 Chemical Structure

5.2 Animals

Each phase of this study was conducted using young adult male and female Sprague-Dawley (Crl:CD(SD)CD®) rats obtained from Charles River Laboratories, Wilmington, Massachusetts. All animals were housed in temperature-, relative humidity-, and light-controlled rooms with the target conditions of 68–72 °F, 30–70% humidity, and a 12:12 light/dark cycle (reference 14). Animal room environmental data were automatically recorded in 10-minute increments 24 hours per day using the MetaSys® Building Automation System. Mean temperature and humidity during all three study phases, as well as out-of-range periods, are summarized below in Table 2. These deviations were not considered to have compromised the integrity or validity of the study results. A certified pesticide-free rodent chow (Harlan Teklad®, 2016C Certified Rodent Diet) and drinking quality water were available *ad libitum*, except during overnight fasting before acute dosing and final blood collection for the subacute and subchronic studies. Acute study rats were initially same-sex pair-housed but were individually housed once dosed. Subacute and subchronic study rats were same-sex pair-housed by dosage group. Subchronic male pairs with rats exceeding 500 grams each were monitored weekly for signs of inadequate cage space and were individually housed for the remainder of the study if deemed necessary. All rats were housed in individually-ventilated, suspended polycarbonate boxes with Sani-Chip® bedding. Each rat was uniquely identified by number via cage card and tail marking. Research was conducted in compliance with DoD and federal statutes and regulations relating to animals and experiments involving animals and adhered to principles stated in the *Guide for the Care and Use of Laboratory Animals,* Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, National Academy Press, Washington, DC, 2011. The studies reported herein were performed in animal facilities fully accredited by AAALAC International.

Table 2. Animal Room Environmental Conditions

Acute	**08/07/19 – 09/10/19**	**Mean 71.2±0.6 °F**	**Mean 52.3±1.1%**
Out of Range	**Date (Time)***	**Temperature °F**	**Relative Humidity %**
	08/20/19 (0920–1000)	73.00	
Subacute	**02/17/21 – 03/12/21**	**Mean 72.4±0.2 °F**	**Mean 40.8±8.0%**
Out of Range	**Date (Time)***	**Temperature °F**	**Relative Humidity %**
	02/17/21 (0200–1140)		25.31–29.99
	02/18/21 (0030–2020)		25.95–29.81
	02/19/21 (0300–2200)		28.12–29.87
	02/20/21 (0820–2350)		25.39–29.89
	02/21/21 (0010–1440)		25.46–29.89
	02/22/21 (0210–0820)		28.00–29.89
	02/23/21 (2040–2310)		29.76–29.92
	02/24/21 (0300–0550)		29.28–29.84
	02/25/21 (0510–2350)		27.33–29.89
	02/26/21 (0040–1210)		27.48–29.89
	03/01/21 (1840–2230)		28.52–29.85
	03/02/21 (0010–2330)		26.21–29.87
	03/03/21 (0020–1650)		26.89–29.97
	03/04/21 (0130–1240)		28.55–29.99
	03/05/21 (0040–2340)		23.62–29.89
	03/06/21 (0000–2310)		26.13–29.88
	03/07/21 (0050–2340)		26.12–29.96
	03/08/21 (0000–1840)		24.65–29.97
	03/09/21 (0640)		29.73
Subchronic	**07/14/21 – 11/05/21**	**Mean 71.6±0.1 °F**	**Mean 48.2±1.6%**
Out of Range	**Date (Time)***	**Temperature °F**	**Relative Humidity %**
		N/A	N/A

Legend:
N/A = not applicable
°F = degrees Fahrenheit
Note:
*Animal room could be intermittently out of range between each day's beginning and end times.

5.3 Quality Assurance

The DCPH-A Quality Assurance Unit audited critical phases of this study. Appendix B provides the dates of these audits, the phases audited, and the dates on which the results of the inspections were reported to the Study Director and Management.

5.4 Study Personnel

Appendix C contains the names of persons contributing to the performance of this study.

6 Methods

6.1 Acute Study

The acute oral toxicity of FOX-7 was assessed using the Sequential Stagewise Probit (SSWP) method (references 15, 16, and 17). The SSWP method proceeds in stages in which groups of rats are dosed, and the responses are observed to determine doses used in the next dosing stage. In the first stage of dosing, four different doses were selected at approximately up to the limit dose of 2,000 mg/kg to span the entire dose response curve. In the absence of historical toxicity data, doses for the first stage are recommended to start at the default value of 175 mg/kg with half-log increasing and decreasing dose intervals. Neither constant concentration nor constant volume per body mass dosing could be achieved for most of the acute study due to the large range of doses and dosage volume limits for rats. Rats used for each stage of dosing were weighed daily during the week and observed for signs of toxicity, morbidity, and mortality for a 14-day recovery period. Subsequent stages were typically separated by a 24–48-hour period once a determination could be made regarding the survival of the animals dosed. A probit analysis was performed to determine the doses for subsequent stages of dosing, which uses the results from each stage to calculate the LD_{50}, 95% confidence interval, and slope of the dose response curve at the completion of dosing. The staged dosing continues until either the variation around the LD_{50} is less than 0.40 (95% upper confidence limit minus 95% lower confidence limit/2x the LD_{50}), a total of 30 rats per sex are used, or ≥3 of 6 rats survive the limit dose of 2,000 mg/kg.

Thirty male and female Sprague Dawley rats each, approximately 8 weeks old, were acclimated to the animal facility for 5 days before initiation of dosing. Dosing of stages occurred over 2 weeks, with male rats weighing 285.2 ± 39.7 grams and female rats weighing 204.7 ± 19.3 grams at the time of dosing. All doses were administered according to body mass measured on the day of dosing with a stainless steel, 16-gauge x 2-inch gavage needle. All rats were observed for 14 days, during which clinical observations and body mass were measured daily during the week and on weekends if necessary. Following the observation period or at the time of moribund euthanasia, rats were euthanized with carbon dioxide (CO_2) and submitted for gross pathological evaluation. In the event of mortality during the observation period, rats were submitted for gross pathological evaluation as soon as feasible.

6.2 Subacute Study

Upon evaluating the results of the SSWP, a 14-day subacute oral toxicity study was performed to determine the toxicity of repetitive daily dosing with FOX-7 and to assist with dose group determination for the subchronic study. Genotoxicity was assessed via the *in vivo* micronucleus assay, which was performed concurrently with the subacute study on the highest three male FOX-7 dose groups with sufficient survival.

6.2.1 Dose Selection and Test Substance Administration

Forty-eight male and female Sprague Dawley rats each, 8 weeks old, weighing 244.4 ± 29.5 and 186.2 ± 11.2 grams, respectively, at the start of dosing, were used for this phase of the study. Following a 7-day acclimation period, six rats of each sex were randomly distributed into seven FOX-7 treatment groups and a corn oil control group. Assignment to dose groups was accomplished by cage due to pair-housing using a stratified random procedure, with pairs of animals stratified according to body mass and dose groups assigned randomly. Paired body mass did not differ among dose groups before initiation of dosing. Male and female rats were each divided into two time-separated necropsy groups, with animals from each test group approximately evenly distributed across necropsy groups.

Dose selection for the subacute study was based on the results of the SSWP and was set at 400, 200, 100, 50, 25, 12.5, 6.25 mg/kg-d (e.g., 0.5x, 0.25x, 0.125x, 0.0625x, .03125x, .01563x, and .00781x the LD_{50}). All FOX-7 and control doses were administered based on the most recent body mass obtained at a rate of 5 milliliters per kilogram (mL/kg) for both male and female rats. Animals were dosed daily (7 days/week) at a similar time using a stainless steel, 16-gauge x 2-inch gavage needle.

6.2.2 Body Mass, Food Consumption, and Observations

All rats were weighed twice pre-study and on study days 0, 1, 3, 7, 13, and 14. The day-14 body mass was obtained following overnight fasting before necropsy. Feed was provided *ad libitum* 7 days per week in weighed feeder bins except for overnight fasting before necropsy. Feeders were reweighed on study days 0, 7, and 13, and the mass of the empty feeder was subtracted from the mass of the full feeder to determine the grams of food consumed for each pair of animals. Because rats were pair-housed and individual food consumption could not be determined, food consumption was reported as grams consumed per pair of animals.

A thorough physical examination of each animal was performed each day concurrently with the dosing procedure. During dosing, observations for mortality and signs of toxic effects were made in the morning. Cage-side observations, primarily for mortality, were made each afternoon, except on weekends when observations were only performed in the morning. Observations included but were not limited to, evaluation of the skin and fur, eyes and mucous membranes, respiratory and circulatory effects, autonomic effects (e.g., salivation (SAL)), central nervous system effects (e.g., tremors and convulsions), changes in the level of activity, gait, and posture, reactivity to handling (RH) or sensory stimuli, altered strength, and stereotypes or changes in behavior (e.g., self-mutilation).

6.2.3 Necropsy

Following 14 days of treatment, or when determined to be moribund, all surviving rats were anesthetized with CO_2, blood was collected via intracardiac puncture, and rats were euthanized using CO_2 (references 18 and 19). Necropsies were scheduled over 4 days based on the staggered experimental start dates. Rats that died during the study were also submitted for necropsy as soon as possible after the discovery of mortality.

A complete, detailed gross necropsy, including a careful examination of the external surface of the body, all orifices, and the cranial, thoracic and abdominal cavities and their contents, was performed on all rats following euthanasia. At necropsy, the adrenals, brain, heart, kidneys, epididymides, liver, ovaries, uterus, spleen, testes, and thymus were removed, trimmed, and weighed. Kidneys, adrenals, testes, and ovaries were weighed as pairs. Tissues collected but not weighed included: all gross lesions, eye (including retina), lacrimal gland (exorbital), salivary gland, esophagus, trachea, lung, lymph nodes (both superficial and deep), pancreas, stomach (forestomach, glandular stomach), ileum, duodenum, jejunum, cecum, colon, rectum, vagina, urinary bladder, mammary gland (obligatory for female rats and, if visibly dissectible, from male rats), skin, skeletal muscle, peripheral nerve, spinal cord, fresh bone marrow aspirate, and Harderian gland. All organs and tissues, except for the testes and epididymides from each male rat, were fixed in 10% buffered formalin for at least 24 hours. The testes and epididymides were placed in modified Davidson's fixative overnight (no longer than 24 hours), rinsed, and placed in 70% ethanol.

6.2.4 Clinical Chemistry and Hematology

Blood was obtained from CO_2-anesthetized fasted animals via intracardiac puncture at the termination of the study. Blood for clinical chemistry analyses was transferred to tubes free of additives, allowed to clot for at least 20 minutes, and centrifuged for approximately 2.5 minutes at 12,000 x g to obtain serum. The following clinical chemistry parameters were evaluated using the DiaSys respons®910VET Analyzer: amylase (AMY), lipase (LPS), albumin (ALB), albumin/globulin ratio (ALB/GLOB), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium (CA), cholesterol (CHOL), creatinine kinase (CK), creatinine (CREA), glucose (GLU), globulin (GLOB calc.), phosphate (PHOS), total bilirubin (TBIL), total protein (TP), and triglycerides (TRIG) (reference 20).

Blood for electrolyte analysis was transferred to lithium heparin microtubes and evaluated using the NOVA Biomedical Stat Profile Prime Plus® Analyzer. The following electrolyte parameters were evaluated: pH, hematocrit (Hct), total hemoglobin (tHb), sodium (Na), potassium (K), chloride (Cl), ionized calcium (iCa), ionized magnesium (iMg), GLU, and lactate (Lac).

Blood for hematology analyses was transferred to tripotassium ethylenediamine-tetraacetic acid (K_3EDTA) microtubes and evaluated using the Sysmex XN-1000™ Analyzer. The following hematology parameters were evaluated: white blood cell count (WBC), WBC differential (neutrophils (NEUT), lymphocytes (LYMPH), monocytes (MONO), eosinophils (EOS), basophils (BASO), RBC, hemoglobin (HGB), Hct, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), platelets (PLT), red blood cell distribution width (RDW-SD and RDW-CV), mean platelet volume (MPV), nucleated red blood cells (NRBC), reticulocytes (RET), immature reticulocyte fraction (IRF), reticulocyte hemoglobin equivalent (RET-He), and platelets fluorescent (PLT-F) (reference 21).

Blood for average prothrombin time was transferred to a sodium citrate microtube, centrifuged for approximately 2.5 minutes at 12,000 x g, and analyzed using the Siemens BFT II Analyzer.

6.2.5 Histopathology

Histopathology was not performed on tissues from the subacute study since it was primarily used to determine doses for the more definitive subchronic study. Collected tissues from the subacute study were preserved and will be retained for 10 years in the DCPH-A wet tissue archive from the time of collection if needed for future evaluation.

6.2.6 Micronucleus Assay

Following the 14-day study period, blood was collected from the lateral saphenous vein of male rats in the corn oil control and the 25-, 50-, and 100-mg/kg-d FOX-7 dose groups for use in the micronucleus assay. In addition, two groups of six male rats/group were added to the 14-day study regime, with one group serving as the untreated negative control group and one group serving as the positive control group. The untreated negative control group was added to ensure that the corn oil diluent had no genotoxic properties. The positive control group received two 200-mg/kg doses of a known genotoxic agent (ethyl methanesulfonate, CASRN 62-50-0) on the 2 days before necropsy for assay verification. Peripheral blood collection was accomplished by puncturing the lateral saphenous vein with a 20-gauge needle and collecting approximately 120 microliters (µL) of blood using a pipette tip that was pre-coated in a kit-provided anti-coagulant. The blood was placed in a microcentrifuge tube containing 0.35 mL of anticoagulant and stored at 4–6 °C before fixing. The blood/anticoagulant was fixed by rapidly pipetting 180 µL of blood/anticoagulant into centrifuge tubes containing 2 mL of methanol at -80 °C, vortexing briefly, and returning to -75 to -85 °C for storage until analysis. Before shipping to Litron Laboratories, samples were washed at 4 °C by adding 12 mL of buffer solution to each sample, inverting it once to mix, centrifuging the sample tubes at 300 x g for 5 minutes, then aspirating the supernatant, leaving less than 50 µL supernatant. Cells were resuspended in 1 mL of long-term storage solution, transferred to a cryovial, and stored at -75 to -85 °C. Processed samples were then shipped to Litron Laboratories (Rochester, New York) for flow cytometric analysis.

6.2.7 Statistical Analysis

Experimental data generated during this study were recorded by hand and tabulated, summarized, and/or statistically analyzed using Microsoft® Excel, SAS®, and SPSS®. Data from the SSWP were analyzed according to the methods of Feder et al. (references 15 and 16) to determine the LD50, 95% confidence interval, and slope of the dose response curve.

Data from the subacute study were analyzed based on the type of data collected and the frequency of collection. Variables measured only at the end of the study (i.e., clinical pathology, organ mass ratios, and micronucleus assay) were analyzed using a one-factor Analysis of Variance (ANOVA) with the dose group as the main effect. Parameters measured multiple times during the study (i.e., body mass, food consumption, and body mass change) would typically be analyzed using a repeated measures ANOVA with a sample day as the within-subject factor and the dose group as the between-subject factor. However, if any sample points were missing for a particular animal (e.g., missing food consumption due to shredding food or missing body weight or weight gain due to pre-term morbidity), the repeated measures ANOVA eliminated that

animal from analysis for the entire study period. Therefore, these data were also analyzed using a one-factor ANOVA for each sampling day. Data were tested for normality and either log transformed or ranked if not normally distributed. If the dose group effect was significant ($p \leq 0.05$), post-hoc tests were used to compare pairs of dose groups and dose groups to the control group; a Tukey's multiple comparison test was used if the variance of the groups were similar and a Dunnett's T3 test if the variances were unequal. Variance equality was determined by a Levene's test. Absolute organ mass was analyzed by Analysis of Covariance (ANCOVA), with the dose group as the main effect and body mass at the end of the study as the covariate to account for heavier animals having heavier organs. If the dose group effect was significant, a least significant differences post-hoc test was used to compare pairs of dose groups and dose groups to the control group.

6.3 Subchronic Oral Toxicity Study

Upon analysis of the results of the subacute study, these data were used to set doses for a 90-day repeated dose oral toxicity study with FOX-7. The highest dose was intended to induce signs of toxicity but not result in mortality or moribund euthanasia. Lower doses were calculated based on a 4-fold interval.

6.3.1 Test Substance Administration

Fifty male and 50 female Sprague Dawley rats were used for this phase of the study. Following a 14-day acclimation period, 10 rats of each sex were randomly distributed into 4 FOX-7 treatment groups and a corn oil control group. Assignment to dose groups was accomplished by cage due to pair-housing using a stratified random procedure, with pairs of animals stratified according to body mass and dose groups assigned randomly. Paired body mass did not differ between dose groups before initiation of dosing. At the start of dosing, 8-week-old male and female rats weighed 262.3 ± 17.1 and 205.4 ± 16.8 grams, respectively. Male and female rats were each divided into three time-separated necropsy groups, with animals from each test group approximately evenly distributed across necropsy groups.

Dose selection for the subchronic study was based on the subacute study results and was set at 70, 17.5, 4.38, and 1.09 mg/kg-d. All FOX-7 and control doses were administered based on the most recent body mass obtained at a rate of 5 mL/kg for both male and female rats. Animals were dosed daily (7 days/week) at a similar time for 90 days using a stainless steel 16-gauge x 2-inch gavage needle.

6.3.2 Body Mass, Food Consumption, and Observations

All rats were weighed twice pre-study and weekly throughout the study. Terminal body mass was obtained following overnight fasting before necropsy. Feed was provided *ad libitum* 7 days per week in weighed feeder bins except for overnight fasting before necropsy. Feeders were reweighed weekly, and the mass of the empty feeder was subtracted from the mass of the full feeder to determine the grams of food consumed for each pair of animals. Because rats were pair-housed and individual food consumption could not be determined, food consumption was reported as both grams of food consumed per pair of animals as well as grams of food

consumed per gram of rats in a cage. Food efficiency was calculated as a ratio of food consumed per pair to total body mass gained per pair.

A thorough physical examination of each animal was performed each day concurrently with the dosing procedure. Observations for mortality and signs of toxic effects were made in the morning during dosing. Cage-side observations, primarily for mortality, were made each afternoon, except on weekends when observations were only performed in the morning. Observations included but were not limited to, evaluation of the skin and fur, eyes and mucous membranes, respiratory and circulatory effects, autonomic effects (e.g., SAL), central nervous system effects (e.g., tremors and convulsions), changes in the level of activity, gait, and posture, RH or sensory stimuli, altered strength, and stereotypes or changes in behavior (e.g., self-mutilation).

6.3.3 Neurobehavioral Evaluations

Potential neurotoxic effects of FOX-7 were evaluated using the functional observation battery (FOB) and motor activity assessment. The FOB protocol used in this study followed the methods described in McDaniel et al. (reference 22). Animals were divided into two subsets for each sex, using a stratified random procedure based on dose group. The FOB was conducted on each animal before initiation of dosing and weekly thereafter, with one subset of animals being assessed per day. The order of animals evaluated each day was randomly determined weekly. The FOB was performed at the same time each morning before dosing. Each rat was removed from its cage and held by the observer to conduct the handheld observation of reactivity and appearance. The rat was then placed on a cart to conduct the open-arena observations of gait, arousal, rears, and excretions. Home-cage observations were performed weekly on all animals on the same day. During week 11 of dosing, sensorimotor responses were tested after the open-arena observations. Motor activity was measured after week 11 of dosing using an open-field chamber with automated detection devices. The same evaluator performed observations and FOB throughout the study; the evaluator was blind to the treatment groups.

The home-cage observations included signs of agitation, convulsions, tremors, posture, mutilation, and the area mutilated. Each rat was assigned a number corresponding with the observed response. Agitation and mutilation were scored as present (1) or absent (2); area mutilated was only described if present. Convulsions and tremors were scored as absent (1), slight (2), or severe (3). Posture was scored for the following positions: lying down (1), sit/stand (2), rearing (3), flattened (4), lying on side (5), crouched with head down (6), and/or head bobbing (7). Animals demonstrated one or more body postures in one observation.

For handheld observations, each animal was removed from the home cage, and the following observations were recorded: ease of removal (ER), RH, lacrimation (LAC), SAL, barbering (BAR), piloerection (PIL), palpebral closure (PC) of left and right eye, exophthalmos (EXO), and pupillary status (PS) of the left and right eye. ER describes the removal of the rat from the home cage and was scored 1–6: very easy, easy, moderately difficult, rat flinches, difficult, and very difficult. RH was scored 1–5: very low, low, moderately low, moderately high, and high. LAC, SAL, EXO, and absence of hair from the forelimbs due to BAR were scored as present (1) or

absent (2). PC describes the eye lid and was scored for the left and right eyes as normal (1), squinted (2), or closed (3). PS was scored for the left and right eyes as normal (1), dilated (2), or constricted (3).

Open Arena was conducted following the handheld observations. Each rat was placed on a 36-inch x 24-inch cart lined with paper. The rat was allowed to move freely around the arena for 3 minutes. During this time, observations were scored by an observer blind to the treatment groups. The following observations were recorded: number of rears and grooms, arousal, gait, fecal boli, fecal description, and urine. Rears were defined as the front limbs being lifted from the floor, supported or unsupported. Grooms were defined as any licking, biting, or scratching.
Arousal was scored:

1) very low
2) low (some head/body movement and exploration)
3) normal
4) high (slight excitement, sudden darting/freezing)
5) very high (hyper alert, excited, sudden bouts of running/movement)

Gait, the movement/coordination of the rat, was scored:

1) normal
2) too little movement to determine gait
3) ataxia
4) hind-limb impairment
5) forelimb impairment
6) walking on toes
7) hunched
8) body drags
9) no movement
10) unable to move

Fecal boli was the absence (1) or presence (2) of fecal matter. If fecal boli were present, fecal description was scored:

1) normal
2) diarrhea
3) soft
4) mucoid
5) bloody.

After the 2-minute assessment, the rat was returned to the home cage and the arena cleaned before the assessment of subsequent rats.

Elicited responses were evaluated by testing reactivity to different types of stimuli. Each rat was scored for reaction to the approach of a closed pen, auditory startle response to a loud click, tail-pinch response, pinna response, and pupillary response to a pen light.
Approach was scored:

1) no reaction
2) slow approach
3) approaches energetically
4) jumps/avoids
5) freezes

6) bizarre/attack

Auditory/startle was scored:

1) no reaction
2) slight (ear flick)
3) energetic/vocalize
4) jumps
5) freezes
6) bizarre/attacks.

Tail pinch was scored:

1) response
2) no visible response

Pinna response was scored:

1) response
2) no visible response

Pupillary response was scored:

1) eye constricts
2) does not constrict

Righting reflex was measured by placing the rat on its back on a padded surface. The rat was scored on how quickly it turned over onto its feet.

Righting reflex was scored:

1) normal
2) impaired (greater than 2 seconds to right)
3) totally impaired (remains on back or side)

To score aerial righting, the rat was held in the air at 20 centimeters (cm) with its back horizontal to a padded surface. The rat was released and scored on its ability to turn over to land on its feet.

Aerial righting was scored:

1) normal
2) slightly uncoordinated
3) lands on side
4) lands on back

To measure hind-limb landing foot splay, the back feet of each rat were moistened with water. The rat was held by the scruff of the neck and the base of the tail and dropped from 20 cm onto a cage pad to show foot impressions. Foot splay was measured as the distance between the centers of the footprints, to the nearest 0.5 cm. This was repeated twice, and the measures were averaged. Forelimb and hind-limb grip strength was assessed following these measurements. Grip strength was measured using Chatillon Model DFM-10® Digital Force Meters that were verified using standard weights. The force meters were set to measure the peak force in kilograms, trials were repeated twice, and the average was calculated. Forelimb test: the animal was held by the base of the tail and allowed to place forepaws on the grate, and the animal was pulled away from the grate at a continuous rate until its grip was released and the reading was recorded. For the hind-limb test, the animal was held by the base of the tail and allowed to grasp the grate with its hind paws. The animal was pulled away from the grate at a continuous rate until its grip was released, and the reading was recorded.

Motor activity was assessed using a Hamilton Kinder SmartFrame® Open Field Activity System. The system consisted of four Plexiglas motor activity chambers (41 x 41 x 38 cm) each surrounded by a frame containing 32 evenly-spaced (16x and 16y, 2.5 cm apart) infrared photocells. The floor of each chamber was equipped with a hole board containing nine holes equipped with infrared photocells to detect nose poke activity. Activity was measured as basic movement, immobility, x and y ambulation, and nose pokes based on the number of photobeam breaks recorded using the Kinder Scientific MotorMonitor® software (Version 7.00). After acclimation to the test room for at least 30 minutes, animals were removed from the home cage and placed individually into an open-field arena for 15 minutes. Data were collected automatically by the system at 15 equally-spaced times while each rat was within the enclosure. After completion of the test, the rat was returned to its home cage and the chamber cleaned before testing of subsequent animals. Functioning of the software and chambers was verified before each test session by manually disrupting the beams and running a software diagnostic test (reference 23).

6.3.4 Ophthalmic Examinations

All study animals were examined pre-study and surviving animals from the control and high - dose (70 mg/kg-d) groups were examined within 1 week of the conclusion of the study. On each occasion the fundus and anterior chamber of the eye were examined using a Welch Allyn ophthalmoscope after instillation of tropicamide ophthalmic solution (1%) (reference 24).

6.3.5 Urinalysis

During the night before necropsy, each animal was placed in a metabolism cage capable of separating urine and feces for one overnight period of approximately 14 hours during which free-catch urine was collected. Animals were fasted during this period, but water was available *ad libitum* via a water bottle containing a measured volume of water. Urine samples were transferred to clear, graduated conical centrifuge tubes and the volume, color, and appearance of each sample were recorded. The color of each sample was determined based on comparison with a urine color chart with 9 colors ranging from pale yellow/straw to dark amber. Specific gravity was tested using a refractometer. Siemens Chek-Stix™ Test Strips were used to conduct chemical analyses including pH, protein, glucose, ketones, bilirubin, blood, urobilinogen, nitrites, and leukocytes (reference 25). Water consumption was determined by pouring all water from spill containers back into the water bottle, reading the current empty volume, and subtracting that volume from the initial full volume.

6.3.6 Necropsy

Following 90 days of treatment, or when determined to be moribund, all rats were anesthetized with CO_2, blood was collected via intracardiac puncture, and rats were euthanized using CO_2. Necropsies were scheduled over 6 days based on the staggered experimental start dates.

A full, detailed gross necropsy including a careful examination of the external surface of the body, all orifices, and the cranial, thoracic and abdominal cavities, and their contents was performed on all rats following euthanasia. At necropsy, the adrenals, brain, heart, kidneys,

epididymides, prostate, seminal vesicles, liver, ovaries, uterus, spleen, testes, and thymus were removed, trimmed, and weighed. Kidneys, adrenals, testes, and ovaries were weighed as pairs. The thyroid and pituitary were weighed after fixation to prevent damaging the tissue during removal. Tissues collected but not weighed included: all gross lesions, eye (including retina), lacrimal gland (exorbital), salivary gland, esophagus, trachea, lung, lymph nodes (both superficial and deep), pancreas, stomach (forestomach, glandular stomach), ileum, duodenum, jejunum, cecum, colon, rectum, vagina, urinary bladder, mammary gland (obligatory for female rats and, if visibly dissectible, from male rats), skin, skeletal muscle, peripheral nerve, spinal cord, fresh bone marrow aspirate, and Harderian gland. All organs and tissues, except for the testes and epididymides from each male rat, were placed in 10% buffered formalin for at least 24 hours for fixation. The testes and epididymides were placed in modified Davidson's fixative overnight (no longer than 24 hours), rinsed, and placed in 70% ethanol.

6.3.7 Animal Health Monitoring

Due to the staggered start dates for male and female rats, pre-study health monitoring samples were collected from male rats 16 days after arrival in the test facility and from female rats 9 days after arrival. A combination of oral and fur swabs were collected from selected rats for the pre-study sampling. All samples were subsequently pooled and sent to Charles River Research Animal Diagnostic Services for polymerase chain reaction (PCR) analysis. Health monitoring at the end of the study was accomplished via environmental sampling using Exhaust Air Dust (EAD) samples from each of the two ventilated animal racks used throughout the study. These samples were collected during week 13 of the study for male rats and week 12 for female rats. EAD samples were also sent to Charles River Research Animal Diagnostic Services for PCR analysis (reference 26).

6.3.8 Clinical Chemistry and Hematology

Blood was obtained from CO_2 anesthetized fasted adult animals via intracardiac puncture at the termination of the study. Blood for clinical chemistry analyses was transferred to tubes free of additives, allowed to clot for at least 20 minutes, and centrifuged for approximately 2.5 minutes at 12,000 x g to obtain serum. The following clinical chemistry parameters were evaluated using the DiaSys respons®910VET Analyzer: AMY, LPS, ALB, ALB/GLOB, ALP, ALT, AST, BUN, CA, CHOL, CK, CREA, GLU, GLOB calc., PHOS, TBIL, TP, and TRIG (reference 20).

Blood for electrolyte analysis was transferred to lithium heparin microtubes and evaluated using the NOVA Biomedical Stat Profile Prime Plus® Analyzer. The following electrolyte parameters were evaluated: pH, Hct, tHb, Na, K, Cl, iCa, iMg, GLU, and lactate Lac.

Blood for hematology analyses was transferred to K_3EDTA microtubes and evaluated using the Sysmex XN-1000 Analyzer. The following hematology parameters were evaluated: WBC, NEUT, LYMPH, MONO, EOS, BASO, RBC, HGB, Hct, MCV, MCH, MCHC, PLT, RDW-SD and RDW-CV, MPV, NRBC, RET, IRF, RET-He, and PLT-F. Age-appropriate normal ranges for Sprague-Dawley rat clinical pathology parameters were obtained from data compiled by Charles River Laboratories (references 21 and 27).

Blood for average prothrombin time was transferred to a sodium citrate microtube, centrifuged for approximately 2.5 minutes at 12,000 x g, and analyzed using the Siemens BFT II Analyzer.

6.3.9 Thyroid Hormone Analysis

Blood for triiodothyronine (T_3), thyroxine (T_4), and TSH analysis was transferred to tubes free of additives, allowed to clot for at least 20 minutes, and centrifuged for approximately 2.5 minutes at 12,000 x g to obtain serum. Serum samples were frozen at approximately -30 °C before analysis. Levels of T_3, T_4, and TSH were measured in serum collected from a cardiac blood draw in the anesthetized rats using the MILLIPLEX® MAP Rat Thyroid Hormone Panel magnetic bead multiplexing assay (Catalog # RTHYMAG-30, Lot # 3729914), coupled with a Luminex MAGPIX® analyzer run with xPONENT® 4.2 software. Briefly, serum samples were diluted 1:6 and loaded onto a flat bottom 96-well plate at proportions of 1-part diluted sample, 1-part assay buffer supplied with the kit, 1-part anti-T_3/T_4/TSH magnetic bead solution, and 1-part horseradish peroxidase conjugate. The following were loaded onto the plate along with a serum matrix provided with the kit in place of the assay buffer component of the sample wells: a standard curve of seven 2-fold dilutions for T_3, T_4, and TSH with the highest concentration of 10,000, 200,000, and 4,000 picograms per milliliter (pg/mL) for each analyte respectively; a background control consisting of assay buffer to complete the standard curves with a 0-pg/mL standard point; two quality control (QC) samples provided with the kit (Lot # RTH-115 for the low QC sample [expected range 941–1,954 pg/mL]; Lot # RTH-215 for the high QC sample [expected range 2,012–4,179 pg/mL]). All background, standard, QC samples and rat serum samples were run in duplicate.

Plates were incubated at 4 °C on an orbital shaker for 16–20 hours; then washed with wash buffer supplied with the kit; then incubated with detection antibody provided with the kit at room temperature (RT) for 1 hour with shaking; then incubated with streptavidin-phycoerythrin provided with the kit at RT for 30 minutes with shaking; then washed and reconstituted in MAGPIX Drive Fluid; then loaded onto the analyzer. Median Fluorescent Intensity (MFI) values were generated and processed using GraphPad Prism 9. The standard curves for each analyte were fitted to a 4-parameter logistic curve. QC checks included ensuring that all points on the standard curves fell within <15% coefficient of variance (CV) for MFI values and calculated concentrations, the recovery of the points on the standard curve fell within 85–115%, and the QC sample calculated concentrations fell within the expected ranges as provided by the kit. The limit of detection for each analyte was established as half of the lowest point on the curve that fell within the 15% CV and 85–115% recovery criteria.

6.3.10 Sperm Analysis

Cauda epididymal sperm counts were determined using a computer-assisted sperm analyzer (TOX IVOS II™-CASA). The cauda was weighed and placed in a well of a petri dish containing 10 mL M199 medium at 34–37 °C, and the surface was minced using a scalpel to release sperm. The cauda was incubated for 5 minutes at 34–37 °C, gently mixed to uniformly suspend the sperm, and 0.5 mL of the suspension was transferred to another well containing 5 mL of medium. A sample of this suspension was then loaded onto a 2-well, 100-micron (µm) Leja slide

(SC100-01-02-A-CE; lot# 112153C1). The number of sperm, number of motile sperm, and number of progressive sperm was determined for 10 frames per animal.

6.3.11 Histopathology

Tissues were fixed in formalin, trimmed into cassettes, processed, embedded in paraffin, sectioned via a microtome to a thickness of 4–5 µm, and stained with hematoxylin and eosin using an automatic stainer. Additionally, the testis and epididymis were initially fixed in modified Davidson's solution and stained with the Periodic Acid Schiff stain. Sections of the brain were trimmed according to OECD and International Harmonization of Nomenclature and Diagnostic Criteria trimming guidelines (OECD 1997, Kittel et al. 2004, Morawietz et al. 2004, Ruehl-Fehlert et al. 2003) and included seven sections of the brain.

The tissues/slides from the high-dose group (70 mg/kg-d), vehicle control, and animals that were euthanized before the designated endpoint (premature deaths) were processed and analyzed. Tissues from other groups were evaluated when a significant difference was observed in lesion incidence or organ weight between the high-dose group compared to the control group. The general criteria for establishing histologic scores included the following: scores: '0' = the tissue is essentially normal or observed in <1% of the sampled tissue; '1' = minimum (<5% of tissue affected); '2' = mild (6–20% of tissue affected); '3' = moderate (21–40%); '4' = marked (41%–80% of tissue affected); '5' = severe (>80% of tissue affected); Absent = not present for microscopic examination due to sampling error, out of the plane of section, or other similar reason.

6.3.12 Statistical Analysis

Data from the subchronic study were also analyzed based on the type of data collected and the frequency of collection. Variables measured only at the end of the study (i.e., clinical pathology, sperm analysis, and organ mass ratios) were analyzed using a one-factor ANOVA with the dose group as the main effect. Parameters measured multiple times during the study (i.e., body mass, food consumption, and body mass change) would normally be analyzed using a repeated measures ANOVA with the sample day as the within-subject factor and dose group as the between-subject factor. However, if any sample points are missing for a particular animal (e.g., missing food consumption due to shredding food or missing body weight or weight gain due to pre-term morbidity), the repeated measures ANOVA eliminates that animal from analysis for the entire study period. Therefore, these data were also analyzed using a one-factor ANOVA for each sampling day. Data were tested for normality and either log transformed or ranked if not normally distributed. If the dose group effect was significant ($p \leq 0.05$), post-hoc tests were used either to compare pairs of dose groups and dose groups to the control group; a Tukey's multiple comparison test if the variance of the groups were similar and a Dunnett's T3 test if the variances were unequal. Variance equality was determined by a Levene's test. Absolute organ mass was analyzed by ANCOVA, with the dose group as the main effect and body mass at the end of the study as the covariate to account for heavier animals having heavier organs. If the dose group effect was significant, a least-significant-differences, post-hoc test was used to compare pairs of dose groups and dose groups to the control group.

Ordinal urinalysis data were coded for analysis, and both ordinal and continuous data were analyzed using a Kruskal-Wallis test due to a lack of normality. Thyroid hormone data were tested for normality and homogeneity of variances using a one-sample Kolmogorov-Smirnov test and Levene's test, respectively. In the case that the assumption of normality was violated, the data were ranked. An ANCOVA was run on male and female T_3, T_4, and TSH data separately, with the plate as a covariate. If the plate covariate was found to be insignificant ($p \geq 0.05$), it was removed from the analysis, and the data were run as a one-way ANOVA. This was followed by a Tukey's post-hoc test if the assumption of homogeneity was not violated or a Dunnett's T3 test if it was violated.

Neurobehavioral data were also a combination of categorical and continuous. The five home-cage and nine handheld weekly observational endpoints were all categorical. Elicited responses measured during week 11 were a combination of seven categorical and three continuous parameters. Week 11 motor activity measurements were only continuous parameters. Continuous neurobehavioral data were first tested for normality and subsequently ranked if the assumption of normality was violated. Homogeneity of variances was tested using a Levene's test. Continuous data were then analyzed as a one-way ANOVA, followed by a Tukey's post-hoc test if the assumption of homogeneity was not violated, or a Dunnett's T3 test if it was violated. Typically, categorical data would be analyzed using the Chi-square test. However, one of its assumptions is that the expected counts of each contingency table cell are greater than 5. This assumption was frequently violated with the categorical neurobehavioral data. To adjust for this violation, a Fisher's exact test can be run. Without the exact test module, SPSS will only run the Fisher's exact test on 2 by 2 contingency tables. Categorical neurobehavioral data that could not be analyzed using the Chi-square or Fisher's exact tests were analyzed using a non-parametric Kruskal-Wallis test.

7 Results

7.1 Analytical Results

The analytical chemistry results for the subacute and subchronic studies are summarized in Tables 3 and 4. The results of the 4-week stability study indicated that the FOX-7 concentration in corn oil remained within acceptable ranges and did not exhibit a decreasing trend. Weekly recovery percentages ranged from 77 to 96% throughout the sampling period. Homogeneity testing of the most concentrated subacute FOX-7/corn oil suspension (80 mg/mL) and subchronic suspension (14 mg/mL) indicated that both suspensions were sufficiently homogenous for study conduct. Verification of the subacute dosing suspension concentrations before use yielded recovery percentages ranging from 84 to 100% of the nominal concentrations, and this portion of the study only required one batch to be mixed. Verification of the subchronic dosing suspension concentrations before use yielded recovery percentages ranging from 86 to 114% of the nominal concentrations for all six batches. Given the concentrated nature of these suspensions and the acceptable limits of the extraction/analytical method, these analytical results were considered within acceptable ranges. All of the dosage levels for the subacute and subchronic studies are reported using the nominal concentrations.

Table 3. Stability and Homogeneity Results

Nominal Concentration (mg/mL)	Analytical Concentration (mg/mL)
1 (initial stability)	0.96
1 (week 1stability)	0.77
1 (week 2 stability)	0.95
1 (week 3 stability)	0.96
1 (week 4 stability)	0.91
80 (subacute homogeneity top)	72
80 (subacute homogeneity middle)	74
80 (subacute homogeneity bottom)	70
14 (subchronic homogeneity top)	13
14 (subchronic homogeneity middle)	13
14 (subchronic homogeneity bottom)	14

Legend:
mg/mL = milligrams per milliliter

Table 4. Dosing Solution/Suspension Concentration Results

Nominal Concentration (mg/mL)	Analytical Concentration (mg/mL)					
	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6
80 (subacute)	70					
40 (subacute)	36					
20 (subacute)	19					
10 (subacute)	10					
5 (subacute)	4.2					
2.5 (subacute)	2.4					
1.25 (subacute)	1.2					
14 (subchronic)	14	12	13	13	14	16
3.5 (subchronic)	3.7	3.2	3.3	3.5	3.4	3.9
0.875 (subchronic)	0.76	0.75	0.85	0.86	0.81	0.96
0.2188 (subchronic)	0.2	0.21	0.23	0.22	0.25	0.25

Legend:
mg/mL = milligrams per milliliter

7.2 Sequential Stagewise Probit (SSWP) Acute Study

Acute exposure was conducted in five dosing stages. Clinical signs including squinting, lethargy, hunched posture, jerky non-fluid movement, diarrhea, changes in respiratory effort, rearing, dried-red material around the nose, and soft stool were noted on the day of dosing in male and female rats given doses of 550 mg/kg FOX-7 and greater. These clinical signs typically appeared approximately 3–5 hours following dosing and persisted for the remainder of the day in surviving animals. Mortality or intervention euthanasia during the recovery period typically occurred on the day after dosing. However, two male rats (1,047 and 1,698 mg/kg) and one female rat (1,445 mg/kg) died on the same day of dosing, and one male (1,445 mg/kg) and one female rat (1,698 mg/kg) were euthanized on recovery days 6 and 5, respectively, due to rapidly failing health and/or body mass loss. Table 5 summarizes the mortality observed for the five dosing stages. Except for the two rats that were euthanized later in the 14-day recovery period, most surviving rats given ≥550 mg/kg lost body mass on recovery days 1 or 2 but started to recover by day 3. Possible neurological signs including non-fluid movement, hyperactivity, seizure activity, tremors, and rearing with loss of coordination were observed, more frequently in male rats than female, at doses ≥550 mg/kg but were not always associated with morbidity/mortality.

Table 5. Summary of Acute Study Mortality

Male Rats			Female Rats		
Dose (mg/kg)	**Mortality**	**Percent**	**Dose (mg/kg)**	**Mortality**	**Percent**
55	0/1	0	55	0/1	0
175	0/1	0	175	0/1	0
550	1/7	14	550	1/7	14
646	1/4	25	646	2/4	50
759	0/2	0	759	1/2	50
891	2/4	50	891	2/4	50
966	1/2	50	966	1/2	50
1,047	4/4	100	1,047	3/4	75
1,445	1/2	50	1,445	2/2	100
1,698	2/2	100	1,698	2/2	100
2,000	1/1	100	2,000	1/1	100

Legend:
mg/kg = milligrams per kilogram

Gross pathology observations included increased firmness/dehydration of stomach ingesta, congestion of the subcutaneous, mesenteric, and/or meningeal vessels, diarrheal staining, distended stomach, distended and/or flaccid cecum, reddish-brown discoloration of the glandular stomach or intestines, inflammation of the stomach lining, red discoloration of the end of the toes, ulcerative foci in the glandular stomach, yellow ingesta or fluid in the stomach, increased firmness of adhesion between the skin and subcutaneous layer, prominence of subdermal vessels, dilation of the renal pelvis, pale areas of the liver, shrunken right kidney, mass on the left kidney, fluid in the diaphragm, pleural mediastinal clear tan fluid, lung firmness, congested and prominent coronary vessels, and dark purple streaks on the right ventricle. The

resulting LD_{50} from the probit analysis for male rats was 875 mg/kg, with a confidence interval of 708–1,082 mg/kg and a slope of 4.9. For female rats, the LD_{50} was 805 mg/kg with a confidence interval of 668–971 mg/kg and a slope of 5.4. See Appendix E for details of the SSWP acute study.

7.3 Subacute Study

7.3.1 Clinical Observations and Mortality

Irritability and dried red material around the nose were occasionally observed in the 25-, 50-, and 100-mg/kg-d male rats and the 12.5-, 25-, 50-, and 100-mg/kg-d female rats. Additional clinical signs noted in the 200- and 400-mg/kg-d male and female rats during the first week of dosing included dried red material on the mouth, face, and front limbs, rearing while waving front limbs, congested breathing, lethargy, diarrheal staining, shaking, decreased body temperature, labored breathing, hyperactivity, urine staining, ataxia, and seizure activity.

All male and female rats in the 200- and 400-mg/kg-d groups died or were euthanized due to moribund condition by the seventh day of dosing. All other rats survived until scheduled study termination. See Appendix N for details of clinical observations during the subacute study.

7.3.2 Body Mass and Food Consumption

Female body mass did not differ between treated and control groups at any time point throughout the study. At the time of early termination for the 400- and 200-mg/kg-d male rats (days 3 and 7, respectively), body mass was reduced by 14 and 23%, respectively, compared to controls. However, this body mass reduction was not statistically significant. Fasted body mass of the male 100-mg/kg-d group was 11% less than controls on the day of termination but was also not statistically significant. See Appendix F for details of subacute individual and summary of body mass.

Male and female body mass generally increased over time at dosages of 100 mg/kg-d and below. Male body mass gain in the 100-, 200-, and 400-mg/kg-d groups was reduced compared to controls between days 0–1 (82, 172, and 188%; p=0.014, p=0.019, and p=0.009, respectively) and in the 200- and 400-mg/kg-d groups between days 1–3 (214 and 255%; p=0.002 and p=0.001, respectively). Male rats in the 100-mg/kg-d group gained 60% less total weight than controls (p=0.014) from day 1 through day 13. Female rats in the 200- and 400-mg/kg-d groups gained less weight than controls between days 1–3 (204 and 151%, respectively; p=0.000 for both) and in the 100-mg/kg-d group from day 1 through day 13 (48%; p=0.001). See Appendix G for details of subacute individual and summary of body mass change.

Paired food consumption could not be determined for the 200- and 400-mg/kg-d dose groups due to the early termination of these groups. Male and female paired food consumption did not differ among any of the remaining treatment groups at any time point. Food consumption by male rats in the 100-mg/kg-d group was 35% lower than that of controls between days 0 and 7

but returned to control levels between days 7 and 13. See Appendix H for details of subacute individual and summary of paired food consumption.

7.3.3 Hematology

Platelets (PLT) and RET-He were reduced, relative to the control group, in the male 100-mg/kg-d FOX-7 group (0.5 and 0.9-fold; p=0.001 and p=0.006, respectively). Platelets (PLT) exceeded normal ranges in all dose groups except the 100-mg/kg-d group (reference 27). Mean platelet volume (MPV) and MONO counts were increased, relative to the control group, in the male 100-mg/kg-d FOX-7 group (1.2 and 2.3-fold; p=0.002 and p=0.001, respectively). Monocyte counts in all male-treated and control groups exceeded normal ranges.

Female WBC counts were elevated, relative to concurrent controls and published normal ranges in the 100-mg/kg-d FOX-7 group (1.7-fold and p=0.022). Female HGB, percent HCT, PLT, and RET% were reduced relative to the control (0.9, 0.9, 0.5, and 0.5-fold; p=0.008, p=0.012, p=0.000, and p=0.001, respectively) in the 100-mg/kg-d FOX-7 group. The 100-mg/kg-d HGB and HCT values were within published normal ranges, while PLT was below. However, HGB, HCT, and PLT values for all other female FOX-7 and control groups were above normal ranges. Red blood cell distribution width – standard deviation was increased, relative to control, in the female 50-mg/kg-d FOX-7 group (1.1-fold and p=0.018). Female MPV generally increased with dose but only differed from control in the 50- and 100-mg/kg-d FOX-7 groups (1.1 and 1.2-fold; p=0.017 and p=0.000, respectively). Lymphocyte count in the female 100-mg/kg-d FOX-7 group was increased relative to control (1.7-fold and p=0.022) and was above normal ranges. See Appendix I for details of subacute individual and summary of hematology data.

7.3.4 Clinical Chemistry

Male ALB concentrations remained within published normal ranges but were increased, relative to the control, in the male 100-mg/kg-d FOX-7 group (1.1-fold and p=0.003). Blood urea nitrogen levels were generally below normal ranges and were increased in the male 100-mg/kg-d group relative to the control (1.9-fold and p<0.001). Male TP values in the 100-mg/kg-d group were elevated compared to normal ranges and concurrent controls (1.1-fold and p=0.014). Male AMY concentration was decreased (0.6-fold and p=0.011) in the 100-mg/kg-d group relative to the control. Blood urea nitrogen to creatinine ratios (1.5 and 1.7-fold; p=0.006 and p=0.001) and CHOL (1.4 and 1.6-fold; p=0.006 and p=0.001) levels were increased in the male 50- and 100-mg/kg-d groups compared to the control. All male CHOL group means were above normal ranges except for the 6.25-mg/kg-d group. Additional differences, relative to the control, in male clinical chemistry values included decreases in ALT in the 50-mg/kg-d group (0.7-fold and p=0.002), AST in the 12.5- and 50-mg/kg-d groups (0.8 and 0.8-fold; p=0.023 and p=0.035, respectively), CK in the 12.5-mg/kg-d group (0.5-fold and p=0.027), and CREA in the 50-mg/kg-d group (0.8-fold and p=0.041). None of these male blood chemistry values exhibited dose-dependent decreases, and all dose groups were generally outside of published normal ranges.

Female BUN/CREA ratios and CHOL values were increased in the 100-mg/kg-d group relative to the control (1.5 and 1.8-fold; p=0.004 and p=0.003, respectively). Female CHOL group means were generally all above normal ranges, except for the 12.5-mg/kg-d group. Creatinine

levels were decreased, relative to the control, in the female 50- and 100-mg/kg-d groups (0.8 and 0.8-fold; p=0.020 and p=0.025, respectively); however, all groups exceeded normal ranges except the 50-mg/kg-d group. Triglycerides (TRIG) in the female 12.5-mg/kg-d group exhibited a non-dose dependent decrease relative to the controls (0.6-fold and p=0.008). See Appendix J for details of subacute individual and summary of clinical chemistry data.

7.3.5 Electrolytes and Prothrombin Time

Male and female electrolyte and prothrombin time values were not affected by FOX-7 administration relative to the controls. See Appendix K for details of subacute individual and summary of electrolytes and prothrombin time data.

7.3.6 Organ Mass and Ratios

Mean male brain, adrenal, kidney, and spleen mass and/or mass ratios differed between the 50- and 100-mg/kg-d FOX-7 groups relative to the control. Mean absolute adrenal and kidney mass were increased (1.1-fold for both) in the male 100-mg/kg-d group relative to the control (p=0.032 and p=0.000, respectively) when analyzed using body mass as a covariate. Male brain mass relative to the control was increased in the 50-mg/kg-d (1.05-fold and p=0.016) and 100-mg/kg-d (1.02-fold and p=0.013) groups. Male spleen mass was also increased in the 50-mg/kg-d (1.3-fold and p=0.007) and 100-mg/kg-d (1.5-fold and p=0.000) FOX-7 groups. Brain, adrenal, and kidney-to-body mass ratios were increased in the male 100-mg/kg-d group (p=0.031, p=0.044, p=0.000, respectively). Male spleen-to-body mass ratios were increased in the 50- and 100-mg/kg-d groups (p=0.001, p<0.001, respectively), while male spleen-to-brain weight ratios were only increased in the 100-mg/kg-d group (p=0.006). Male heart, thymus, liver, testes, and epididymides mass were unaffected by FOX-7 treatment.

Mean female kidney, spleen, heart, liver, and ovary mass and/or mass ratios differed between the FOX-7 groups and the control. Mean absolute spleen mass was increased in the female 50-mg/kg-d (1.3-fold and p=0.020) and 100-mg/kg-d (1.3-fold and p=0.000) groups relative to the control when analyzed using body mass as a covariate. Heart mass was increased in the female 6.25-, 25-, 50-, and 100-mg/kg-d groups (1.1, 1.1, 1.1, and 1.04-fold, respectively) relative to the control (p=0.015, p=0.000, p=0.008, and p=0.001, respectively). Mean absolute liver mass in the female 12.5-mg/kg-d group and ovary mass in the 100-mg/kg-d group was decreased (0.9 and 0.8-fold, respectively) relative to controls (p=0.039 and p=0.024, respectively). Female kidney- and spleen-to-body mass ratios were increased in the 100-mg/kg-d group (p=0.047 and p=0.004, respectively). Female heart-to-body mass ratio was increased in the 25- and 100-mg/kg-d groups (p=0.008 for both) relative to the control. Female brain, adrenal, thymus, and uterus mass were unaffected by FOX-7 treatment. See Appendix L for details of subacute organ mass and mass ratios.

7.3.7 Micronucleus Assay

The frequency of micronucleated reticulocytes (%MN-RET) ranged from 0.14 to 0.18% in male rats treated with 25-, 50-, and 100-mg/kg-d doses of FOX-7 in corn oil. Treatment with FOX-7 did not increase the frequency of %MN-RET in the peripheral blood of male rats. These results

indicate that FOX-7 is not genotoxic in rat peripheral blood at the doses tested. See Appendix M for details of the micronucleus assay.

7.3.8 Pathology

Minimal gross observations were noted in male rats receiving 100 mg/kg-d of FOX-7 and below. One control male rat had a mottled orange liver and one additional male control had a 3-millimeter white mass on the liver. Scant dark red material adjacent to the pyloric mucosa was noted in one 12.5-mg/kg male rat. Dried stomach contents and scant dark red material adjacent to the pyloric mucosa was observed in one 50 mg/kg-d male rat. Observations in 200- and 400-mg/kg-d male rats that died or were euthanized before the end of the study period were primarily limited to the gastrointestinal system. Distended stomach with firm and or dried ingesta was noted in four 200-mg/kg-d and five 400-mg/kg-d male rats. Five 200-mg/kg-d and six 400-mg/kg-d male rats were noted with varying grades of irritation and/or the apparent presence of blood in the stomach. Congestion, prominence, or discoloration of the mesenteric lymph nodes was observed in four 200-mg/kg-d and six 400-mg/kg-d male rats. Discoloration, irritation, or observation of a material that was likely blood in the intestines was observed in two 200-mg/kg-d and four 400-mg/kg-d male rats. Congestion of the subcutaneous vessels was only observed in one 200-mg/kg-d male rat but was present in all 400-mg/kg-d male rats. The seminal vesicles appeared smaller than normal in four of the 400-mg/kg-d male rats, and one 200-mg/kg-d male rat was observed with approximately 1 mL of pleural serosanguinous fluid.

Gross pathology observations in female rats were very similar to those in male rats with minimal observations at 100 mg/kg-d and below and primarily gastrointestinal abnormalities at 200 mg/kg-d and above. One 25-mg/kg-d female rat was observed with minimal abdominal fat, one 50-mg/kg-d female rat had a pale nutmeg-colored liver, and one 50-mg/kg-d female rat was observed with a pronounced lobular pattern on the thymus. One 50-mg/kg-d and one 100-mg/kg-d female rats were noted with a fluid-filled uterus. Distended stomach with varying mixtures of normal or desiccated ingesta was noted in two 200-mg/kg-d and all of the 400-mg/kg-d female rats. Three 200- and three 400-mg/kg-d female rats appeared to have irritated regions of the pyloric stomach occasionally associated with the appearance of blood. Congestion and/or discoloration of the mesenteric lymph nodes were noted in one 200-mg/kg-d and one 400-mg/kg-d female rats. Additional female gross observations noted sporadically included: mottled/discolored thymus (one 200 mg/kg-d), empty stomach and intestinal tract (one 200 mg/kg-d), empty colon (one 400 mg/kg-d), red/irritated ovaries (one 400 mg/kg-d), enlarged spleen (one 400 mg/kg-d), red staining on the nose (one 400 mg/kg-d), and diarrheal staining (one 400 mg/kg-d). See Appendix N for a summary of the subacute gross pathology observations.

7.4 Subchronic Oral Toxicity Study

7.4.1 Clinical Observations and Mortality

Morbidity was observed in one male and one female rat in the 70-mg/kg-d group and one female rat in the 17.5-mg/kg-d group. The male rat was euthanized on day 74 following observations of excessive loss in body mass, hunched posture, squinting, and twitching. Both

female rats were euthanized due to masses that had subsequently ulcerated and presented an infection risk. The 70-mg/kg-d female rat was euthanized on day 62 with a subcutaneous mass on the ventral neck, and the 17.5-mg/kg-d female rat was euthanized on day 78 with a suspected mammary fibroadenoma on the left chest wall behind the elbow. Clinical signs of toxicity were similar between male and female rats and included excitability, irritability, chromodacryorrhea, lethargy, rough haircoat, disorientation, and squinting in the 70-mg/kg-d groups. In addition, seizures were also observed in 30% of the 70-mg/kg-d male and female rats. Clinical signs observed in the 17.5-, 4.38-, and 1.09-mg/kg-d male and female rats were very similar and included irritability, dried red material on front paws, scabs, sores, hair loss, and excitability. One 1.09-mg/kg-d male rat exhibited congested breathing, and one 1.09-mg/kg-d female rat was observed with bright yellow urine. Clinical signs observed sporadically throughout all dose groups, including controls, were limited to BAR, dried red material around the nose, and hair loss. See Appendix W for details of the clinical observations during the subchronic study.

7.4.2 Body Mass, Food Consumption, and Food Efficiency

7.4.2.1 Male Rats

Body mass generally increased with time for all dose groups throughout the study, except for overnight fasting just before necropsy. The body mass of male rats given 70 mg/kg-d FOX-7 was reduced (16-24%) relative to controls, from week 3 through week 13 ($p=0.003$, $p=0.003$, $p=0.004$, $p=0.002$, $p=0.001$, $p=0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p=0.001$, and $p<0.001$). Final-fasted body mass in the 70-mg/kg-d group was reduced (26%) relative to controls on day 91 ($p=0.001$). Male body mass in all other FOX-7 dose groups did not differ from controls at any time during the study. Body mass change in the 70-mg/kg-d male rats was reduced (24, 66, 34, 56, 54, 58, and 86%, respectively), relative to controls, during weeks 1, 3, 4, 6, 7, 8, and 9 of the study ($p=0.036$, $p<0.001$, $p=0.028$, $p<0.001$, $p=0.015$, $p=0.027$, and $p=0.002$, respectively). Total body-mass change for the 13-week study period was 43% lower than that of corn oil controls ($p<0.001$). Body-mass change in all other FOX-7 dose groups did not differ from controls during the study. Male paired food consumption, reported as grams of food consumption per gram rat, only differed from controls during week 12 ($p<0.001$) in the 70-mg/kg-d group and was reduced by 17%. Paired food efficiency was reduced, relative to controls, in the 70-mg/kg-d group during week 3 (64%; $p<0.001$) and for the entire study period (34%; $p=0.030$). See Appendices O, P, and Q for details of male subchronic body mass, body-mass change, food consumption, and food efficiency.

7.4.2.2 Female Rats

Body mass in all female dose groups increased with time during weeks 1 through 9. Mean body mass in the 1.09-, 4.38-, and 17.5-mg/kg-d FOX-7 groups decreased between weeks 11 and 12. Mean body mass in the 70-mg/kg-d female rats decreased between weeks 9 and 10, 11 and 12, and 12 and 13. The body mass of female rats given 70 mg/kg-d of FOX-7 was reduced (10-16%), relative to controls, from week 5 through week 13 ($p=0.020$, $p=0.012$, $p=0.005$, $p=0.003$, $p=0.008$, $p=0.003$, $p=0.003$, $p=0.001$, and $p<0.001$). Final-fasted body mass in the 70-mg/kg-d group was reduced (16%) relative to controls on day 91 ($p<0.001$). Body-mass change in the

70-mg/kg-d female rats was reduced (49, 55, and 180%) compared to controls during weeks 2, 3, and 13 (p=0.042, p=0.015, and p=0.032). Body-mass change in the 17.5-mg/kg-d female rats, relative to controls, was increased during week 10 (83%; p=0.013) and decreased during week 13 (53%; p=0.023). Female paired food consumption, reported as grams of food consumption per gram rat, did not differ among any of the FOX-7 treatment groups and controls at any time point. Paired food efficiency was reduced, relative to controls, in the 70-mg/kg-d group during week 3 (52%; p=0.035) and for the entire study period (51%; p=0.046). Food efficiency was increased in the 17.5-mg/kg-d female rats during week 10 (84%; p=0.010). See Appendices O, P, and Q for details of female subchronic body mass, body-mass change, food consumption, and food efficiency.

7.4.3 Neurobehavioral Evaluations

7.4.3.1 Home Cage Observations

No weekly differences between male and female FOX-7 treatment groups and controls were observed in any of the home-cage parameters: agitation, convulsions, tremors, posture, and mutilation. Severe convulsions and tremors were observed in one female 70-mg/kg-d rat during week-7, home-cage observations.

7.4.3.2 Handheld Observations

No weekly differences between male and female FOX-7 treatment groups and controls were observed for the handheld parameters: RH, LAC, SAL, BAR, PIL, PC (each eye), exophthalmos, or PS (each eye). The female 70-mg/kg-d group had an increased incidence (p=0.028) of rats that were classified as either slightly difficult or very difficult to remove from the cage during week 10. Mean reactivity to handling and ER scores in the 70-mg/kg-d male rats were slightly higher than controls during week 11; however, these handheld observations did not differ between any of the FOX-7 treatment groups relative to control during any week of observation.

7.4.3.3 Open Arena Observations

No weekly differences between male and female FOX-7 treatment groups and controls were observed for the open-arena observations grooms, gait, fecal boli, fecal description, or urine. Beginning during week 6 of open-arena observations, male rats in the 70-mg/kg-d began to exhibit higher mean arousal scores; however, the increased arousal scores were only significant relative to controls during week 9 (p=0.023). Mean arousal scores in the female 70-mg/kg-d group were generally lower than all other dose groups each week and were reduced, relative to the control, during weeks 3 and 9 (p=0.009 and p=0.006, respectively). Rear counts in the female 1.09-, 4.38-, and 70-mg/kg-d groups were reduced, relative to the control, during week 3 of open-arena observations (p=0.003, p=0.036, and p=0.002, respectively). Rear counts for male rats did not differ between any of the FOX-7 treatment groups relative to control during any week of observation.

7.4.3.4 Elicited Responses

There were no differences between male and female FOX-7 treatment groups and controls in any of the elicited responses evaluated during week 11: approach, auditory startle response, tail pinch, pinna response, pupillary response, righting reflex, aerial righting, landing foot splay, forelimb grip strength, and hindlimb grip strength.

7.4.3.5 Motor Activity

There were no differences between male and female FOX-7 treatment groups and controls during week 11 motor activity evaluations in basic movement, immobility, X and Y ambulation, and nose pokes.

7.4.4 Ophthalmic Examinations

During the pre-study ophthalmic exams, one male rat was observed with an enlarged/dilated optic disk in the left eye relative to the right. This rat was later randomized into the 70-mg/kg-d group and was examined again near the end of the study. No difference in the abnormality was appreciated during the term optic exam. No other abnormalities were observed in all male rats during the pre-study eye exam or in the surviving control and 70-mg/kg-d male rats during the term exam.

A total of four female rats were observed with mild-to-moderate stromal defects in either the left or right cornea during the pre-study ophthalmic exams. None of these rats were subsequently randomized into the control or 70-mg/kg-d groups; however, they were also examined again during the term exam. Two of the female rats no longer had the stromal defect, and the other two still had the defect at the same severity observed during the pre-study exams. Two additional 70-mg/kg-d female rats were also observed with this same defect in one or both corneas during the term exams. Since this abnormality was observed during the pre-study ophthalmic exams and did not increase in severity throughout the study, it was not considered to be related to the administration of FOX-7, and the remaining female dose groups were not examined during the term exam.

7.4.5 Animal Health Monitoring

The pooled, pre-study health monitoring sample was positive for Group B *Streptococcus agalactiae* (Beta Strep. Grp. B), *Klebsiella peneumoniae*, *Staphylococcus aureus*, and *Proteus mirabilis*. The health report sent with the animals at delivery indicated that the rats had tested positive for Beta Strep. Grp. B, *Klebsiella peneumoniae*, and *Staphylococcus aureus* before shipment to the test facility. EAD samples collected and analyzed near the end of the study indicated the presence of Beta Strep. Grp. B and Pseudomonas aeruginosa in the female cage rack only, and *Klebsiella peneumoniae* and *Proteus mirabilis* in both the male and female cage racks. These bacteria are commonly found in laboratory rats, and there is no known interference with research associated with the carrier states (reference 28).

7.4.6 Clinical Chemistry

7.4.6.1 Male Rats

Alanine aminotransferase and AST levels in the 17.5- and 70-mg/kg-d groups were lower (0.8-fold for all) than in the control group (p=0.002, p=0.026 and p=0.009, p=0.020, respectively). Alanine aminotransferase and AST levels did not decrease in a dose-dependent manner and remained within normal ranges for all dose groups. Creatinine kinase levels decreased in a dose-dependent manner, were lower (0.5- and 0.4-fold, respectively) in the 17.5- and 70-mg/kg-d groups relative to controls (p=0.001 and p<0.001), and levels for all dose groups were below normal ranges. Glucose levels in the 70-mg/kg-d group were decreased (0.7-fold; p=0.045) and BUN/CREA ratios were decreased (0.8-fold; p=0.038) in the 17.5-mg/kg-d group relative to controls. See Appendix R for details of individual and summary male subchronic clinical chemistry.

7.4.6.2 Female Rats

Aspartate aminotransferase (AST) and TRIG levels in the 70-mg/kg-d group were reduced (0.6-fold for both) relative to the control group (p=0.008 for both). The AST levels in the 4.38- and 70-mg/kg-d groups were within normal ranges, while the remainder of the dose groups were above. The TRIG levels for all dose groups were below normal ranges except for the 4.38-mg/kg-d group, which was within normal levels. Cholesterol levels increased in a dose-dependent manner and were elevated (1.3- and 1.7-fold, respectively) in the 17.5- and 70-mg/kg-d groups compared to controls (p=0.004 and p<0.001). The 17.5- and 70-mg/kg-d groups were also above normal ranges. Globulin levels in the 17.5- and 70-mg/kg-d groups exhibited minor increases (1.1-fold for both) relative to controls, but the increase was only significant in the 17.5-mg/kg-d group (p=0.037). Serum PHOS levels in the 1.09- and 70-mg/kg-d groups were decreased (0.9-fold for both) relative to controls (p=0.034 and p=0.013, respectively); however, the PHOS levels for all dose groups were above normal ranges. See Appendix R for details of individual and summary of female subchronic clinical chemistry.

7.4.7 Hematology

7.4.7.1 Male Rats

Differences in hematological parameters, relative to controls, were primarily observed in the highest FOX-7 dose group of 70 mg/kg-d. White blood cell counts in the 70-mg/kg-d group were increased (1.9-fold) relative to the control group, but WBC counts were above reported normal ranges for all dose groups. Neutrophil, LYMPH, and MONO counts in the 70-mg/kg-d group were increased (1.8-, 1.9-, and 2.2-fold; p=0.008, p=0.005, and p=0.001, respectively) compared to controls. The NEUT, LYMPH, and MONO counts were generally all above normal ranges for all dose groups, except for the LYMPH counts in the control and 4.38-mg/kg-d groups. Eosinophil counts and percent EOS were below normal ranges and were reduced, relative to the control group, in the 70-mg/kg-d group (0.3- and 0.1-fold, respectively; p<0.001 for both). Basophil counts in the 70-mg/kg-d group were increased (2.3-fold; p=0.004) relative to

controls and were above normal ranges in the 70-mg/kg-d group. Percent BASO in the 1.09-mg/kg-d group were increased (1.4-fold; p=0.046) compared to concurrent controls.

Red blood cell counts, percent HCT, and MCV in the 70-mg/kg-d group were reduced relative to the control (0.9-, 0.9-, and 0.95-fold; p=0.001, p<0.001, and p=0.040, respectively) but remained within normal published ranges. Hemoglobin concentrations were below normal ranges in the 70-mg/kg-d group and were reduced in the 17.5- and 70-mg/kg-d groups compared to concurrent controls (0.95- and 0.9-fold; p=0.007 and p<0.001, respectively). Platelets were below normal ranges in the 70-mg/kg-d group and were reduced relative to the control (0.6-fold and p<0.001). The PLT counts in all other dose groups were above normal ranges. Mean platelet volume was increased in the 70-mg/kg-d group relative to the control group (1.2-fold; p<0.001). See Appendix S for details of individual and summary of male subchronic clinical chemistry.

7.4.7.2 Female Rats

White blood cell counts were slightly above published normal ranges in the 70-mg/kg-d group (1.3-fold) but were not increased relative to concurrent controls. Percent EOS were below normal ranges in the 70-mg/kg-d group and were reduced relative to the control (0.5-fold; p=0.008).

Red blood cell counts (RBCs), HGB, percent HCT, and PLT in the 70-mg/kg-d group were reduced relative to controls (0.8-, 0.8-, 0.8-, and 0.7-fold, respectively; p<0.001 for all) and were below normal ranges. The remaining dose groups remained within or slightly above normal ranges for these hematological parameters. Red blood cell distribution width in the 70-mg/kg-d group was slightly increased (1.1-fold) and was significantly different from concurrent controls (p=0.008). Mean platelet volume increased in a dose-dependent manner and was increased relative to the control in the 17.5- and 70-mg/kg-d groups (1.05- and 1.2-fold; p=0.017 and p<0.001, respectively). See Appendix S for details of individual and summary of female subchronic clinical chemistry.

7.4.8 Electrolytes and Prothrombin Time

7.4.8.1 Male Rats

Sodium and GLU levels in the 70-mg/kg-d group were decreased relative to the control (0.97- and 0.7-fold; p<0.001 and p=0.041, respectively). No other differences between FOX-7-treated male rats and controls were observed for electrolytes or average prothrombin time. See Appendix T for details of male subchronic individual and summary of electrolytes and prothrombin time data.

7.4.8.2 Female Rats

Glucose was decreased in a dose-dependent manner and was significantly reduced relative to controls in the 70-mg/kg-d group (0.7-fold; p=0.003). Ionized calcium (iCa) and Lac levels in the 70-mg/kg-d group were also reduced relative to controls (0.95- and 0.6-fold; p=0.026 and

p=0.003, respectively). No other differences between FOX-7-treated female rats and controls were observed for electrolytes or average prothrombin time. See Appendix T for details of female subchronic individual and summary of electrolytes and prothrombin time data.

7.4.9 Organ Mass and Ratios

7.4.9.1 Male Rats

Male brain, kidney, spleen, heart, thymus, liver, testes, epididymides, thyroid, and pituitary mass and/or mass ratios differed between the 17.5- and 70-mg/kg-d FOX-7 groups and the control. Mean absolute spleen and thyroid mass were increased (1.4- and 2.1-fold) in the 70-mg/kg-d group relative to the control ($p<0.001$ for both) when analyzed using body mass as a covariate. Spleen-to-body mass ratios in the 17.5- and 70-mg/kg-d groups were increased ($p=0.002$ and $p<0.001$, respectively) as well as spleen-to-brain mass ratios in the 70-mg/kg-d group only ($p=0.005$). Thyroid-to-body and brain mass ratios in the 70-mg/kg-d group were increased ($p<0.001$ for both). Mean absolute epididymides mass was decreased in the 70-mg/kg-d group (0.6-fold; $p=0.035$). Epididymides-to-body and brain mass ratios were also reduced in the 70-mg/kg-d group ($p=0.035$ and $p<0.001$, respectively). Although absolute brain mass in the 70-mg/kg-d group was only increased compared to the 17.5-mg/kg-d group using body mass as a covariate, brain-to-body mass ratios were increased in the 70-mg/kg-d group compared to controls ($p<0.001$). Heart- and kidney-to-body mass ratios were increased in the 70-mg/kg-d group ($p=0.006$ and $p=0.003$, respectively); however, heart- and kidney-to-brain mass ratios were decreased in this group ($p=0.022$ and $p=0.017$, respectively). Thymus-, liver-, and testes-to-brain mass ratios were all decreased in the 70-mg/kg-d group ($p=0.003$ for all). Pituitary-to-brain mass ratios were increased in the 70-mg/kg-d group ($p=0.030$). Male adrenal, prostate, and seminal vesicle mass were unaffected by FOX-7 treatment. See Appendix U for details of male subchronic organ mass and organ mass ratios.

7.4.9.2 Female Rats

Female brain, adrenal, kidney, spleen, heart, liver, and thyroid mass and/or mass ratios differed between the 17.5- and 70-mg/kg-d FOX-7 groups and the control. Mean absolute spleen and thyroid mass were increased (1.2- and 1.5-fold) in the 70-mg/kg-d group relative to the control ($p=0.001$ and $p<0.001$, respectively) when analyzed using body mass as a covariate. Absolute spleen mass was also increased (1.2-fold) in the 17.5-mg/kg-d group ($p=0.008$). Spleen- and thyroid-to-body mass ratios were increased in the 70-mg/kg-d group ($p<0.001$ for both), but only thyroid-to-brain mass ratios were increased in the 70-mg/kg-d group ($p=0.002$). Absolute adrenal and liver mass were decreased (0.9-fold for both) relative to the control in the 17.5-mg/kg-d group ($p=0.008$ and $p=0.045$, respectively). Brain- and kidney-to-body mass ratios were increased in the 70-mg/kg-d group ($p=0.003$ and $p=0.033$, respectively). Adrenal-, heart-, and liver-to-brain mass ratios were decreased in the 70-mg/kg-d female rats relative to the control ($p=0.001$, $p=0.045$, and $p=0.022$, respectively). See Appendix U for details of female subchronic organ mass and organ mass ratios.

7.4.10 Sperm Analysis

Sperm count adjusted for cauda weight ranged from 41 to 163 million/gram and was decreased in the 70-mg/kg-d male rats compared to controls (0.3-fold; p=0.005). The proportion of motile and progressively-motile sperm ranged from 7 to 22% and 0.6 to 1.2%, respectively. The proportion of motile sperm in the 70-mg/kg-d male rats was decreased compared to controls (0.3-fold; p=0.004); however, progressively motile sperm did not differ between FOX-7 treatment groups and control. See Appendix V for details of the sperm analysis results.

7.4.11 Pathology

7.4.11.1 Male Rats

The gross pathological examination of the one 70-mg/kg-d, pre-term, moribund euthanized rat indicated dried red material on the front paws and nose, rough exterior spleen surface, mottled liver, dark red areas on the interior surface of the stomach, dark red material in the large intestine, pink cecum contents that lack consistency, and bright white mesenteric lymph nodes and pancreas. No macroscopic findings were noted in any of the control male rats. One 1.09-mg/kg-d male rat had numerous 1-millimeter (mm) red dots on the surface of the thymus and two male rats (one 4.38 and one 17.5 mg/kg-d) had a 2- to 3-mm yellowish white mass on the tip of the liver. Swollen and mottled brown/yellow pancreas was noted in one 17.5-mg/kg-d and one 70-mg/kg-d male rat. Hair loss on the left side of the abdomen, thorax, and face was observed in one 17.5 mg/kg-d male rat. Additional findings noted in surviving 70-mg/kg-d male rats included numerous 1- to 2-mm hemorrhagic spots on the thymus (3 of 9), unkempt haircoat (2 of 9), porphyrin staining around nose (1 of 9), mottled brown mesenteric lymph nodes (1 of 9), gas in the large intestine (1 of 9), flaccid testis (2 of 9), lack of digesta in small intestine (1 of 9), and swollen rectum with four small red dots on the mucosal surface (1 of 9). See Appendix W for a summary of the subchronic male gross pathology findings.

7.4.11.2 Female Rats

Two female rats (one 17.5 mg/kg-d and one 70 mg/kg-d) were euthanized early due to the formation of masses that ulcerated. The masses are described in paragraph 7.4.1. Upon necropsy, the 17.5-mg/kg-d female rat was also observed with a pale jejunum and a 7-mm dark red/orange mass adjacent to the terminal esophagus that may have been a lymph node. The 70-mg/kg-d, pre-term euthanasia was also observed with an enlarged right cervical lymph node (2-3x normal) and slight yellow discoloration of the brain. One control was noted with a gas-filled cecum and one control had hair loss on both front limbs. Flaccid/dilated and reddened small intestines was noted in one control, one 1.09 mg/kg-d, one 17.5 mg/kg-d, and two 70-mg/kg-d female rats. Yellow discoloration of the liver was observed in one control, one 1.09 mg/kg-d, two 17.5 mg/kg-d, and three 70-mg/kg-d female rats. One 4.38 mg/kg-d and three 70-mg/kg-d female rats had noticeably less body fat than expected. One 1.09-mg/kg-d female rat was noted with a 2-mm white mass on the medial edge of the liver lobe and one 4.38-mg/kg-d female rat had hair loss on the right abdomen. Brownish-gray discoloration of the kidneys was observed in two 70-mg/kg-d female rats. Thymus findings, including pink/red discoloration and/or reduction

in size, was observed in two 70-mg/kg-d female rats. See Appendix W for a summary of the subchronic female gross pathology findings.

7.4.12 Urinalysis

In male rats, urine volume was increased (3.5-fold) in the 70-mg/kg-d group (p=0.002). Water intake also increased in a dose-dependent manner in the 1.09-, 4.38-, 17.5-, and 70-mg/kg-d groups (1.2-, 1.3-, 1.5-, and 1.8-fold, respectively); however, these increases were not significant. Urine nitrite and leukocytes were also increased in the 70-mg/kg-d male rats relative to controls (p<0.001 for both). Urine specific gravity was decreased in the 70-mg/kg-d group (p=0.001). The remaining urine parameters: color, appearance, glucose, bilirubin, ketone, blood, pH, protein, and urobilinogen did not differ between the FOX-7 male dose groups and the control group.

In female rats, urine volume was increased (2.6-fold) in the 70-mg/kg-d group (p=0.006), and water intake was decreased (0.5-fold) in the 4.38-mg/kg-d female rats (p=0.012). Urine pH and urine nitrite were increased in the 70-mg/kg-d female rats relative to controls (p=0.020 and p<0.001, respectively). Urine specific gravity was decreased in the 70-mg/kg-d group (p=0.003). The remaining urine parameters: color, appearance, glucose, bilirubin, ketone, blood, pH, protein, urobilinogen, and leukocytes did not differ between the FOX-7 female dose groups and the control group. See Appendix X for details regarding male and female subchronic urinalysis.

7.4.13 Thyroid Hormone Analysis

T_3 levels did not differ from controls with oral exposure to FOX-7 in either male or female animals. T_4 levels in the 70-mg/kg-d male rats decreased 15 and 21% relative to the control and 1.09-mg/kg-d groups; however, this decrease was only significant compared to the 1.09-mg/kg-d male rats (p=0.007). T_4 levels decreased 25% relative to controls (p=0.012) in female rats dosed with 70-mg/kg-day FOX-7 and was also significantly lower compared to female rats dosed with all other FOX-7 concentrations. TSH in male rats dosed with 70-mg/kg-d FOX-7 was increased (3.3-fold; p=0.007) compared to the control and was also increased 2.7 – 4.6-fold relative to the other male FOX-7 treatment groups. TSH in female rats dosed with 70-mg/kg-d FOX-7 was increased (8.7-fold; p=0.002) compared to the control and was also increased 9.1 – 12.7-fold relative to the other female FOX-7 treatment groups. See Appendix Y for details of the subchronic thyroid hormone analysis.

7.4.14 Histopathology

7.4.14.1 Male Rats

Treatment-related changes were observed in the thyroid, testes, epididymides, and seminal vesicles of the 70-mg/kg-d FOX-7 male rats only. Tissues were collected and microscopically evaluated from the 70-mg/kg-d male rat that was euthanized due to rapidly failing health on day 74. Histopathology results from this rat were included in the final analysis. Follicular cell hypertrophy in the thyroid was observed in all 10 high-dose male rats (p<0.001, mean severity 1). The hypertrophy was observed in essentially all of the follicular epithelial cells and appeared

to compress the interstitial spaces. Follicle colloid depletion was also appreciated in the high-dose male rats relative to controls.

In the testes, 6 of 10 high-dose male rats (p=0.011) were observed with atrophy/degeneration/loss of spermatogonia (average 92.5% loss), diffuse tubular atrophy (mean severity 1.2), hypospermia/aspermia (mean severity 5), and increased interstitial cellularity (mean severity 1). Interstitial edema was also observed in the testes of high-dose male rats at an increased incidence and severity (9 of 10, mean severity 1.3) relative to controls (p=0.001). Increased interstitial clear space was observed at an equal incidence and severity between high-dose and control male rats. Interstitial edema was also observed in the testes of both control and high-dose male rats; however, both incidence and severity (9 of 10, mean severity 1.3) were increased (p=0.005) in the high dose.

Hypospermia/aspermia of the epididymides was observed in 8 of 10 high-dose male rats (p=0.001, mean severity 1). All high-dose male rats also had coagulating gland cellular hypertrophy of the seminal vesicles (p<0.001, mean severity 1).

The thyroid, testes, and epididymides from the 17.5-mg/kg-d male rats were microscopically evaluated but were deemed normal relative to controls. Other incidental changes noted in organs examined in the high-dose male rats were either not of increased incidence relative to controls or were background lesions that were not of biologic or toxicologic relevance. See Appendix Z for the histopathology report.

7.4.14.2 Female Rats

Treatment-related changes were observed only in the thyroid of the 70-mg/kg-d FOX-7 female rats. Tissues were collected and microscopically evaluated from the 70-mg/kg-d female rat that was euthanized on day 62 due to an ulcerated mass. Histopathology results from this rat were included in the final analysis.

Like male rats, follicular cell hypertrophy in the thyroid was observed in all 10 high-dose female rats (p<0.001, mean severity 1). The hypertrophy was observed in essentially all of the follicular epithelial cells and appeared to compress the interstitial spaces. Follicle colloid depletion was also appreciated in the high-dose female rats relative to controls.

Thyroid sections from the 17.5-mg/kg-d female rats were microscopically evaluated, including the rat that was euthanized on day 78 due to an ulcerated mass. Follicular cell hypertrophy was not observed in any of the rats from this dose group. Other incidental changes noted in organs examined in the high dose female rats were either not of increased incidence relative to controls or were background lesions that were not of biological or toxicological relevance. See Appendix Z for the histopathology report.

7.4.15 Benchmark Dose

Several endpoints were modeled using Benchmark Dose Software (BMDS 3.3.2) to determine goodness of fit; however, most significant endpoints were only observed in the highest dose

evaluated and did not display a dose response. Alterations in red blood cell indices (RBC, HGB, HCT) indicative of anemia displayed the clearest dose-dependent response in both sexes, and HGB concentration was identified as the critical effect. BMDS was used to fit mathematical models to the mean male and female HGB concentrations for each dose group and calculate a lower-bound confidence limit on a dose corresponding to a 1 standard deviation response rate (BMDL). Although male HGB concentrations exhibited significant reductions in both the 17.5- and 70-mg/kg-d groups, the mean female HGB results provided the best fitting biologically plausible model. Based primarily on the lowest Akaike Information Criterion value, the BMDS recommended the Linear model as the best representation of the data, with a BMD of 12 mg/kg-d and a BMDL of 10 mg/kg-d. All models of the male HGB concentration provided questionable curve fits but were also in agreement with a BMDL of 10 mg/kg-d. See Appendix AA for details of the BMD analysis.

7.4.16 Standing Operating Procedure Deviations

The Standing Operating Procedure (SOP) for ophthalmic examinations (QSARC SOP 716) states that the animal room lights will remain off for 2 hours following the pre- and post-study eye exams (reference 24). Following the advice of the Attending Veterinarian, the animal room lights remained off for the remainder of the light cycle after the eye exams rather than the 2 hours specified in the SOP. The protocol stated that the lights would remain off for a minimum of 2 hours, so this does not represent a protocol deviation.

The protocol was written and approved well before the subacute and subchronic phases were initiated. The protocol referenced the use of the VetLyte electrolyte analyzer to determine electrolyte values (TOX SOP 011) and the use of Cell-Dyn hematology analyzer for hematological analyses (TOX SOP 013) (references 20 and 21). New electrolyte and hematology analyzers were subsequently received and used for the subacute and subchronic clinical pathology but did not yet have SOPs referencing their use. The use of these new analyzers was documented in the clinical pathology records and in this technical report.

The Toxicology Directorate SOP for the Neurotoxicity Screen and the FOB (TOX SOP 62) states that the grip-strength meter will be verified using standard weights and recorded in the FOB notebook each day before use (reference 23). The self-test procedure for the motor activity chambers is also supposed to be performed each day before use. The FOB technician confirmed that both were performed each day; however, records of these verification procedures were not documented in the FOB notebook. This SOP deviation is not believed to have affected the quality of the data collected. All grip-strength measurements were performed using the same device and the results compared to controls. They were not compared to a standard grip-strength measure for rats. In addition, the motor activity software will not function properly if one of the chambers fails the self-test. All chambers functioned properly throughout the week 11 motor activity assessments.

8 Discussion

FOX-7, a nitroenamine, insensitive energetic compound, has been identified as a potential replacement fill material for RDX in conventional munitions (reference 29). The health effects

stemming from exposure to RDX are well-documented and include epileptiform seizure neurotoxicity in addition to possible carcinogenicity. *In silico* modeling predicted the acute oral toxicity of FOX-7 in rats to be 1,200 mg/kg, while an *in vitro* Neutral Red Uptake assay predicted a median lethal oral dose of 1,764 mg/kg (reference 11). This study was designed to investigate the acute, subacute, and subchronic oral toxicity of FOX-7 in rats.

Clinical signs of toxicity, primarily consisting of gastrointestinal distress and neurological signs, were observed in male rats at doses of 550 mg/kg and greater and in female rats at doses of 55 mg/kg and greater during the acute study. Although there appeared to be a large difference in dosage between male and female rats displaying clinical signs, morbidity or intervention euthanasia, the resulting median lethal dose estimates were similar between sexes. Gross pathology revealed that FOX-7 appeared to have desiccating properties within the stomach of many of the animals. At lower doses, the stomach frequently appeared distended and contained ingesta that was more firm than normal. Increased adhesion of the skin to the body wall and congestion of the subcutaneous and/or meningeal vessels were also frequently noted at necropsy. Both findings were likely associated with dehydration and the resulting increased osmolality of the blood. Signs of inflammation in the stomach and/or intestines, including ulcerations, hemorrhage, and contents that appeared to be blood, were noticeable with higher doses. Neurological signs at lower doses primarily consisted of hyperactivity/agitation and jerky, non-fluid movement that persisted throughout the observation period in surviving rats. At higher doses, more severe neurological signs included tremors/shaking, rearing with loss of coordination, and tonic/clonic seizures (only observed in one 1,445-mg/kg male rat) were observed as late as 6 days post-dosing. These clinical signs were used to assist in setting dose groups for the subacute study and provided initial information regarding the organ systems affected following a single oral exposure.

Subacute oral exposure to FOX-7 resulted in similar clinical signs of toxicity as well as gross pathological observations to those observed in the acute study. Irritability was occasionally observed in male rats at 25 mg/kg-d and above and in female rats at 12.5 mg/kg-d and above. Severe gastrointestinal irritation resulted in a 100% mortality rate in male and female rats at 200 and 400 mg/kg-d within 7 days of dosing initiation. In addition, mortality or moribund euthanasia typically occurred within 2 days of the onset of clinical signs of toxicity. Few clinical signs of gastrointestinal irritation were observed in the 100-mg/kg-d group resulting in a rather steep dose response. Seizures were only observed in one 200-mg/kg-d female rat; however, additional signs of neurotoxicity (ataxia, hyperactivity) were observed in both sexes at 200 and 400 mg/kg-d. Significance in clinical pathology parameters was primarily limited to the 100-mg/kg-d group. Thrombocytopenia was apparent in the 100-mg/kg-d male and female rats and may have resulted from either gastrointestinal irritation or bleeding that was not grossly observed at necropsy or excess pooling of PLT within the spleen. Histopathology was not performed on any subacute tissues due to the subsequent subchronic study. Mean platelet volume was also increased in both sexes indicating that the bone marrow was responding accordingly and increasing platelet production. Anemia was also indicated with a dose-dependent decrease in RBCs in surviving animals; however, the reduction was only significant in the 100-mg/kg-d female rats. Significant reductions in HGB and Hct were observed in the 100-mg/kg-d group: more so in 100-mg/kg-d female rats than male rats. Further classification of the anemia in this group was complicated by the short duration of this subacute study along with

a lack of significance in mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Reticulocyte indices (percent RET in female rats and reticulocyte-hemoglobin equivalent in male rats) in the-100 mg/kg-d group were reduced providing further evidence of early onset iron loss anemia. Similar effects on red blood cell mass can occur following long-term stress (reference 30); however, given the severe gastrointestinal irritation and mortality observed at 200 mg/kg-d, in addition to an atypical stress leukogram, the observed changes in red blood cell mass in the 100-mg/kg-d group were not likely solely due to stress. Although male and female leukocyte counts and differentials generally increased with dosage, only monocyte counts in 100-mg/kg-d male rats as well as leukocyte counts and lymphocyte concentrations in 100-mg/kg-d female rats were increased relative to concurrent controls. Leukocytosis can result from chronic inflammation and may have been caused by FOX-7-induced gastrointestinal irritation (reference 31). Increased absolute spleen mass and mass ratios were observed in the 100-mg/kg-d male and female rats and occasionally in the 50-mg/kg-d group. Splenomegaly is consistent with the hematological findings of anemia and reduced PLT, but the increase in leukocyte production does not suggest splenic dysfunction.

The most striking and dose-dependent clinical chemistry results from subacute exposure to FOX-7 were increases in BUN, BUN/creatinine ratios, and cholesterol. These increases were apparent in the 50- and 100-mg/kg-d male and female rats. The elevated BUN/creatinine ratios primarily resulted from increased BUN, as plasma creatinine was only reduced 0.8-fold in the 50-mg/kg-d male and female rats and 100-mg/kg-d female rats. Increased BUN coupled with slight decreases in creatinine levels suggest dehydration, malnutrition, or upper gastrointestinal bleeding rather than prerenal azotemia or renal injury; although electrolytes were unaffected (reference 32). Male and female kidney mass and kidney-to-body mass ratios were elevated in the 100-mg/kg-d group, but histology would be required to confirm if the increased mass was the result of direct renal insult. Increased serum cholesterol can also be indicative of kidney toxicity through impaired lipid clearance. However, dehydration can also result in increased serum cholesterol by decreasing blood volume and flow. Serum samples from moribund euthanasia rats in the 200- and 400-mg/kg-d groups were collected, frozen, and run concurrently with samples from surviving rats at scheduled necropsy. Similar but more pronounced increases in BUN (1.6 – 3-fold), BUN/creatinine ratios (4.2 – 6.2-fold), and cholesterol (2 – 2.1-fold) were observed in the moribund euthanasia rats relative to concurrent controls. In addition, creatinine levels were reduced (2.2 – 2.5-fold), and TRIG were elevated (3.2 – 7.6-fold). Additional parameters significantly different from concurrent controls were not part of relevant dose-related trends and included increased ALB and TBIL (100-mg/kg-d male rats), decreased ALT and AST (50-mg/kg-d male rats), decreased creatinine kinase (12.5-mg/kg-d male rats), and decreased AMY (100-mg/kg-d male rats).

Subchronic oral administration of FOX-7 at dosages of 70 mg/kg-d and below resulted in one compound-related mortality. One male rat in the 70-mg/kg-d group presented with similar clinical signs to those observed in the higher doses of the subacute study (body-mass loss, squinting, shaking, porphyrin staining on front limbs, lethargy, rough haircoat, hunched posture, twitching) starting on day 72. This rat was subsequently euthanized due to moribund status on day 74. Gross pathological evidence of gastrointestinal irritation along with discoloration of the spleen, liver, pancreas, and mesenteric lymph nodes was observed at necropsy. A serum sample collected from this rat at necropsy and analyzed with concurrent controls at day 91

revealed a similar clinical chemistry profile to the moribund euthanasia rats in the subacute study. These differences included 1.7- and 1.5-fold increases in BUN and CHOL, respectively, and a 0.4-fold decrease in AMY. Serum creatinine (1.5-fold increase) and TRIG (0.35-fold decrease) exhibited reverse trends relative to the higher dose groups in the subacute study. Microscopic evaluation of the tissues collected from this rat was not informative in determining a cause for the moribund status.

Except for the one male rat in the 70-mg/kg-d group, the signs of gastrointestinal irritation observed in the subacute study were not observed in the subchronic study. Body mass in the male 70-mg/kg-d group was significantly reduced for the study duration beginning on week 3 and in the 70-mg/kg-d female group beginning on week 5. Reductions in male and female body mass change, paired food consumption, and paired food efficiency for this group were more sporadic throughout the study period. The initial insult to the gastrointestinal system over the first several weeks was believed to be sufficient to result in reduced body mass at 70 mg/kg-d, but the dosage was not high enough to induce morbidity/mortality. As food consumption returned to an amount like concurrent controls, the 70-mg/kg-d group began to gain weight at a normal rate but remained below all other groups throughout the study period. Weekly paired food efficiency in the 70-mg/kg-d group was slightly, but insignificantly, reduced; however, final mean paired food efficiency for the 70-mg/kg-d male and female rats was significantly reduced relative to controls. The standard practice of pair-housing animals leads to less accurate food consumption and food efficiency determinations.

Gross observations of FOX-7-induced gastrointestinal toxicity at necropsy were rare and limited only to the 17.5- and 70-mg/kg-d male and female rats. Histology revealed occasional autolysis in the ileum and colon that was of minimal severity and not of increased incidence in the 70-mg/kg-d group relative to controls. FOX-7 shares structural similarities with the multifunctional nitroenamine neonicotinoid nitenpyram as well as the over-the-counter pharmaceuticals ranitidine and nizatidine used to treat heartburn (reference 33). Although nitenpyram has not been as extensively evaluated in mammals as the nitroguanidine neonicotinoid imidacloprid, oral doses of 62.5 to 148 mg/kg nitenpyram did induce salivation, reduced appetite, vomiting, soft feces, and occasionally diarrhea in cats (reference 34). The acute oral median lethal dose of nitenpyram is 1,575 mg/kg in female rats and 1,680 mg/kg in male rats. However, an *in vivo* metabolism study suggested that nitenpyram metabolism by the mitochondrial cytochrome P450 Cyp12a5 (expressed in digestive tissues) results in the formation of a product of higher toxicity than the parent compound (reference 35). Additional studies have found that pre-mating exposure to nitenpyram in mice led to imbalances of gut microbiota and fecal metabolites in male and female offspring as well as induction of esophageal squamous papilloma in chronically exposed rats (references 36, 37, and 38). In contrast, more severe epidemiological findings of oral and gastroesophageal erosions and hemorrhagic gastritis have been reported following acute oral exposure to the nitroguanidine neonicotinoid imidacloprid (reference 39). Hydrolysis experiments on neonicotinoid pesticides, including nitenpyram, indicated that the urea derivative was the most common hydrolysis product found, which could add insight into the elevated BUN levels at higher FOX-7 concentrations during the subacute study (reference 40).

Many of the significant electrolyte and urinalysis parameters observed in the high-dose male and female rats could likely be attributed to excessive thirst induced by the apparent desiccating

properties of FOX-7 in the gastrointestinal tract. Water consumption was not monitored throughout the study but was monitored overnight during timed urine collection. Water consumption was generally elevated, albeit insignificantly, in the high-dose rats, while urine volume was significantly increased. Additional indications of increased water consumption included reduced urine-specific gravity, blood glucose, and blood sodium as well as increased urine pH. The high-dose urine samples were also more frequently positive for nitrites and leukocytes. These effects were more pronounced in high-dose male rats than female. Histologically, mild increases in lymphocytic infiltrates and tubular basophilia with crowding were the only evidence of FOX-7-induced nephrotoxicity in 70-mg/kg-d male rats.

Tonic/clonic seizures, very similar to those observed following oral administration of RDX, were once again observed during the subchronic study. These seizures were only observed in the 70-mg/kg-d group and were of slightly shorter duration, occurred in fewer dosed rats, first occurred much later after study initiation, and did not result in mortality compared to those arising from RDX exposure. Except for one 70-mg/kg-d female rat that was observed undergoing seizures on day 35, all other seizures in this group were observed on day 70 or after. Also like RDX, these seizures appeared to be frequently induced by external stimuli such as handling or dosing. The mechanism of RDX-induced seizures has been investigated in rats and suggested that RDX accumulates at a sufficient concentration in the brain to inhibit the majority of $GABA_A$ receptors resulting in seizure (reference 41). The etiology of FOX-7-induced seizures is not completely understood but could, once again, be related to the structural similarities with the neonicotinoid nitenpyram. The efficacy of neonicotinoids as insecticides results from the agonist effect on the insects' postsynaptic nicotinic receptors for acetylcholine (reference 42). Although these nicotinic receptors are also found in the central and peripheral nervous system of mammals, they are only found in the central nervous system of insects and nitenpyram is approximately 3,500 times more selective for the insect receptors (references 34 and 35). Having a systemic mode of action, nitenpyram is rapidly and nearly completely absorbed in mammals. At effective prescribed doses in dogs and cats, minimal distribution to the central nervous system occurs due to only small amounts crossing the blood-brain barrier. However, at doses of 100 mg/kg and above (100 times the theurapeutic dose), clinical signs of nitenpyram intoxication appeared including fatigue, salivation, convulsions, lethargy, difficult (rapid) breathing, unstable gait, tremor, and involuntary muscle contraction (reference 34). Many of these same clinical signs were observed in the higher doses of the FOX-7 acute study and the 200- and 400-mg/kg-d groups of the subacute study. The highest dose of 70 mg/kg-d in the subchronic study was likely low enough to result in delayed severe neurotoxic signs (convulsions) but sufficient for incomplete elimination between doses. Over time the FOX-7, or possibly an unknown metabolite, may have accumulated enough in a select few of 70-mg/kg-d rats to cross the blood-brain barrier. Brain-to-body mass ratios were increased in the 70-mg/kg-d male and female rats; however, brain histopathology was unremarkable and changes in brain mass alone are rarely indicative of neurotoxicity (reference 43). Seizures were also observed in female mice at doses exceeding 2,000 mg/kg during an acute oral toxicity study using nitroguanidine, a military explosive that is closely related to the neonicotinoid pesticide imidacloprid (reference 44). Additional neurotoxic signs of lesser severity, including excitability, irritability, lethargy and hyperreactivity, were also sporadically observed in many of the acute, subacute, and subchronic FOX-7 dose groups. These clinical signs closely resemble the

symptoms of nitenpyram (nicotine) intoxication and are also consistent with those observed during a teratogenicity study with FOX-7 at doses up to 45 mg/kg-d (references 12 and 34).

Although the microscopic findings of extramedullary hematopoiesis and pigment deposition were observed at nearly equal incidence and severity in the 70-mg/kg-d male and female rats compared to concurrent controls, clinical pathology indicated a FOX-7-induced anemia. The anemia was present in the 70-mg/kg-d group both in absolute number of erythrocytes as well as red blood cell mass (HGB and Hct). A relatively consistent, but insignificant, dose response in erythrocyte parameters was observed throughout all the other FOX-7 dose groups. In the 70-mg/kg-d male rats, the anemia could be further classified as regenerative (splenomegaly and increased RDW-SD), microcytic (decreased MCV), and mildly hypochromic (decreased MCH). Reticulocyte counts and IRF were slightly increased, and the reticulocyte-hemoglobin equivalent was slightly decreased; all insignificantly. The anemia in the high-dose male rats was accompanied by a nearly 2-fold increase in leukocytes. Apart from an increased red blood cell distribution width, further classification of the anemia in the 70-mg/kg-d female rats was complicated by equivocal reticulocyte indices and mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration results. Bone marrow smears did not indicate any difference between the 70-mg/kg-d group and concurrent controls. Like the anemia, leukocytosis was not as evident in the high-dose female rats with an insignificant 1.3-fold increase. The anemia observed in this study is consistent with several additional oral toxicity studies using explosive compounds (nitrotriazolone, 2,4,6-trinitro-3-bromoanisole, trinitrotoluene) as well as nitenpyram-induced hematotoxicity (references 45, 46, 47, and 48). Thrombocytopenia in the 70-mg/kg-d male and female rats was consistent with the higher doses in the subacute study but was contrary to the results obtained in rats subacutely dosed with nitenpyram (reference 48).

Subchronic oral exposure to FOX-7 resulted in a marked increase in circulating male and female TSH levels and a decrease in T_4 (only significant in female rats) at the highest dose. Associated increases in mean thyroid mass and mass ratios as well as incidence of follicular cell hypertrophy with colloid depletion were also observed in the high-dose male and female rats. Similar changes in thyroid hormone levels and thyroid histopathology have been described in male rats chronically exposed to the herbicide thiazopyr. Thiazopyr alters thyroid hormone homeostasis via induction of hepatic T_4-uridine diphosphate glucuronyl transferase (UGT) leading to elevated T_4 hepatic metabolism and biliary excretion. The reduction in circulating T_4 causes the pituitary gland to increase TSH output. If sustained, the elevated TSH levels induce thyroid hypertrophy/hyperplasia and eventually neoplasia (reference 49). This mode of action for FOX-7-induced thyroid toxicity remains speculative as certain discrepancies in endpoints measured and significance observed exist. The increased incidence of thyroid neoplasia with thiazopyr was only observed in male rats. In the current study, reductions in circulating T_4 levels and subsequent increases in TSH were more pronounced in female rats. Hepatic UGT activity and T_4 biliary elimination were not measured endpoints, and subchronic administration of FOX-7 resulted in decreased female liver mass rather than increased with thiazopyr. Hepatocellular hypertrophy was not observed in the FOX-7 high dose male and female rats, and the observed cytoplasmic vacuolization occurred at a nearly equal incidence in the high dose compared to controls. It should be noted that rats, male in particular, are more susceptible to compensatory increases in TSH from decreased T_4 than humans (reference 49).

Effects on the male rodent reproductive system are commonly observed following oral toxicity testing with explosives (trinitrotoluene, nitrotriazolone, 2,4-dinitroanisole) and result from FOX-7 exposure (references 45, 47, and 50). Mean testicular mass was insignificantly reduced in the 70-mg/kg-d male rats, but epididymal mass was significantly reduced. Six of 10 male rats in this group, including the rat euthanized pre-term, had severe degeneration/atrophy of the testicular spermatogonia and diffuse tubular atrophy with minimal-to-mild interstitial edema and increased interstitial cellularity. These microscopic changes in the testes were frequently accompanied by minimal hypospermia of the epididymites, and individual sperm counts correlated well with histopathology. Although the mechanism of FOX-7-induced testicular toxicity is not apparent from the results of this study, various classifications of anemia are also frequently reported with the male reproductive findings in toxicity studies with explosives.

Epidemiological studies have documented a link between iron deficiency anemia and male infertility (references 51 and 52). Recent animal studies further showed that the iron deficiency affects male reproductive functions by increasing oxidative stress and decreasing antioxidant enzymes (reference 53). The scope of this initial toxicity evaluation of FOX-7 did not allow for a complete classification of the anemia. However, several of the individual 70-mg/kg-d male red blood cell indices, particularly HGB and Hct, exhibited reasonable correlation with the reproductive histopathological findings. The severe gastrointestinal irritation observed in higher doses of the subacute study was not grossly or microscopically observed in the subchronic study, which confounded an iron deficiency diagnosis from blood loss. However, blood loss can result from several other conditions including vasculitis, thrombocytopenia, or fibrinolysis (reference 31). Further investigation with additional endpoints would be required to confirm the mechanism of action for the male reproductive toxicity observed.

Although the results of this study showed that FOX-7 is certainly not devoid of toxic effects from oral exposure, it should be considered a less toxic alternative to RDX. A similar series of acute, subacute, and subchronic oral toxicity studies in rats was performed using pure RDX. An acute approximate lethal dose of 68 mg/kg was reported, and mortality was induced at doses of 17 mg/kg-d and above during the 14-day subacute study. Mortality was observed at doses of 8 mg/kg-d and above during the subchronic study and a No Observed Adverse Effect Level of 4 mg/kg-d was established based on mortality. In nearly all cases, tonic/clonic seizures were observed before death (reference 54). The EPA derived a human-equivalent $BMDL_{05}$ of 1.3 mg/kg-d that resulted in an RfD of 0.004 mg/kg-d. In addition, the EPA has determined that suggestive evidence of the carcinogenic potential for RDX exists, which was not observed in FOX-7 based on the subacute micronucleus assay (reference 9). Median lethal dose estimates and subacute doses inducing mortality were approximately 12-fold higher for FOX-7 relative to RDX. The benchmark dose value ($BMDL_{10}$) for FOX-7 was approximately 8-fold higher than that derived for RDX ($BMDL_{05}$) based on subchronic oral dosing.

9 Conclusions

The estimated FOX-7 LD_{50} from the acute study was 875 mg/kg for male rats and 805 mg/kg for female rats with a combined-sexes LD_{50} of 839 mg/kg. Subacute administration of FOX-7 resulted in 100% mortality at doses ≥200 mg/kg-d within one week of initiation. Clinical and

gross pathological signs of gastrointestinal irritation were observed at doses ≥100 mg/kg-d. The rat peripheral blood micronucleus assay, run concurrently with the subacute study, was negative for genotoxicity.

In the subchronic repetitive oral exposure study, FOX-7 induced mortality only occurred in one male rat in the highest dose group (70 mg/kg-d) on day 74. Gross pathology indicated that this was most likely the result of direct gastrointestinal irritation, but histopathology was not informative. Male and female rats in the 70-mg/kg-d group experienced excitability/irritability, seizures, lethargy, rough haircoat, disorientation, and squinting. Excitability/irritability was also occasionally observed throughout all FOX-7 dose groups. Weekly neurotoxicity assessments or analysis of motor activity at week 11 did not indicate any significant neurological differences from controls, except for some sporadic open-arena observations.

Weekly male and female body mass in rats from the 70-mg/kg-d group was reduced for much of the study after week 3, while paired food consumption was only reduced in male rats during week 12. Paired food efficiency was reduced during week 3 for both sexes. Timed urine collection yielded increased volume and nitrite concentration with reduced specific gravity in both sexes at 70 mg/kg-d. Male rats in this group additionally had increased leukocytes, and female rats had increased urine pH.

Thyroid and spleen mass was increased in both sexes at 70 mg/kg-d. The increased thyroid mass was associated with increased TSH, decreased T_4 (female rats only), and microscopic findings of follicular cell hypertrophy. Although thrombocytopenia was observed at the highest dose, histopathology did not indicate increased incidence of splenic findings. Anemia, in the form of reduced RBC, Hct, and HGB, was apparent in the 70-mg/kg-d male and female rats. Male rats at 17.5 mg/kg-d also exhibited reduced hemoglobin. Leukocytosis was observed in both sexes at 70 mg/kg-d; however, this effect was only significant in male rats. Decreased mass of the epididymites and atrophy and degeneration of the testicular spermatogonia with hypospermia were observed in the 70-mg/kg-d group.

The critical effect selected for BMD analysis was a dose-dependent reduction in HGB concentration in female rats. The best fitting viable model resulted in a BMD of 12 mg/kg-d and a BMDL of 10 mg/kg-d.

11 Point of Contact

Questions pertaining to this report should be referred to Lee C.B. Crouse at DSN 584-3980, commercial 410-436-3980, or by e-mail: usarmy.apg.medcom-phc.mbx.tox-info@health.mil.

Prepared By:

CROUSE.LEE.1239523265 Digitally signed by CROUSE.LEE.1239523265 Date: 2024.05.06 08:12:18 -04'00'

LEE C.B. CROUSE — Date
Biologist
Toxicity Evaluation Division (TEV)

BOHANNON.MEREDITH.ENA BARTON.1557233284 Digitally signed by BOHANNON.MEREDITH.ENA BARTON.1557233284 Date: 2024.05.06 08:50:36 -04'00'

MEREDITH E. BOHANNON — Date
Biologist
Toxicity Evaluation Division (TEV)

GUIGNI.BLAS.ANSELMO.1239214122 Digitally signed by GUIGNI.BLAS.ANSELMO.1239214122 Date: 2024.05.06 09:31:26 -04'00'

BLAS A. GUIGNI — Date
Biologist
Toxicity Evaluation Division (TEV)

BAZAR.MATTHEW.A.1241429322 Digitally signed by BAZAR.MATTHEW.A.1241429322 Date: 2024.05.06 09:48:43 -04'00'

MATTHEW A. BAZAR — Date
Biologist
Toxicity Evaluation Division (TEV)

BROWN.TARYN.KAWAIONALANI MALAMA.1453940205 Digitally signed by BROWN.TARYN.KAWAIONALANI MALAMA.1453940205 Date: 2024.05.08 11:07:24 -04'00'

TARYN K. BROWN — Date
Biological Science Technician
Toxicity Evaluation Division (TEV)

Approved By:

SUSSAN.THOMAS.EDWARD.JR.1537772626 Digitally signed by SUSSAN.THOMAS.EDWARD.JR.1537772626 Date: 2024.05.08 12:49:53 -04'00'

THOMAS E. SUSSAN — Date
Division Chief, Toxicity Evaluation

QUINN.MICHAEL.J.1282372092 Digitally signed by QUINN.MICHAEL.J.1282372092 Date: 2024.05.08 12:27:36 -04'00'

MICHAEL J. QUINN — Date
Acting Director, Toxicology

Appendix A

References

1. Department of the Army (DA). 2007. Regulation 200–1, *Environmental Protection and Enhancement*. https://armypubs.army.mil

2. DA. 2007. Regulation 40–5, *Preventive Medicine*. https://armypubs.army.mil

3. DA. 2003. Regulation 70–1, *Army Acquisition Policy*. https://armypubs.army.mil

4. Department of Defense Directive (DoDD) 4715.1E, *Environment, Safety, and Occupational Health (ESOH),* 2005, Change 1, 2018. https://www.esd.whs.mil/

5. Army Environmental Requirements and Technology Assessments. 2012. Requirement PP-3-02-05, *Compliant Ordnance Lifecycle For Readiness of the Transformation and Objective Forces.* Joint Base San Antonio, Texas.

6. Defense Science and Technology Organisation. 2001. FOX-7 – A New Insensitive Explosive. DSTO-TR-1238, Prepared by I.J. Lochert, DSTO Aeronautical and Maritime Research Laboratory, 506 Lorimer St., Fishermans Bend, Victoria 3207, Australia.

7. Safety Data Sheet. 1,1-diamino-2,2-dinitroethene, Eurenco Groupe SNPE, Explosive Charges & Additives Business Unit, 12 quai Henri IV – 75004 Paris – France. 2012.

8. Agency for Toxic Substances and Disease Registry. Toxicological Profile for *RDX (Cyclonite).* https://www.atsdr.cdc.gov/toxprofiledocs/index.html

9. EPA. 2018. Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX); CASRN 121-82-4, in *Integrated Risk Information System (IRIS) Chemical Assessment Summary*. Washington, DC.

10. Stenmark, H and S Sjöqvist. Undated. Eurenco Fact Sheet. Toxicological Testing of ADN, GuDN (Fox-12) and Fox-7. Eurenco Bofors AB, SE-691 86 Karlskoga, Sweden.

11. U.S. Army Public Health Center (APHC). 2016. Toxicology Assessment for ETAP Work Unit CA 10-04: *1,1-diamino-2,2-dinitroethene [FOX-7; DADNE].* Prepared by M.A. Williams and W.S. Eck. Aberdeen Proving Ground, Maryland.

12. Liu, Z, P Zhang, H Wang, J Gao, Q Lu, H Yue, and J Xia. 2016. Study of teratogenicity of 2, 2-dinitroethene-1, 1-diamine in sprague dawley rats. *Chinese Journal of Industrial*

Hygiene and Occupational Diseases 34(1):47-9. DOI: 10.3760/cma.j.issn.1001-9391.2016.01.013

13. American Society for Testing and Materials (ASTM). 2008. E2552-16, *Standard Guide for Assessing the Environmental and Human Health Impacts of New Compounds for Military Use*. West Conshohocken, Pennsylvania: ASTM International.

14. APHC 2017. Quality Systems and Regulatory Compliance Office (QSARC) 707, *Animal Health Technician Animal Husbandry and Vivarium Duties*. Aberdeen Proving Ground, Maryland.

15. Feder PI, CT Olson, DW Hobson, MC Matthews, and RL Joiner. 1991. Stagewise, group sequential experimental designs for quantal responses. one-sample and two-sample comparisons. *Neurosci Biobehav Rev* 15(1):129-33. DOI: 10.1016/s0149-7634(05)80104-6

16. Feder PI, CT Olson, DW Hobson, MC Matthews, and RL Joiner. 1991. Stagewise, adaptive dose allocation for quantal response dose-response studies. *Neurosci Biobehav Rev* 15(1):109-14. DOI: 10-1016/s0149-7634(05)80101-0

17. ASTM. 2011. E1163-10, *Standard Test Method for Estimating Acute Oral Toxicity in Rats, Biological Effects and Environmental Fate.* West Conshohocken, Pennsylvania: ASTM International.

18. APHC 2017. QSARC 800, *Animal Euthanasia*. Aberdeen Proving Ground, Maryland.

19. APHC 2017. QSARC 805, *Animal Bleeding Technique*. Aberdeen Proving Ground, Maryland.

20. APHC 2018. Toxicology Directorate (TOX) SOP 11.003, *Clinical Chemistry Analysis of Blood Specimens*. Aberdeen Proving Ground, Maryland.

21. APHC 2018. TOX SOP 13.003, *Cell-Dyn Hematology Analyzer*. Aberdeen Proving Ground, Maryland.

22. McDaniel, KL and VC Moser. 1993. Utility of a neurobehavioral screening battery for differentiating the effects of two pyrethroids, permethrin and cypermethrin. *Neurotoxicol Teratol.* 15(2):71-83. DOI: 10.1016/0892-0362(93)90065-v.

23. APHC 2016. TOX SOP 062.002, *Neurotoxicity Screen and Functional Observation Battery*. Aberdeen Proving Ground, Maryland.

24. APHC 2017. QSARC 716, *Ophthalmic Examinations*. Aberdeen Proving Ground, Maryland.

25. APHC 2018. TOX SOP 003.003, *Urinalysis*. Aberdeen Proving Ground, Maryland.

26. APHC 2017. QSARC 706, *Animal Quality Assurance and Quality Control/Health Monitoring Procedures*. Aberdeen Proving Ground, Maryland.

27. Giknis, MLA., and CB Clifford. 2006. *Clinical Laboratory Parameters for Crl:CD(SD) Rats* Charles River Laboratories. Wilmington, Massachusetts. Available at www.criver.com.

28. Technical Data Sheet. 2023. *Infectious Agent Technical Information*. Charles River Laboratories. Wilmington, Massachusetts. Available at https://www.criver.com/products-services/research-models-services/animal-health-surveillance/infectious-agent-information?region=3601.

29. Shang, F, T Wang, Y Ma, M Lv. 2022. Theoretical study on several important decomposition paths of FOX-7 and its derivatives. *Computational and Theoretical Chemistry*. Volume 1217. DOI: https://doi.org/10.1016/j.comptc.2022.113895

30. Everds, NE, PW Snyder, KL Bailey, B Bolon, DM Creasy, GL Foley, TJ Rosol, and T Sellers. 2013. Interpreting Stress Responses during Routine Toxicity Studies: A Review of the Biology, Impact, and Assessment. *Toxicologic Pathology*. 41:560-614. DOI: 10.1177/0192623312466452

31. Evans, G.O. 2009. *Animal Hematotoxicology: A Practical Guide for Toxicologists and Biomedical Researchers*. Boca Raton, Florida: Taylor and Francis Group, LLC.

32. Evans, G.O. 2009. *Animal Clinical Chemistry: A Practical Handbook for Toxicologists and Biomedical Researchers*. Boca Raton, Florida: Taylor and Francis Group, LLC.

33. Wang, W, MJ Ezell, PSJ Lakey, KZ Aregahegn, M Shiraiwa, and BJ Finlayson-Pitts. 2020. Unexpected formation of oxygen-free products and nitrous acid from the ozonolysis of the neonicotinoid nitenpyram. *Proceedings of the National Academy of Sciences*, 117(21):11321-11327. DOI: 10.1073/pnas.2002397117.

34. Parasitipedia. Nitenpyram: Safety Summary for Veterinary Use in Dogs and Cats. Poisoning, Intoxication, Overdose, Antidote. https://parasitipedia.net/index.php?option=com_content&view=article&id=2689&Itemid=3011

35. National Center for Biotechnology Information (2023). PubChem Annotation Record for, *Nitenpyram*, Hazardous Substances Data Bank (HSDB). https://pubchem.ncbi.nlm.nih.gov

36. Yan, S, S Tian, Z Meng, J Yan, M, Jia, R Li, Z Zhou, and W Zhu. 2020. Imbalance of gut microbiota and fecal metabolites in offspring female mice induced by nitenpyram exposure during pregnancy. *Chemosphere*. 260:127506. DOI: https://doi.org/10.1016/j.chemosphere.2020.127506

37. Yan, S, W Sun, S Tian, Z Meng, J Diao, Z Zhou, L Li, and W Zhu. 2024. Pre-mating nitenpyram exposure in male mice leads to depression-like behavior in offspring by affecting tryptophan metabolism in gut microbiota. *Journal of Environmental Sciences*. 137:120-130.
DOI: https://doi.org/10.1016/j.jes.2023.02.011

38. Xing, LG, YL Wu, HN Zheng, YY Jia, GF Wu, and C Yang. 2018. Induction of esophageal cancers by nitenpyram (NIT) in rats. *Eur Rev Med Pharmacol Sci*. 22(24):8698-8711.
DOI: 10.26355/eurrev_201812_16635

39. Noushadali, SK, K Noorulla, and K Manohar. 2022. Imidacloprid Poisoning – A Potentially Fatal Chemical Poisoning in Humans? *International Journal of Science and Research*. 11(7):478-481.
DOI: 10.21275/SR22760150042

40. Todey, SA, AM Fallon, and WA Arnold. 2018. Neonicotinoid insecticide hydrolysis and photolysis: Rates and residual toxicity. *Environ Toxicol Chem*. 37:2797-2809.
DOI: https://doi.org/10.1002/etc.4256

41. USACHPPM. 2009. Toxicology Study No. 87-XE-0BT9-09, Mechanism of RDX-Induced Seizures in Rats. Aberdeen Proving Ground, Maryland.

42. Nistor, N, OE Fŕasinariu, and V Streanǧa. 2017. Acute Poisoning with Neonicotinoid Insecticide. In Poisoning - From Specific Toxic Agents to Novel Rapid and Simplified Techniques for Analysis. ed. Ntambwe Malangu. InTech.
DOI: 10.5772/65817

43. Sellers, RS, D Morton, B Michael, N Roome, JK Johnson, BL Yano, R Perry, and K Schafer. 2007. Society of Toxicologic Pathology Position Paper: Organ Weight Recommendations for Toxicology Studies. *Toxicologic Pathology*. 35:751–755.
DOI: 10.1080/01926230701595300

44. Letterman Army Institute of Research. 1988. Institute Report No. 265, Acute Oral Toxicity of Nitroguanidine in Mice. Presidio of San Francisco, California.

45. U.S. Army Public Health Command. 2014. Addendum to Toxicology Study No. 85-XC-0A6W-08, Subchronic Oral Toxicity of 3-Nitro-1,2,4-Triazol-5-One (NTO) in Rats. Aberdeen Proving Ground, Maryland.

46. DCPH-A. 2023. Toxicology Study No. S.0059803-18, Effects of Acute and Subacute Oral 2,4,6-Trinitro-3-Bromoanisole (TNBA) Exposure to Rats (Rattus Norvegicus). Aberdeen Proving Ground, Maryland.

47. Levine, BS, EM Furedi, DE Gordon, PM Lish, JJ Barkley. 1984. Subchronic toxicity of trinitrotoluene in Fischer 344 rats. *Toxicology*. 32(3):253-265.
DOI: https://doi.org/10.1016/0300-483X(84)90078-7

48. Khan, M and SS Ali. 2015. Nitenpyram-induced hematotoxicity in rat, *Rattus norvegicus*. *Pakistan J. Mol. Med.* 2(1):11-21. www.pjmm.uol.edu.pk

49. Dellarco, VL, D McGregor, Sir Colin Berry, SM Cohen and AR Boobis. 2006 Thiazopyr and Thyroid Disruption: Case Study Within the Context of the 2006 IPCS Human Relevance Framework for Analysis of a Cancer Mode of Action. *Critical Reviews in Toxicology*, 36:10, 793-801. DOI: 10.1080/10408440600975242

50. U.S. Army Institute of Public Health. 2012. Toxicology Study No. 87-XE-0DBP-10, The Subchronic Oral Toxicity of 2,4-Dinitroanisole (DNAN) in Rats. Aberdeen Proving Ground, Maryland.

51. Soliman, A, M. Yassin, O Abdelrahmanm, V Desanctis, and A Elawwa. 2013. Effects of iron therapy on pituitary gonadal axis and sperm parameters in adults with iron deficiency anemia (IDA). *Endocrine Abstracts*. 32:P643. DOI: 10.1530/endoabs.32.P643

52. Akhter, MS, HA Hamali, J Igbal, AA Mobarki, H Rashid, G Dobie, AM Madkhali, BY H Arishi, EOO Ageeli, and OSH Laghbi. 2021. Iron Deficiency Anemia as a Factor in Male Infertility: Awareness in Health College Students in the Jazan Region of Saudi Arabia. *Int. J. Environ. Res. Public Health*. 18(24):12866. DOI: 10.3390/ijerph182412866

53. Tsao, C-W, Y-R Liao, T-C Chang, Y-F Liew, and C-Y Liu. 2022. Effects of Iron Supplementation on Testicular Function and Spermatogenesis of Iron-Deficient Rats. *Nutrients*. 14(10):2063. DOI: 10.3390/nu14102063

54. USACHPPM. 2006. Toxicology Study No. 85-XC-5131-03, Subchronic Oral Toxicity of RDX in Rats. Aberdeen Proving Ground, Maryland.

Appendix B

Quality Assurance Statement

For Protocol No. 38-18-12-01, titled "Subchronic Oral Toxicity of 1,1-Diamino-2,2-Dinitroethene (FOX-7) in Rats", the following critical phases were inspected/audited by the Quality Assurance Unit:

Critical Phase Inspected/Audited	Date Inspected /Audited	Date Reported to SD/Management
Study Protocol Good Laboratory Practice Standards and Animal Care Review	10/24/2018-11/06/2018	11/06/2018
Test Article Storage, Control, Mixing, Labeling and Administration via Oral Gavage	08/15/2019	08/22/2019
Test System - Facilities, Identification, Husbandry & Food and Water Supply	08/15/2019	08/22/2019
Pre and Post-procedural Provisions, Observations and Body Weight Determination	08/15/2019	08/22/2019
Test Article - Purity Analysis, Receipt, Storage and Control	03/04/2021	03/18/2021
Test System - Facilities, Identification, Husbandry & Food and Water Supply	03/11/2021	03/25/2021
Test Substance - Mixing, Labeling, Administration via Oral Gavage & Initial Test System Observations	03/11/2021	03/25/2021
Necropsy Procedures, Maintenance and Calibration of Equipment and Good Documentation Procedures	03/11/2021	03/26/2021
Euthanasia, Gross Necropsy, Tissue Collection and Tissue Preservation Procedures	03/11/2021	03/26/2021
Necropsy Study Personnel Qualifications, Training Records Review and Good Documentation Procedures	03/11/2021	03/26/2021
Study Final Report and Raw Data Laboratory Practice Review	02/02/2024-02/24/2024	02/24/2024

Note 1: *Any findings were made known to the Study Director and the Program Manager at the time of the audit/inspection. If there were no findings during the inspection, the inspection was reported to Management and the Study Director on the date shown in the table.*

Note 2: *This report has been audited by the Quality Assurance Unit and is considered to be an accurate account of the data generated and of the procedures followed.*

Note 3: *In addition to the study specific critical phase inspections listed here, general facility and process-based inspections not specifically related to this study may also be listed here.*

KEFAUVER.MICHAEL.P.1229209678 Digitally signed by KEFAUVER.MICHAEL.P.1229209678
Date: 2024.04.19 09:26:06 -04'00'

Michael P. Kefauver
GLP Quality Assurance Specialist

Date

APPENDIX C

ARCHIVES AND STUDY PERSONNEL

C-1. ARCHIVES

All raw data, documentation, records, protocol, and a copy of the final report generated as a result of this study will be archived in the DCPH-A Toxicology Directorate archives for a minimum of 10 years following submission of the final report to the Sponsor.

Records on animal receipt, diet, and facility environmental parameters will be archived by the Veterinary Support Office, Directorate of Technical Services, for a minimum of 10 years following submission of the final report to the Sponsor.

Some ancillary records pertaining to this study, such as instrument maintenance logs, animal room observation logs, etc., will not be archived until those logbooks have been completed. Once complete they will be archived in the DCPH-A Toxicology Directorate archives.

Wet tissues, histology slides, and paraffin blocks are stored in the Pathology Division archives.

C-2. PERSONNEL

C-2.1 Management

Management (In-Life): Dr. Mark S. Johnson, Ph.D., Director, Toxicology; Arthur J. O'Neill, Division Chief, Toxicity Evaluation Division (TEV); Dr. Michael J. Quinn, Ph.D., Division Chief, Health Effects Division (HEF).

Management (Report): Dr. Michael J. Quinn, Ph.D., Acting Director, Toxicology; Dr. Thomas Sussan, Ph.D., Division Chief, Toxicity Evaluation Division (TEV); Dr. Michael J. Quinn, Ph.D., Division Chief, Health Effects Division (HEF).

C-2.2 Study Director

Lee Crouse, Biologist, TEV.

C-2.3 Quality Assurance

In-Life: Michael P. Kefauver, Quality Assurance Specialist, Quality Systems and Regulatory Compliance (QSARC).

Report: Allison M. Seyfert and Michael P. Kefauver, Compliance, Accreditation, and Monitoring Office.

C-2.4 Veterinary Support and Animal Care

MAJ Alicia Gehling, DVM, MPH, DACVPM, Attending Veterinarian.

Rebecca Kilby, Animal Health Technician; Lindsey Ward, Animal Health Technician.

C-2.5 Pathology Lab Coordinator

Alicia Shiflett, Histotechnician, DTP.

C-2.6 Histopathology

In-Life: LTC Norman Kreiselmeier, DVM, ACVP, Pathologist, DTP.

Report: MAJ(P) Robert Kim, DVM, ACVP, Pathologist, DTP.

C-2.7 In-Life Support

Dr. Meredith Bohannon, Ph.D., Biologist, TEV.

Dr. Blas Guigni, Ph.D., Biologist, TEV.

Taryn Brown, Biological Science Technician, TEV.

C-2.8 Hematology, Clinical Chemistry

Matthew A. Bazar, Biologist, TEV.

C-2.9 Archivist

Lee Crouse, Biologist, TEV.

Appendix D

Study Protocol with Modifications

ANIMAL USE PROTOCOL
ARMY PUBLIC HEALTH CENTER
ABERDEEN PROVING GROUND MD 21010-5403

PROTOCOL TITLE: The Subchronic Oral Toxicity of 1,1-diamino-2,2-dinitroethene (FOX-7) in Rats (*Rattus norvegicus)*

PROTOCOL NUMBER: 38-18-12-01

DATE OF APPROVAL: 6 December 2018

STUDY DIRECTOR/PRINCIPAL INVESTIGATOR (SD/PI):

Lee Crouse
Biologist
Toxicity Evaluation Division
(410) 436-5088
lee.crouse.civ@mail.mil

PRIMARY CO-INVESTIGATOR:

Emily May Lent, Ph.D.
Toxicologist
Toxicity Evaluation Division
(410) 436-7749
emily.m.lent.civ@mail.mil

CO-INVESTIGATORS:

Theresa L. Hanna
Biological Science Technician
Toxicity Evaluation Division
(410) 436-5072
theresa.l.hanna.civ@mail.mil

Mark R. Way
Biologist
Toxicity Evaluation Division
(410) 436-5089
mark.r.way2.civ@mail.mil

PROJECT SPONSOR:

Kimberly Watts
Deputy Director
RDECOM/ETAP

Aberdeen Proving Ground, MD

ACRONYMS:

ALB: albumin
ALD: approximate lethal dose
ALKP: alkaline phosphatase
ALT: alanine aminotransferase
AMYL: amylase
ANCOVA: Analysis of Covariance
ANOVA: Analysis of Variance
APHC: U.S. Army Public Health Center
APHIS: Animal and Plant Health Inspection Service
AST: aspartate aminotransferase
ASTM: American Society for Testing and Materials
AV: Attending Veterinarian
AVMA: American Veterinary Medical Association
BMD: Bench Mark Dose
BUN: blood urea nitrogen
CA: calcium
CFR: Code of Federal Regulations
CHOL: cholesterol
CO_2: carbon dioxide
CREA: creatinine
Crl(CD): Charles River Laboratories (Sprague-Dawley)
DOC: document
ECBC: Edgewood Chemical Biological Center
EPA: United States Environmental Protection Agency
FOB: Functional Observational Battery
FOX-7: 1,1-diamino-2,2-dinitroethene
GLOB: globulin
GLP: Good Laboratory Practices
GLU: Glucose
HSD: honest statistical difference
IACUC: Institutional Animal Care and Use Committee
IAW: in accordance with
LAB: Laboratory Sciences Directorate, APHC
LD_{50}: median lethal dose
LDH: lactate dehydrogenase
mL: milliliters
mlc: median lethal concentration
MRL: minimum risk level
N/A: not applicable
NRC: National Research Council
OECD: Organisation for Economic Cooperation and Development

OPPTS: Office of Prevention, Pesticides and Toxic Substances, Environmental Protection Agency
PHOS: inorganic phosphate
PI/SD: Principal Investigator/Study Director
PPE: personal protective equipment
PVC: polyvinyl chloride
QSARC: Quality Systems and Regulatory Compliance Office, Army Public Health Center
RDECOM/ETAP: Research, Development and Engineering Command, Environmental Technology Acquisition Program
RDX: Research Department Explosive (cyclotrimethylenetrinitramine)
SAS: Statistical Analysis System
SOP: Standing Operating Procedure
SPSS: Statistical Package for the Social Sciences
SSWP: Sequential Stage-Wise Probit
TBD: to be determined
TBIL: total bilirubin
TiO_2: titanium dioxide
TOX: Toxicology Directorate, APHC
TP: total protein
TSCA: Toxic Substances Control Act
USDA: United States Department of Agriculture
VMO: Veterinary Medicine Office

I. NON-TECHNICAL SYNOPSIS:

Three studies using rats will be conducted to determine oral toxicity to a compound called 1,1 –diamino-2,2-dinitroethene, also called FOX-7. FOX-7 is an explosive being evaluated for its use in conventional ammunition. This work consists of three specific studies: an acute test to determine the dose that is lethal to half of the test animals; a 14 day repeated daily dose test, and a 90 day repeated dose test to evaluate the oral toxicity in rats. An evaluation of the acute oral toxicity data will include the relationship, if any, between the exposures of the rats to the test substance and the incidence and severity of abnormalities, including behavioral and clinical abnormalities, the reversibility of observed abnormalities, gross lesions, body weight changes, effects on mortality, and any other toxic effects. Rats are the recommended test species based on previous oral toxicity studies and regulatory test guidelines. Rats will be dosed with FOX-7 via oral administration (gavage) and monitored throughout the study observation periods for body mass and clinical signs. At the end of each study, rats will be euthanized and a necropsy will be completed to evaluate tissues for signs of disease.

II. BACKGROUND

II.1. Background:

FOX-7 (CASRN 145250-81-3) is a bright yellow crystalline insensitive energetic compound which was developed by the Swedish military in the late 1990s as a

replacement for RDX (Lochert, 2001). It should be pointed out that the acronym DADNE is gaining acceptance to describe 1,1-diamino-2,2-dinitroethene. For purposes of simplicity and consistency, this compound will be referred to in abbreviated form as FOX-7 throughout this document and the ensuing studies. FOX-7 shows significant improvements in sensitivity compared with RDX, particularly in its response to impact and friction stimuli (Lochert, 2001). Experimental data indicate that the performance of FOX-7 is approximately equal to that of the benchmark nitramine explosive RDX (Eurenco, 2002). Although toxicity data is generally lacking, the abstract for a Chinese publication was identified summarizing a teratogenicity study that was performed on FOX-7. The results indicated that repeated oral administration of FOX-7 can induce maternal reproductive toxicity, fetus toxicity, and teratogenicity hazards in rats (Liu et al., 2016). FOX-7 is not currently fielded by the U.S. military as an explosive, therefore, a complete toxicological test series will be conducted to assess its toxicity before it can be used by military personnel. Additionally, this acute, subacute, and subchronic test series must be conducted to establish occupational exposure levels for workers who will be required to handle FOX-7 (USAPHC, 2016).

II.2. Literature Search for Duplication:

II.2.1. Literature Source(s) Searched: Databases Used: AGRICOLA, TOXNET, NIH RePORT. Proquest Collection which includes; ABI/INFORM Collection, Biology Database, Continental Europe Database, Health & Medical Collection, Health Management Database, Military Database, Psychology Database, Public Health Database, Research Library. AMEDD Collection which includes; Ovid, JAMA Network, CINAHL, MEDLINE, PsycINFO, PubMed.

*The SD/PI also conducted an additional search (16 October 2018) using TOXNET and PubMed and found no additional references.

II.2.2. Date of Search: 03 April 2018, 03 October 2018

II.2.3. Period of Search: 1990-2018

II.2.4. Key Words of Search:

energetic compound or 1,1-diamino-2,2-dinitroethene or FOX-7 AND LD_{50} or toxicity or oral toxicity or median lethal dose or respiratory AND rat or rats

II.2.5. Results of Search:

The literature search identified a total of seven references. One toxicity study utilizing the same test material was found; however, this study investigated only the teratogenicity of FOX-7 in pregnant Sprague-Dawley rats. Therefore, the study being proposed in this protocol is not a duplication of previous research. Because the goal of this study is to determine the effects of oral exposure of FOX-7 (lethality from a one-time exposure to determine the LD_{50} as well as sublethal effects from repeated exposure in the 14- and 90-day studies) the observation of illness associated with exposure is necessary.

III. OBJECTIVE/HYPOTHESIS:

The objective of this study is to determine the oral LD_{50} resulting from the acute oral administration of FOX-7. The study will also seek to determine if adverse effects occur from a subacute (14-day) and subchronic (90-day) repetitive oral exposure regimen of FOX-7 to the laboratory rat.

IV. MILITARY RELEVANCE:

FOX-7 is being evaluated as a replacement for RDX in conventional ammunition (Lochert, 2001). Historically, Military munitions and propellants have been developed and fielded based solely on their effectiveness on the battlefield. Any potential toxicity associated with the manufacture and use of these munitions was not investigated until after the material had been fielded and the contamination already occurred. RDX has been reported in sediment and groundwater samples taken near Military munition depots and test ranges in the U.S. The health effects associated with environmental and occupational exposure to RDX are also well-documented. RDX-induced epileptiform seizure neurotoxicity has been reported in rodent toxicity studies as well as from incidental human exposure. The Center for Disease Control, Agency for Toxic Substances and Disease Registry has developed an MRL of 0.2 mg/kg-day for acute-duration oral exposure to RDX and an MRL of 0.1 mg/kg-day for intermediate- and chronic-duration oral exposure. RDX is also classified as a possible carcinogen (ATSDR, 2012).

Research, development, testing, and training with explosives and pyrotechnics which are potentially less hazardous to human health and the environment is vital to the readiness of the U.S. Army. The Army Environmental Quality Technology, Ordnance Environmental Program is dedicated to finding replacements for substances causing environmental and/or occupational risks to health. Toxicity assessments such as this proposed study are necessary for safeguarding the health of Soldiers, civilians, and the environment and, if begun early in the research, development, testing, and evaluation process, can save significant time and effort by identifying unacceptable replacement compounds (ASTM, 2008).

V. MATERIALS AND METHODS

Test Article: This study will be conducted with FOX-7. A purity analysis will be provided by the manufacturer since LAB cannot perform this analysis without a secondary source of neat test substance. FOX-7 will be mixed with an appropriate diluent to be determined once the material is received. Appropriate diluents, in order of preference, include drinking quality water, corn oil, methylcellulose, and polyethylene glycol 200. Samples for stability and homogeneity (if necessary) will be determined prior to the subacute study. All dosing solutions/suspensions will be analyzed by LAB or other appropriate analytical laboratory for concentration verification. Neat test material will be stored in Velostat™ bags at the ECBC explosive storage facility.

V.1. Experimental Design and General Procedures:

This study consists of three phases: an acute (LD_{50}) test (SSWP), a 14-day repeated dose test, and a 90-day repeated dose test to evaluate the oral toxicity of FOX-7 in rats. During the acute phase, rats will be dosed with FOX-7 via oral gavage and monitored throughout the study observation period for changes in body mass and clinical signs. At the conclusion of the exposure/observation period for each phase of the study, test animals will be anesthetized, blood samples will be collected (in the 14-day and 90-day tests), euthanized, and a gross necropsy will be performed on each animal. For both the 14-day and 90-day tests, a vehicle control group will be included. Table 1 outlines the planned animal use for the 3 tests.

Table 1

Dose Group	**Pain Category**	**Test Animals**		
ACUTE STUDY:		Males	Females	
LD_{50}	C	15	15	
LD_{50}	E	15	15	
Sub-Total:		**30**	**30**	**60**
14-DAY STUDY:		Males	Females	
Vehicle Control	D	6	6	
Dose TBD	D	6	6	
Dose TBD	D	6	6	
Dose TBD	D	6	6	
Dose TBD	D	6	6	
Dose TBD	E	6	6	
Dose TBD	E	6	6	
Dose TBD	E	6	6	
Sub-Total:		**48**	**48**	**96**
90-DAY STUDY:		Males	Females	
Vehicle Control	D	10	10	
Dose TBD	D	10	10	
Dose TBD	D	10	10	
Dose TBD	E	10	10	
Dose TBD	E	10	10	
Health Monitoring Animals	C	4	4	
Sub-Total:		**54**	**54**	**108**

GRAND TOTAL:		**132**	**132**	**264**

V.1.1. Administration of Test Substance

Oral dosing will be performed using a stainless steel 16-18 gauge x 2 inch gavage needle. As per OECD Test Guidelines, the dosage volume to be administered will not exceed 10 mL/kg of body mass (OECD, 2018). Purity information will be provided by the manufacturer in the certificate of analysis shipped with the test material. All concentration verification analyses of dosing solutions and homogeneity tests, as well as stability analyses will be performed by LAB or other appropriate analytical laboratory.

V.1.2. Study Conduct:

The study described will be conducted in a manner consistent with GLP regulations in the Toxic Substances Control Act (TSCA): 40 CFR 792, plus amendments (CFR, 1989). The investigators and technicians will adhere to the Guide for the Care and Use of Laboratory Animals (National Research Council, 2011).

V.1.3. Experiment 1: Acute Study (LD_{50}):

The acute toxicity of FOX-7 will be assessed using the SSWP method (Feder et al., 1991a, Feder et al., 1991b, ASTM, 2010). This method proceeds in stages in which groups of rats of each sex are dosed and the responses observed. These responses are then used in determining the doses and animal numbers used in the next stage of dosing. In the first stage, approximately three to five different doses of the test compound will be selected with the goal that the doses span the entire dose response curve. In the absence of historical data, such as with FOX-7, it is recommended that doses for the first stage of dosing start at the default starting value of 175 mg/kg with half-log dose intervals (3.2 dose progression factor) (EPA, 2002). One animal of each sex will likely be given each dose in the first stage of the study. In all subsequent stages of dosing, one to four doses will be used, with one to three animals of each sex at each dose. Each group of animals dosed during the individual stages will have an observation period of up to 14-days in which animals are observed for signs of toxicity, changes in body mass, morbidity, and mortality. Subsequent stages are typically separated by a 24-48 hour period once a determination can be made regarding the survival of the animals dosed. A probit analysis of the results from all previous stages of dosing will be used to determine the doses for subsequent stages of dosing. The analysis uses survival results from each stage to calculate the LD_{50}, slope, and 95% confidence interval for each sex. Dosing of stages will continue until the variation around the LD_{50} is less than 0.40 (95% upper confidence limit minus 95% lower confidence limit/2x the LD_{50}) or a maximum of 30 rats per sex have been utilized. In particular circumstances, dosing may continue when the variation is less than 0.40 upon statistical consultation and whether it is advisable to further refine the confidence intervals. If no deaths are observed at the highest dose level (2000 mg/kg) in the first stage of dosing, a limit test will be conducted. In the limit test, five additional animals

will be dosed at 2000 mg/kg. Three or more animals must survive the limit test for the LD_{50} to be reported as greater than the limit dose. The maximum number of animals needed for this test is 60 (30 male and 30 female).

V.1.4. Experiment 2: 14-Day Repeated Dose Test (Subacute)

The purpose of the 14-day range finding study is to determine if there are adverse effects from short-term repeated oral exposures to FOX-7 and to acquire sufficient data to set dosage levels for the 90-day subchronic study. This test will be carried out among seven dose groups, consisting of 12 individuals per dose group (six males and six females), along with vehicle control group [N=(6+6)X8=96]. Randomization will be based on stratification by body mass taken on the day prior to initiation of dosing. The rats will be dosed with FOX-7 in an appropriate vehicle (as determined prior to testing) via oral gavage for 14 days (seven days per week). Dosage selection will depend upon the results of the SSWP (e.g., 1X, 0.75X, 0.5X, 0.25X, 0.125X, 0.0625X, 0.03125X of the LD_{50}). The vehicle control group will receive a dosage volume equivalent to that of the highest concentration exposure group. Table 2 outlines the dosage selection for the 14-day study, in relationship to the LD_{50}.

Table 2:

Dose Group	**Pain Category**	**Test Animals**		
14-DAY STUDY		Males	Females	
Vehicle Control	D	6	6	
1X	E	6	6	
0.75X	E	6	6	
0.5X	E	6	6	
0.25X	D	6	6	
0.125X	D	6	6	
0.0625X	D	6	6	
0.0325X	D	6	6	
Total:		**48**	**48**	**96**

On the day following the administration of the final dose, animals will be anesthetized, bled via cardiac puncture as described in V.4.4.3.1., euthanized, and gross necropsies will be performed.

The following organs and tissues, or representative samples thereof, will be preserved in 10% buffered formalin (Davidson's fixative will be used to preserve testes and epididymides) for possible future histopathological examinations if needed: all gross

lesions, brain (including sections of the medulla/pons and both cerebellar and cerebral cortices), pituitary, thyroid/parathyroid, thymus, lungs and trachea, pharynx, larynx, nose, heart, bone marrow (either femur, sternum, or rib at the costochondral junction), salivary glands, liver, spleen, kidneys, adrenal glands, pancreas, testes, uterus, aorta, esophagus, stomach, duodenum, jejunum, ileum, caecum, colon, rectum, urinary bladder, representative lymph node, peripheral nerve, mammary gland, thigh musculature, eyes, femur (including articular surface), spinal cord (cervical, thoracic, and lumbar); and exorbital lachrymal glands. Additionally, the following organs will be weighed: liver, kidneys, adrenal glands, gonads, spleen, brain, epididymides, uterus, thymus, and heart. The above lists may be altered by the study staff based upon observed toxicity and/or gross pathology findings. Prior to weighing, organs will be carefully dissected and trimmed in order to remove excess adipose tissue and any other heterogeneous tissue in a uniform manner. All gross pathology findings observed during necropsy will be recorded on TOX DOC 4.0. If a necropsy cannot be performed contemporaneously with the discovery of an animal believed to be deceased, a secondary euthanasia method will be performed to confirm death and the carcass will be refrigerated at 4° C to minimize autolysis. A necropsy will then be performed at the next earliest possible time point. The total number of animals necessary for this test is 96.

V.1.5. Experiment 3: 90-Day Subchronic Study

The main element of this study will be the 90-day subchronic oral toxicity test. Because this portion of the study must be conducted in such a way that it can be submitted to the EPA, this test will adhere closely to applicable harmonized test guidelines for performing 90-day oral toxicity studies in rodents (OECD, 2018). The route of exposure will be by oral gavage with the test compound being suspended in appropriate vehicle, and dosed via a 16-18 gauge X 2 inch gavage needle seven days a week for a period of 90 days. Fifty rats of each sex (N=100) will be divided into four dose groups and a vehicle control group (10 rats of each sex per group). Randomization will be based on stratification by body mass taken on the day prior to initiation of dosing. Dose levels will be based on the results of the 14-day repeated dose study.

Four additional animals of each sex (N=8) will be ordered for health monitoring purposes (APHC, 2017a). Two animals of each sex will be sent to an approved vendor to serve as indicators of the colony's health status at the end of the acclimation period, and again as the study nears its conclusion. The total number of rats necessary to perform the 90-day subchronic test, as described, is 108.

Table 3:

90-DAY STUDY:	**Pain Category**	Males	Females	
Vehicle Control	D	10	10	
Dose TBD	D	10	10	
Dose TBD	D	10	10	
Dose TBD	E	10	10	
Dose TBD	E	10	10	
Health Monitoring Animals	C	4	4	
Sub-Total:		**54**	**54**	**108**

All animals in this main study may have an ophthalmological examination by the AV prior to dose administration of FOX-7 (APHC, 2017c). At the termination of the 90-day test, remaining rats in both the high dose and control groups will have a second ophthalmological examination. If changes in ophthalmological health are detected in either the high dose or control group, then all remaining rats will be subjected to a second examination by the AV.

Urinalysis (using timed urine collection) will be performed using metabolism cages on at least eight animals per dose group, during weeks 11-13 of the study as described in V.4.4.3 (APHC, 2018a).

In addition to the general clinical observations taken daily by the principal investigator or co-investigators, an FOB will also be conducted as described in V.4.4.7. and will include a thorough clinical examination of the animals outside of their cage once a week. Once prior to initiation of dosing and once weekly during dosing, a careful clinical examination will be performed, at a similar time of day and outside of the home cage (preferably in a standard arena). Once near the termination of dosing, but not prior to week 11, sensory reactivity to a variety of stimuli (such as responses to visual, auditory, and proprioceptive stimuli), grip strength, and motor activity tests will be conducted. FOB procedures are outlined in TOX SOP 062.002 (APHC, 2016a).

At the termination of the study, on the day after administration of the final dose of test material, each animal will be rendered unconscious with CO_2 gas, bled via cardiac puncture as described in V.4.4.3., euthanized, and submitted for a full gross necropsy.

All gross pathology findings observed during necropsy will be recorded on TOX DOC 4.0. If a necropsy cannot be performed contemporaneously with the discovery of a deceased animal, death will be ensured via thoracotomy and the carcass will be refrigerated at a temperature sufficiently low to minimize autolysis. Full histopathological examinations will be performed on all rats in both the control and highest dose groups. Further histopathological examinations of rats in other dose

groups will be performed on organs and tissues which exhibit lesions similar to those observed in the highest dose group, or when such a need is indicated by clinical observations. The following organs and tissues, or representative samples thereof, will be preserved in 10% buffered formalin (Davidson's fixative will be used to preserve testes and epididymides) for future histopathological examinations: all gross lesions, brain (including sections of the medulla/pons and both cerebellar and cerebral cortices), pituitary, thyroid/parathyroid, thymus, lungs and trachea, pharynx, larynx, nose, heart, bone marrow (either femur, sternum, or rib at the costochondral junction), salivary glands, liver, spleen, kidneys, adrenal glands, pancreas, testes, uterus, aorta, esophagus, stomach, duodenum, jejunum, ileum, caecum, colon, rectum, urinary bladder, representative lymph node, peripheral nerve, mammary gland, thigh musculature, eyes, femur (including articular surface), spinal cord (cervical, thoracic, and lumbar); and exorbital lachrymal glands. Additionally, the following organs will be weighed: liver, kidneys, adrenal glands, gonads, spleen, brain, epididymides, uterus, thymus, and heart. The above lists may be altered by the study staff based upon observed toxicity and/or gross pathology findings. Prior to weighing, organs will be carefully dissected and trimmed in order to remove excess adipose tissue and any other heterogeneous tissue in a uniform manner.

V.1.6. Study Time Frame:

Estimated initiation date for the study is February 2019. Estimated completion date for the study is June 2019.

V.2. Sample Size Evaluation, Data Analysis Plan, and Archiving of Data:

For variables that are measured only at the termination of the study, the dose groups will be compared using a one-way ANOVA. Organ-to-brain and organ-to-body mass ratios will be calculated and analyzed in a manner consistent with other parameters measured at the termination of the study. If the dose group effect is observed to be significant, multiple comparison tests will be used to compare pairs of dose groups, and dose groups to the vehicle control group. A Tukey's HSD multiple comparisons post-hoc test will be used if the variance of the dose groups is similar, and a Dunnett's T3 post-hoc test will be used if the variances are dissimilar. Similarity of variance will be determined by a Levene's test.

For absolute organ weights, a comparison of the dose groups will be made using an ANCOVA, with body mass at the termination of the study being the covariate used. Although the dose groups will be assigned at day 0 to establish similar average body masses among dose groups, these averages can change over the course of the study with respect to dose group. The ANCOVA will adjust for any differences in average body mass among dose groups, based on the idea that larger animals will tend to have larger organs. If the dose group effect is significant, a least significant differences post hoc test will be used to compare the pairs of dose groups, as well as dose groups to the vehicle control group.

Dose groups and sexes will be compared with respect to absolute body masses, as well as weekly changes in body mass and net changes by using a two-way ANOVA. Dose groups and sexes will also be compared with respect to net food consumption over the course of the study using a two-way ANOVA. In the event that the results of the ANOVA are significant, either a Tukey's HSD multiple comparisons post-hoc test (in the event that variances are similar) or a Dunnett's T3 post-hoc test (if the variances are dissimilar). Similarity of variance will be determined by a Levene's test.

For FOB data, a Chi-square test will be used to compare dose groups for categorical data. If significant results are observed, either a Fisher's exact test or a Kruskal-Wallis test will be used to compare pairs of dose groups. Interval data will be analyzed for differences among dose groups using an ANOVA followed by a Tukey's HSD multiple comparisons post-hoc test (in the event that variances are similar) or a Dunnett's T3 post-hoc test (if the variances are dissimilar). Similarity of variance will be determined by a Levene's test. Responses for each week and sex will be analyzed separately.

Other observational data including gross necropsy observations and histopathology data may be converted to categorical data and analyzed using a Chi-square test. If significant effects are observed, either a Fisher's exact test or a Kruskal-Wallis test will be used to compare pairs of dose groups.

SPSS 22.0 or other appropriate version will be used to perform all analyses and statistical significance will be defined at an alpha value of $p \leq 0.05$ for all tests.

Sample sizes were selected IAW OECD Guidelines for the Testing of Chemicals for Repeated Dose 90-Day Oral Toxicity Study in Rodents (OECD, 2018). These sample sizes have been widely used and have been shown to provide adequate statistical power in this test.

Records will be maintained in standard APHC laboratory notebooks and/or three ring binders. Daily records will be collected on survival and observed clinical signs of animals after dosing occurs. Procedures for preparation of any euthanasia solution, drug administration, animal bleeding, observation logs, morbidity/mortality logs, etc. will be stored with the study records. These records will be made available to oversight organizations such as the U.S. EPA and the IACUC. The protocol, any amendments, raw data, statistical analyses, tabular calculations, and graphic analyses of these data will be saved with the study records. Additionally, memoranda to the study file, study logs, signature logs, final reports, final report amendments, and both test and control articles will be archived at APHC.

V.3. Laboratory Animals Required and Justification
V.3.1. Non-animal Alternatives Considered:

The questions addressed in this study pertain to adverse health effects of oral exposure to FOX-7 in the laboratory rat. These data will aid in the development of occupational exposure guidelines and will also be used to compare to the toxicity of currently used

energetic compounds. Currently there are no viable alternative models which do not employ the use of whole organisms (test animals) and would provide sufficient data to assess the oral toxicity of FOX-7, in addition to allowing for accurate comparison with previously obtained toxicity data on other energetic compounds. Therefore it is necessary to perform this study using an animal model.

V.3.2. Animal Model and Species Justification:

Applicable harmonized test guidelines for acute oral toxicity (OPPTS 870.1100 Acute Oral Toxicity) and 90-day oral toxicity (OECD 408) state that the rat is the preferred species. Sprague-Dawley rats have been historically used for oral toxicity studies at the APHC and, therefore, are the recommended species due to the extensive historical database.

V.3.3. Laboratory Animals

V.3.3.1. Genus species: *Rattus norvegicus*

V.3.3.2. Strain / Stock / Breed: Sprague-Dawley (CD)

V.3.3.3. Source / Vendor:

Charles River Laboratories (USDA 14-R-0144) or other APHC approved vendor

V.3.3.4. Age (at use): Acute – 7-9 weeks
14-Day – 6-8 weeks
90-Day – 6-8 weeks

V.3.3.5. Weight: Age appropriate by vendor supplied specifications

V.3.3.6. Sex: Male and Female

V.3.3.7. Special Considerations: None

V.3.4. Number of Animals Required (by Species): 264 Rats

V.3.5. Refinement, Reduction, Replacement (3 Rs):

V.3.5.1. Refinement:

No additional refinements will be employed other than the environmental enrichment strategy and pair housing of rats.

V.3.5.2. Reduction:

The SSWP method uses fewer animals than other traditional methods of LD_{50} determination and provides quantitative estimates of the LD_{50} and confidence intervals. If the limit dose (2000 mg/kg) does not cause mortality in the first stage of the SSWP, then the second stage will revert to the limit test and use a maximum of 5 males and 5 females to estimate the LD_{50}.

V.3.5.3. Replacement:

There is currently no acceptable methodology available to replace these studies and provide the information we seek to obtain.

V.4. Technical Methods:

V.4.1. Pain / Distress Assessment:

V.4.1.1. APHIS Form 7023 Information:

V.4.1.1.1. Number of Animals

V.4.1.1.1.1. Column B: 0

V.4.1.1.1.2. Column C: 38

V.4.1.1.1.3. Column D: 120
V.4.1.1.1.4. Column E: 106

V.4.1.2. Pain Relief / Prevention

V.4.1.2.1. Anesthesia / Analgesia / Tranquilization:

Rats will be rendered unconscious with CO_2 prior to terminal cardiac blood collection. They will be transported to the necropsy room in home cage or transport cage. The stainless steel lid will be placed on the cage. If using the home cage, the grommet will be covered with tape or a magnet. CO_2 will displace 10-30% of the cage volume per minute IAW QSARC 800.00 (APHC, 2017c). Animals will remain in the cage until they are recumbent and breathing is slow and shallow. Once recumbent, a toe or space between the toes will be pinched to assess appropriate depth of unconsciousness. If there is no response to toe pinch, the rat will be removed and blood will be collected (as described in V.4.4.3). Upon completion of blood collection, the rat will be returned to the cage and euthanized as described in section V.4.6.

V.4.1.2.2. Pre- and Post-procedural Provisions:

Urinalysis: During or after week 11 of the 90-day study, at least 8 rats from each dose group will be placed in the metabolism cages overnight (approximately 15-16 hours) for timed urine collection. During this time, rats will be fasted but will have access to water via water bottles. Urinalysis details are described in V.4.4.3.2.

Ophthalmic Exams: Animal room lights will either be dimmed or turned off during instillation of 1% tropicamide opththalmic solution and for a minimum of 2 hours following dilation.

Gavage: Each rat will be monitored for signs of aspiration as they are being returned to their cage following dosing. If test material is observed in or around the mouth of a rat or it appears to be gasping, it will be intermittently checked during the remainder of the dosing period. If any signs of aspiration persist throughout the dosing period, the rat will be check periodically throughout the remainder of the day until the observation disappears.

V.4.1.2.3. Paralytics: N/A

V.4.1.3. Literature Search for Alternatives to Painful or Distressful Procedures:

V.4.1.3.1. Source(s) Searched:

TOXNET, CRIS, NIH RePorter. Proquest Collection which includes; ABI/INFORM Collection, Biology Database, Continental Europe Database, Health & Medical Collection, Health Management Database, Military Database, Psychology Database, Public Health Database, Research Library. AMEDD Collection which includes; Ovid, JAMA Network, CINAHL, MEDLINE, PsycINFO, PubMed.

* The SD/PI also conducted an additional search (18 April 2018) using AGRICOLA, TOXNET, Ovid and PubMed and found no additional references.V.4.1.3.2. Date of Search: 03 April 2018, 18 October 2018

V.4.1.3.3. Period of Search: 1990-2018

V.4.1.3.4. Key Words of Search:

oral toxicity or 1,1-diamino-2,2-dinitroethene or FOX-7 AND LD_{50} or toxicity or oral toxicity or median lethal dose or respiratory AND rat or rats AND pain or distress or refine or reduce or replace or artificial or in vitro or tissue or cell or simulate

Keywords searched by the SD/PI for Alternatives to Painful or Distressful Procedures include: oral toxicity AND LD50 or toxicity or oral toxicity or median lethal dose AND rat or rats AND pain or distress or refine or reduce or replace or artificial or in vitro or tissue or cell or simulate

V.4.1.3.5. Results of Search:

The literature search identified a total of five references. Among these, none pertained to alternatives to painful procedures which would not affect the outcome of the study. One study did provide information on an alternative to the SSWP which could arguably use fewer animals to find an LD_{50}. However, we have received guidance that the SSWP is the method we are to use because it allows for calculating a confidence interval. Because the goal of this study is to determine the effects of oral exposure of FOX-7 (lethality from a one-time exposure to determine the LD_{50}, as well as sublethal effects from repeated exposure in the 14- and 90-day studies) the observation of illness associated with exposure is necessary. Moribund animals or animals in obvious pain which are unlikely to recovery will be humanely euthanized. While alternative methods

of blood collection are available, due to the volume of blood required for both the hematology and clinical chemistry assays, the intracardiac puncture method of blood collection is necessary. For this procedure, the rats will be rendered unconscious with CO_2. Because there are no validated *in vitro* tests currently available which would both replace *in vivo* oral toxicity and provide the same level of data to assess toxicity, these studies must be conducted *in vivo*. As a result, the possibility of painful procedures or an animal experiencing study-related illness cannot be avoided.

V.4.1.4. Unalleviated Painful or Distressful Procedure Justification:

The nature of these studies precludes the complete elimination of procedures which could be considered to be painful or distressful to the test animal. An attempt to relieve pain or distress through the administration of anesthetics, analgesics, or other drugs may alter the manifestation and subsequent identification of responses to toxicity. Typical pain relievers such as narcotic analgesics (opioids), non-steroidal anti-inflammatory drugs, and anesthetics have the ability to mask some of these effects, particularly those arising from pain or distress. Additionally, there can be other unintended side effects which may arise from the administration of these drugs, such as altering blood chemistry or hematology data, which can cause the investigator to misinterpret such changes as clinical effects caused by the test material. The observation of the onset, duration, and/or reversibility of signs of toxicity is a critical part of interpreting the mechanism of toxicity. This is particularly true due to the fact that the acute study will be used to set dose levels for the longer term studies. Toxic signs are defined in QSARC 806.00 (APHC, 2017h). See section V.4.5 for criteria for early removal from testing.

In an effort to prevent undue suffering, moribund animals will be euthanized as described in section V.4.6. Discussions were held with the AV regarding painful procedures. The use of analgesics in this model is untested and may alter the response to the test material, thereby compromising the results of these experiments. The toxicity of the test compound is unknown, so animals receiving higher doses of the test compound are listed in the unalleviated pain and distress category. The actual number of rats in each pain category as determined by the outcome and observations of the animals on study will be reported to the IACUC annually and at the end of the in-life portion of the protocol.

V.4.2. Prolonged Restraint and Restraint Methods: N/A

V.4.3. Surgery: N/A

V.4.3.1. Pre-surgical Provisions: N/A

V.4.3.2. Procedure: N/A

V.4.3.3. Post-surgical Provisions: N/A

V.4.3.4. Location: N/A

V.4.3.5. Surgeon: N/A

V.4.3.6. Multiple Survival Operative Procedures: N/A

V.4.3.6.1. Procedures: N/A

V.4.3.6.2 Scientific Justification: N/A

V.4.4. Animal Manipulations: N/A

V.4.4.1. Injections: N/A

V.4.4.2. Use of Non-pharmaceutical-grade chemicals: The compounds being tested are not available in a pharmaceutical-grade composition. They are under investigation as described in the objective section (III) of this protocol.
V.4.4.3. Biosamples:

V.4.4.3.1. Blood Collection and Analysis:

At the end of the 14- and 90-day studies, blood will be collected from all surviving animals. Terminal blood collection will be via cardiac puncture IAW QSARC 805 (APHC, 2017g). All blood collection via cardiac puncture will be conducted under CO_2 gas (as described in section V.4.1.2.1). Blood collection will be promptly followed by euthanasia as described in section V.4.6.

For hematology samples, blood will be transferred to an EDTA microtube or microvette and immediately inverted gently several times. The remainder of the blood will be transferred to a sodium citrate microtube or microvette for analysis of prothrombin and/or activated partial thromboplastin time. For clinical chemistry samples, blood will be transferred to a serum or serum-gel microtube or microvette and allowed to stand at room temperature for at least 20 minutes to allow sufficient clotting prior to centrifugation. Details concerning clinical chemistry and hematology parameters are outlined in TOX SOPs 011.003, 013.003, and 079.000 (APHC, 2018b, c and 2016b).

V.4.4.3.2. Urinalysis:

Urine will be collected from at least 8 rats per sex per dose group for urinalysis during or after week 11 of the subchronic study. Rats will be placed in metabolism cages capable of separating feces and urine overnight for approximately 15-16 hours for collection of urine samples. Rats will be provided fresh drinking water *ad libitum*; however, due to issues with contamination of the urine sample with food, rats will be fasted while in the metabolism cages. Urine voided by the rat while in the cage will passively collect in the urine collection tube and will be recorded as a volume per sample time. Urine will be removed from the collection cups as soon as possible at the conclusion of the sample collection period and placed in labeled, clear, conical tubes. Procedures will include a physical examination for color, clarity, volume, and specific gravity, and chemical examination with a MultiStix Reagent Strip. Microscopic evaluation is a semi-

quantitative procedure and is considered optional. Urinalysis procedures will be conducted IAW TOX SOP 003.003 (APHC, 2018a).

V.4.4.4. Adjuvants: N/A

V.4.4.5. Monoclonal Antibody (MAb) Production: N/A

V.4.4.6. Animal Identification:

Individual animals will be identified by cage card and tail marking (number written on tail with water-insoluble permanent marker) for the acute,14-day, and 90-day phases of the study. All animals will be assigned a unique identification number as per QSARC 804.00 (APHC, 2017f).

V.4.4.7. Behavioral Studies:

A neurotoxicity screen and an FOB test will be performed on all rats in the 90-day study IAW TOX SOP 062.002 (APHC, 2016a). Once, prior to initiation of dosing, and once weekly during dosing, a careful clinical examination will be performed. These examinations will be performed at a similar time of day, outside of the home cage (preferably in a standard arena). Once near the termination of the dosing exposures, but not prior to week 11, sensory reactivity to stimuli of different types (i.e., elicited responses for visual, auditory, and proprioceptive stimuli), grip strength, and motor activity tests will be conducted.

V.4.4.8. Other Procedures:

V.4.4.8.1 Gavage:

Test material will be administered by oral gavage. The 16-18 gauge x 2 inch gavage needle will be visually confirmed to be the appropriate size (i.e., hub-to-bulb distance spans the length between the mouth and last rib of the rat). Each rat will be gently restrained by placing the index and middle finger on either side of the animal's neck with the remainder of the hand used to support the body, and will be maintained in an upright (vertical) and extended position. Just prior to dosing, the index and middle finger can be used to tilt the animal's head back and the gavage needle inserted into either the side or the top of the mouth. The rat may also be "scruffed" by pinching the skin at the base of the neck, behind the ears, between the thumb and fingers. The bulb of the gavage needle is passed into the mouth of the rat with the bulb directed towards the junction of the palate and cheek (palatoglossal arch). The gavage needle is then gently slid down the animal's esophagus until the hub of the gavage needle is at the opening of the animal's mouth, and the material is dispensed. If any resistance is felt during the advancement of the gavage needle, the gavage needle is removed and the animal is briefly released before the procedure is attempted again. Once the material has been dispensed, the animal is briefly observed for any signs of aspiration. Animals will also undergo cage-side observations to check for welfare/mortality in the afternoon, before study staff leave for the day.

V.4.4.8.2. Observations:

Animals will undergo a thorough daily clinical examination during the dosing period. Observations will be detailed and recorded in a laboratory notebook, or on an appropriate study document specifically designed to accurately capture such information. Observations will include, but not be limited to, evaluation of skin and fur, eyes and mucous membranes, respiratory and circulatory effects, autonomic responses such as salivation, central nervous system effects (including tremors and convulsions), changes in activity, changes in gait and/or posture, changes in reaction to being handled, changes in response to sensory stimuli, altered strength, appearance of bizarre behavior (e.g., self-mutilation or walking backwards). Afternoon observations (weekdays only) will generally be taken cage-side unless a sign is observed that warrants the removal of the rat from its home cage for further observation.

V.4.4.8.3. Eye Exams:

All animals in the subchronic study may undergo an ophthalmic exam prior to any test substance administration (APHC, 2017c). Ophthalmic exams require the instillation of 1% tropicamide ophthalmic solution in each eye of the rats. Animal room lights will be dimmed as much as possible while still allowing study staff to instill the eye drops. After the drops have been placed in the eyes of each rat, the animal room lights will be turned off and will remain off through the completion of the eye exams. If the eye exams are performed in the afternoon, the animal room lights are typically left off for the remainder of the day. If the pre-study eye exams are performed, this procedure will be repeated near the end of the study, starting with the control and high dose animals.

V.4.4.9. Tissue Sharing:

Tissues from animals euthanized on this study may be made available to other personnel with approved protocols if coordinated through the PI/SD. Tissue sharing will be allowed only if doing so does not affect the quality and validity of the study or change the euthanasia methods.

V.4.5. Study Endpoint:

The study endpoint of the acute study (LD_{50}) is intervention euthanasia of moribund animals, study-related mortality, or euthanasia following an observation period not to exceed 14 days.

The study endpoint of both the subacute and subchronic study is intervention euthanasia of moribund animals, study-related mortality, or euthanasia on the day following the final administration of the test substance.
Although some form of euthanasia is the projected study endpoint, the possibility still exists that a compound-related death may occur during an unobserved period (e.g., overnight). The novelty of the compound being tested prevents the assurance that a

compound-related death may not occur. Additionally, the time at which signs of toxicity appear, their duration, and the time to death are important, especially if there is a tendency for deaths or morbidity to be delayed or if the signs of toxicity are reversible or recovery is possible. This is particularly important in the acute study when the type, onset, and duration of toxic signs are still unknown. As such, potentially moribund animals will be monitored, in consultation with the AV, during all test phases for possible reversal and recovery of toxic signs.

Animals will be assessed for morbidity on a case by case basis and assessed for early euthanasia according to the following criteria:

1. Impaired ambulation (which prevents the animal from reaching food/water)
2. Weight loss or failure to gain weight (> 20% body mass loss as compared to controls)
3. Lack of physical activity or mental alertness
4. Prolonged labored breathing (lasting longer than 8 hours and accompanied by lethargy)
5. Unabated seizure activity (lasting longer than 1 hour)
6. Inability to urinate or defecate longer than 24 hours
7. Prolonged inability to remain upright (lasting more than 2 hours)

The AV may be consulted, if needed, to evaluate potentially moribund animals, unless the SD/PI plans to immediately euthanize the animal. Intervention euthanasia will be conducted on animals determined to be moribund. Euthanasia of moribund animals will be performed IAW section V.4.6.

If body weight of dosed animals is observed to decrease relative to controls, measurements may be done more frequently. Animals that exhibit an excessive decrease in weight, defined as > 20% body mass difference as compared to controls (due to either weight loss or failure to gain weight) compared to controls, as described above, will be euthanized IAW section V.4.6.

Any animals not used in the SSWP method will either be transferred to another approved protocol or euthanized as described in section V.4.6.

V.4.6. Euthanasia: Euthanasia will be accomplished by asphyxiation from CO_2 exposure IAW QSARC 800.00 (APHC, 2017d). Death of all rats euthanized by CO_2 will be ensured by thoracotomy or immediate necropsy with perforation of the diaphragm. Thoracotomy will be accomplished by inserting a sharp blade into the chest cavity behind a rib and moving the blade the length of the rib. Alternatively, for animals being immediately necropsied, the abdomen will be opened and a puncture made through the diaphragm via the abdominal cavity.

For any animals believed to be deceased, a secondary method of euthanasia will be performed to confirm death IAW AVMA Guidelines (AVMA, 2013).

V.5. Husbandry & Veterinary Care:

V.5.1. Husbandry Considerations:

Animal rooms will be maintained IAW QSARC 707.01 except as described herein (APHC, 2017b). Animals will be provided *ad libitum* rodent chow that is certified free of contaminants with the exception of overnight fasting prior to dosing for the acute study, fasting while in metabolism cages for the 90-day rats, and prior to necropsy for the 14- and 90-day rats. Water will be provided *ad libitum* by the automated watering system, by reservoirs that feed into the racks, or by water bottles. Light cycle will be 12 hours on and 12 hours off except during ophthalmic exams for the 90-day rats as described in V.4.4.8.2. Room temperature will be set at 68-79ºF and humidity at 30-70%. Cage sanitation will be checked at least once daily by animal care staff. The animals will be housed in plastic, solid-bottom shoebox cages (size appropriate to the body weight of the rat) with Sani-Chip bedding. Rats will be same-sex group housed within dose groups during the subacute (14 day) and subchronic studies (90 day). The acute study rats will be pair housed prior to dosing, and singly housed following dosing due to the unknown toxicity of the compound. Animals showing no signs of toxicity during the first 7±2 days of the observation period may be pair housed again at the discretion of the SD/PI. Pair housed animals showing signs of delayed toxicity will be returned to single housing.

All rats will undergo a 5-day acclimation period. Body weight and observation data may also be collected for rats by study personnel during the acclimation period in an attempt to more accurately monitor the health status of the rats in preparation for their use on study. Initial body weight measurements will be taken by VMO staff, in coordination with study staff immediately upon arrival to the APHC facility. However, animals will not be weighed or handled by study personnel within the first 24 hours after their arrival to the facility.

V.5.1.1. Study Room:

Studies will be conducted at the APHC animal facility, Bldg. E-2100 or Bldg. E-2101, housing room as assigned. All live animal work with the exception of CO_2 gas exposure will occur in the housing room. CO_2 exposure, blood collection, and necropsy will occur in E2100 room 3201.

V.5.1.2. Special Husbandry Provisions:

Food consumption for all subacute and subchronic study animals will be monitored based on the weight of the food hopper. Therefore, feed should not be added to feeders, and feeders should not be replaced without consulting the PI/SD. Food enrichment may not be used due to food consumption monitoring.

Sani-Chip bedding will be used for all phases of this study due to fasting procedures. Previous studies have demonstrated that the rats, especially during fasting, consume

paper bedding products. Absorption of orally administered compounds by the consumed paper bedding in the gastrointestinal tract has unknown impacts on the compound absorption and toxicity.

Prior to study initiation and again during or after week 11, the room lights will be dimmed and/or turned off to allow eye exams to be performed.

At or after week 11 of the study, at least 8 rats per sex per dose group will be singly placed in metabolism cages overnight by study staff. Animals will be placed in the cages no earlier than 1500 hours, and remain there overnight not to exceed 15-16 hours. Water will be provided via water bottles and no food or enrichment will be provided. The animals will be returned to their home cages the following morning. Provisions will be made with VMO staff to coordinate set up, removal, and sanitizing of metabolism cages.

Fasting of subacute and subchronic rats prior to necropsy will not exceed 24 hours.

V.5.1.3. Exceptions:

The acute study animals may be singly housed after dosing due to toxic signs observed from test material administration. Animals showing no signs of toxicity during the first 7±2 days of the observation period may be pair housed again at the discretion of the SD/PI and AV. Pair housed animals showing signs of delayed toxicity will be returned to single housing. Single housing is necessary because the toxicity of the compound is unknown; therefore the toxic signs expected at each dose are unknown. The SSWP method doses one to three animals at each dose and the doses are often widely spaced. Therefore, pair housing could result in co-housing animals which may be showing very different toxic signs. Pair-housing may result in healthy animals being co-housed with animals exhibiting seizure activity or with moribund animals. This practice may result in undue stress to the healthy animal or loss of data from the moribund animal if aggression or cannibalism occurs.

Every attempt will be made to have all animals on the subacute (14-day) and subchronic (90-day) studies remain pair-housed for the duration of the study. The planned exception to this is when selected animals are single-housed overnight in the metabolism cages. Instances of cage mate incompatibility, or the death of a cage mate may result in single housing of some rats. Throughout the 90-day study, animal body weights will be monitored. The PI and VSO will monitor rats that reach the maximum body weight category (greater than 500 grams) as specified in the *Guide* (NRC, 2011), to ensure the animals' housing microenvironment is not adversely affecting their welfare. Animals may be single-housed in the event a pairing of animals becomes an environment in which the needs of both animals cannot be accommodated, resulting in decreased animal welfare. The PI and VSO will make the determinations for these animals on a case by case basis.

V.5.2. Veterinary Medical Care

V.5.2.1. Routine Veterinary Medical Care:

Animals will routinely be observed no less than once daily by assigned veterinary medical personnel for husbandry conditions, humane care, and general health status. IAW current IACUC guidance, in the event an animal becomes ill or injured, veterinary or toxicology personnel will contact the AV or his/her designated backup who will determine the appropriate course of action.

V.5.2.2. Emergency Veterinary Medical Care:

In the event an animal requires after-hours emergency veterinary care, a veterinarian is available 24 hours a day, 7 days a week. In the case of an emergency health problem, if the PI or co-PI is unavailable, or the investigator staff and veterinary staff cannot reach consensus on treatment of a study animal, the veterinarian has the authority to treat the animal, remove it from the experiment, institute appropriate measures to relieve severe pain or distress, or perform euthanasia if necessary. However, all decisions involving the treatment of a study animal in which a consensus cannot be reached will only be made after the veterinarian or designated backup veterinarian has actually observed and examined the animal in question. To facilitate communication, the animal care staff will maintain an emergency contact roster. In an emergency, the animal care staff will phone the numbers (office, home, and mobile) listed for the PI and co-PI. If the PI or co-PI cannot be reached by phone within 1 hour, then they are considered unavailable.

V.5.3. Environmental Enrichment

V.5.3.1. Enrichment Strategy:

All animals used for the 14-day and 90-day studies will be socially housed. Acute animals may be pair-housed at certain times during that phase of the study. All animals will have an enrichment device (e.g., Nylabones™, rodent retreat) in their cage. All animals on this study will receive the same type of enrichment throughout the study. The enrichment plan will be IAW the version of QSARC 802.00 current at the time of study initiation (APHC, 2017e), unless otherwise noted in this section.

V.5.3.2. Enrichment Restrictions:

The acute study animals may be singly housed after dosing (see section V.5.1.3). Food enrichment may not be used due to monitoring of food consumption. Rodent retreats may be removed for observation of animals, but will be replaced immediately following observation periods of no more than eight hours. Rodent retreats and Nylabones™ will not be placed in the metabolism cages when the rats are housed in them for urine collection. Rodent retreats may be removed from cages for paired animals on the 90-day study under consult from the PI and AV (for instances where the larger animals' environments are being closely monitored).

VI. STUDY PERSONNEL QUALIFICATIONS AND TRAINING:

Personnel on Protocol	Activities to be performed on this protocol	Formal Training	Qualifications & Experience
Lee Crouse	Handling & observations	Rodent handling techniques (11/21/96); Rat handling (7/19/07)	M.S., Environmental Sciences 21+ Yrs animal research experience
	Oral Gavage	Rat gavage (07/19/07); Rat oral gavage (05/05/08); rat oral gavage (03/03/08); rat oral gavage, 14 day (05/01/09)	
	CO_2 anesthesia/euthanasia	Rat euthanasia via CO2 (7/19/07; 5/01/09; 10/2014; 11/2014)	
	Cardiac blood collection	Rat bleeding techniques: cardiac under isoflurane (12/17/08); rat blood collection (7/19/07); Terminal cardiac blood draw (5/1/09); Rat bleeding under CO2 anesthesia (10/2014) (11/7/2014) Cardiac blood collection using CO2 anesthesia (5/10/2013)	
Matthew Bazar	Handling & observations	The Care & Use of Laboratory Animals (04/08/02); Short Course on The Care & Use of Laboratory Animals (04/07/03); Rodent and Small Animal Handling Workshop (12/07/04); Rodent Handling Workshop (02/17/04); Rodent Surgical Techniques (hands-on workshop) (02/17/05); Short Course on Small Animal Handling Workshop- Hands on and lecture (proper restraint; IM, IP, SQ injections; euth. techniques. For mouse, rat, g.pig; identification; PPE; safety measures) (08/28/09)	M.S., Biology 20+ Yrs Animal Research Experience

Personnel on Protocol	Activities to be performed on this protocol	Formal Training	Qualifications & Experience
Theresa Hanna	Handling & observations	Animal handling: rat (3/12/92); rat techniques: handling/observations (11/3/08); Rodent small animal handling workshop (2/25/98; 4/2/04; 11/22/05)	ALAT 25+ Yrs animal research experience
	Neurotoxicity screen and FOB	OJT 2009-present	
Mark Way	Handling & observations	Rodent and small animal handling workshop (5/17/07); Rat handling (7/19/07; 7/9/09); Rat handling and saphenous bleeding techniques (12/2016)	B.S. Biology, AALAS-LAT 19+Yrs Animal Research Experience
	Gavage	Rat handling and dosing (7/18/07): Rat oral gavage (3/6/08; 5/5/08; 7/14/14)	
Allison Jackovitz	Handling & observations	Small animal handling workshop (6/4/09); Rat handling (6/12/12); Rat handling and gavage training (09/2013); Rat handling and saphenous bleeding techniques (12/2016, 01/2017)	B.S. Biology, 8+ Yrs Animal Research Experience
	Gavage	Rat oral gavage (6/12/12); Rat oral gavage (7/9-18/2014)	
Emily Lent	Handling & observations	Rat handling (7/19/07); Rat handling and saphenous bleeding techniques (12/2016, 01/2017)	Ph.D., Natural Resources & Environmental Studies; M.S. Wildlife Biology, 18+ Yrs Animal Research Experience
	Gavage	Rat handling and dosing (7/19/07); Rat gavage (3/6/08; 5/1/09)	
Thomas Sussan	Handling & observations	Small animal handling workshop (9/28/17, 6/7/2018); Rat handling 4/26-27/18, 5/1/18)	Ph.D., Biochemistry, Cell, Molecular Biology 17+ Yrs animal research experience
	Gavage	Rat gavage (5/2, 7-9, 14-16, 21-23, 29/18)	
Lindsay Holden	Handling & observations	Rat handling, inhalation anesthesia, euthanasia, blood draw, oral gavage	Ph.D., Biology

Personnel on Protocol	Activities to be performed on this protocol	Formal Training	Qualifications & Experience
		(7/26/16); Rat handling including observation of anesthesia, cardiac stick, CO2 euthanasia (9/26/18)	7+ Yrs animal research experience

VII. BIOHAZARD/SAFETY:

Risks associated with this protocol include bites/scratches/needle sticks, transmission of zoonotic diseases, and the development of animal allergies. To minimize risk, appropriate handling techniques will be used and appropriate PPE will be worn for all animal handling work. This includes (but may not be limited to) facemask, gloves, and disposable lab coat. Personnel will wash their hands upon completion of animal work. Applicable current SOPs and APHC regulations will be followed. These documents specify hazardous waste disposal, bite/scratch procedures, and zoonotic disease prevention. A sharps container will be present at all times when using sharps, and needles will not be recapped after entering animal tissue.

VIII. ENCLOSURES:

A. References

IX. ASSURANCES:

IX.1. As the Principal Investigator on this protocol, I acknowledge my responsibilities and provide assurances for the following:

A. Animal Use: The animals authorized for use in this protocol will be used only in the activities and in the manner described herein, unless a modification is specifically approved by the IACUC prior to its implementation.

B. Duplication of Effort: I have made every effort to ensure that this protocol is not an unnecessary duplication of previous experiments.

C. Statistical Assurance: I assure that I have consulted with a qualified individual who evaluated the experimental design with respect to the statistical analysis, and that the minimum number of animals needed for scientific validity will be used.

D. Biohazard/Safety: I have taken into consideration and made the proper coordination regarding all applicable rules and regulations concerning radiation protection, biosafety, recombinant issues, and so forth, in the preparation of this protocol.

E. Training: I verify that the personnel performing the animal procedures / manipulations / observations described in this protocol are technically competent and have been properly trained to ensure that no unnecessary pain or distress will be caused to the animals as a result of the procedures / manipulations.

F. Responsibility: I acknowledge the inherent moral, ethical and administrative obligations associated with the performance of this animal use protocol, and I assure that all individuals associated with this project will demonstrate a concern for the health, comfort, welfare, and well-being of the research animals. Additionally, I pledge to conduct this study in the spirit of the fourth "R", namely, "Responsibility," which the DOD has embraced for implementing animal use alternatives where feasible and conducting humane and lawful research.

G. Scientific Review: This proposed animal use protocol has received appropriate peer scientific review and is consistent with good scientific research practice.

H. Painful Procedures:

I am conducting biomedical experiments, which may potentially cause more than momentary or slight pain or distress to animals. This potential pain and/or distress WILL / WILL NOT (circle one or both, if applicable) be relieved with the use of anesthetics, analgesics and/or tranquilizers. I have considered alternatives to such procedures; however, I have determined that alternative procedures are not available to accomplish the objectives of this proposed experiment.

I. Unexpected Adverse Events: I acknowledge the responsibility for reporting unexpected adverse events IAW the most current version of IACUC Local Guidance Document 008 "Reportable Events".

LEE CROUSE		6 December 2018
(PRINT)	(Signature)	(Date)

IX.2. As the Primary Co-Investigator on this protocol, I provide the following assurances:

A. Animal Use: The animals authorized for use in this protocol will be used only in the activities and in the manner described herein, unless a modification is specifically approved by the IACUC prior to its implementation.

B. Authority: I understand that, as the Primary Co-Investigator, I am authorized and responsible for performing all procedures and manipulations as assigned to the SD/PI in the SD/PI's absence. This includes euthanasia of distressed animals.

C. Training: I verify that I am technically competent and have been properly trained to ensure that no unnecessary pain or distress will be caused to the animals as a result of the procedures/manipulations.

D. Responsibility: I acknowledge the inherent moral and administrative obligations associated with the performance of this animal use protocol, and I assure that I will demonstrate a concern for the health, comfort, welfare, and well-being of the research animals. Additionally, I pledge to conduct this study in the spirit of the fourth "R", namely "Responsibility," which the DOD has embraced for implementing animal use alternatives where feasible, and conducting humane and lawful research.

E. Painful Procedures: I am conducting biomedical experiments, which may potentially cause more than momentary or slight pain or distress to animals. This potential pain and/or distress WILL or WILL NOT (circle one or both, if applicable) be relieved with the use of anesthetics, analgesics and/or tranquilizers. I have considered alternatives to such procedures; however, I have determined that alternative procedures are not available to accomplish the objectives of this proposed experiment.

F. Unexpected Adverse Events: I acknowledge the responsibility for reporting unexpected adverse events IAW the most current version of IACUC Local Guidance Document 008 "Reportable Events".

EMILY LENT	Emily May Lent	12/10/18
(PRINT)	(Signature)	(Date)

IX.2. As a Co-Investigator on this protocol, I provide the following assurances:

A. Animal Use: The animals authorized for use in this protocol will be used only in the activities and in the manner described herein, unless a modification is specifically approved by the IACUC prior to its implementation.

B. Authority: I understand that, as a Co-Investigator, I am authorized, responsible for, and willing to perform all procedures and manipulations as assigned to me by the SD/PI.

C. Training: I verify that I am technically competent and have been or will be properly trained to ensure that no unnecessary pain or distress will be caused to the animals as a result of the assigned procedures/manipulations performed by me.

D. Responsibility: I acknowledge the inherent moral and administrative obligations associated with the performance of this animal use protocol, and I assure that I will demonstrate a concern for the health, comfort, welfare, and well-being of the research animals. Additionally, I pledge to participate in this study in the spirit of the fourth "R", namely "Responsibility," which the DOD has embraced for implementing animal use alternatives where feasible, and conducting humane and lawful research.

E. Painful Procedures: I am participating in biomedical experiments, which may potentially cause more than momentary or slight pain or distress to animals. I will follow the direction of the SD/PI relative to potential pain and/or distress and relief by use of anesthetics, analgesics, and/or tranquilizers.

F. Unexpected Adverse Events: I acknowledge the responsibility for reporting unexpected adverse events IAW the most current version of IACUC Local Guidance Document 008 "Reportable Events".

Mark R Way	Mark Way	12/6/18
(PRINT) Mark R. Way	(SIGNATURE)	(DATE)
Theresa L Hanna	Theresa Hanna	12/6/18
(PRINT) Theresa L. Hanna	(SIGNATURE)	(DATE)

APPENDIX A

References

Agency for Toxic Substances and Disease Registry (ATSDR) 2012. Toxicological Profile for RDX. Atlanta, GA: Agency for Toxic Substances and Disease Registry. PB2012-105630.

APHC 2016a. TOX SOP 062.002, Neurotoxicity Screen and Functional Observation Battery. Aberdeen Proving Ground, Maryland.

APHC 2016b. TOX SOP 079.000, Prothrombin Time and Activated Partial Thromboplastin Time. Aberdeen Proving Ground, Maryland.

APHC 2017a. QSARC 706, Animal Quality Assurance and Quality Control/Health Monitoring Procedures.

APHC 2017b. QSARC 707, Animal Health Technician Animal Husbandry and Vivarium Duties. Aberdeen Proving Ground, Maryland.

APHC 2017c. QSARC 716, Ophthalmic Examinations. Aberdeen Proving Ground, Maryland.

APHC 2017d. QSARC 800, Animal Euthanasia. Aberdeen Proving Ground, Maryland.

APHC 2017e. QSARC 802, Animal Environmental Enrichment. Aberdeen Proving Ground, Maryland.

APHC 2017f. QSARC 804, Individual Animal Identification. Aberdeen Proving Ground, Maryland.

APHC 2017g. QSARC 805, Animal Bleeding Technique. Aberdeen Proving Ground, Maryland.

APHC 2017h. QSARC 806, Test System Observations. Aberdeen Proving Ground, Maryland.

APHC 2018a. TOX SOP 003.003, Urinalysis. Aberdeen Proving Ground, Maryland.

APHC 2018b. TOX SOP 11.003, Clinical Chemistry Analysis of Blood Specimens. Aberdeen Proving Ground, Maryland.

APHC 2018c. TOX SOP 13.003, Cell-Dyn Hematology Analyzer. Aberdeen Proving Ground, Maryland.

ASTM 2008. Standard Guide for Assessing the Environmental and Human Health Impacts of New Energetic Compounds. Conshohocken, PA.

ASTM 2010. Standard Test Method for Estimating Acute Oral Toxicity in Rats. Conshohocken, PA.

AVMA 2013. AVMA Guidelines for the Euthanasia of Animals: 2013 Edition. Schaumburg, IL.

CFR 1989. Title 40, Code of Federal Regulations (CFR), Part 792, Toxic Substances Control Act (TSCA), Good Laboratory Practice Standards.

EPA 1998a. Health Effects Test Guidelines. OPPTS 870.1100, Acute Oral Toxicity Study in Rodents. EPA 712-C-98-199.

Eurenco 2002. Safety Data Sheet (SDS), 1,1-diamino-2,2-dinitroethene, Eurenco Groupe SNPE, Explosive Charges & Additives Business Unit, 12 quai Henri IV – 75004 Paris – France

Feder, P. I., Hobson, D. W., Olson, C. T., Joiner, R. L. & Matthews, M. C. 1991a. Stagewise, Adaptive Dose Allocation for Quantal Response Dose- Response Studies. *Neuroscience & Biobehavioral Reviews,* 15**,** 109-114.

Feder, P. I., Olson, C. T., Hobson, D. W., Matthews, M. C. & Joiner, R. L. 1991b. Stagewise, Group Sequential Experimental Designs for Quantal Responses. One-Sample and Two-Sample Comparisons. *Neuroscience & Biobehavioral Reviews,* 15**,** 129-133.

Liu, Z., Zhang, P., Wang, H., Gao, J., Lu, Q., Yue, H., and Xia, J. Study of teratogenicity of 2,2-dinitroethene-1,1-diamine in Sprague Dawley rats. In: Chinese Journal of Industrial Hygiene and Occupational Diseases; Xi'an, China; 2016.

Lochert 2001. FOX-7 – A New Insensitive Explosive. DSTO Aeronautical and Maritime Research Laboratory, 506 Lorimer St., Fishermans Bend, Victoria 3207, Australia, DSTO-TR-1238.

National Research Council 2011. Guide for the Care and Use of Laboratory Animals. National Academies Press, Washington, DC.

OECD 2018. Guidelines for the Testing of Chemicals. OECD 408, Repeated Dose 90-Day Oral Toxicity Study in Rodents, OECD Publishing, Paris, France.

U.S. Army Public Health Center (USAPHC). 2016. Toxicology Assessment for ETAP Work Unit CA 10-04: 1,1-diamino-2,2-dinitroethene [FOX-7; DADNE]. Toxicology Report No. S.0043494a-16, Prepared by M.A. Williams and W.S. Eck, APHC, Aberdeen Proving Ground, MD 21010-5403.

ARMY PUBLIC HEALTH CENTER
PROTOCOL REVIEW AND APPROVAL FORM

Test Type: **38** IACUC protocol number: **18-12-01**

TITLE: The Subchronic Oral Toxicity of 1,1-Diamino-2,2-Dinitroethene (FOX-7) in Rats (*Rattus norvegicus)*

1. PRINCIPAL INVESTIGATOR/ STUDY DIRECTOR

Printed Name (First, MI, Last): Lee C Crouse

Title/ Division/ Program/ Directorate: Biologist/Toxicity Evaluation Division/Toxicology Directorate

PHONE: 410-436-5088 EMAIL: lee.crouse.civ@mail.mil

2018-12-06 (*Date*)

CROUSE.LEE.1239523265 Digitally signed by CROUSE.LEE.1239523265 Date: 2018.12.06 14:31:46 -05'00' (*Signature*) *(SD/PI will sign here before submitting protocol to the IACUC office)*

2. SCIENTIFIC/ PEER REVIEW

Printed Name (First, MI, Last)

Title/ Division/ Program/ Directorate

PHONE: EMAIL:

Date *Signature*

3. STATISTICAL REVIEW

Printed Name (First, MI, Last)

Title/ Division/ Program/ Directorate

PHONE: EMAIL:

Date *Signature*

4. ATTENDING VETERINARIAN REVIEW

Printed Name (First, MI, Last): Alicia M Gehling

Title/ Division/ Program/ Directorate: Attending Veterinarian, QSARC

PHONE: 4104368863 EMAIL: alicia.m.gehling.mil@mail.mil

2018-12-06 (*Date*)

GEHLING.ALICIA.MARIE.1364571689 Digitally signed by GEHLING.ALICIA.MARIE.1364571689 Date: 2018.12.06 14:42:19 -05'00' (*Signature*)

5. IACUC APPROVAL

Date: 2018-12-06

Printed Name (First, MI, Last): Kristin T. Newkirk

Signature: NEWKIRK.KRISTIN.TORELL.1014786895 Digitally signed by NEWKIRK.KRISTIN.TORELL.1014786895 Date: 2018.12.07 07:52:39 -05'00'

6. INSTITUTIONAL OFFICIAL REVIEW

Printed Name (First, MI, Last): John J. Resta

Signature: RESTA.JOHN.J.1229129305 Digitally signed by RESTA.JOHN.J.1229129305 Date: 2018.12.07 14:51:23 -05'00'

ARMY PUBLIC HEALTH CENTER
PROTOCOL REVIEW AND APPROVAL FORM

Test Type: **38** IACUC protocol number: **18-12-01**

TITLE: The Subchronic Oral Toxicity of 1,1-Diamino-2,2-Dinitroethene (FOX-7) in Rats (*Rattus norvegicus)*

1. PRINCIPAL INVESTIGATOR/ STUDY DIRECTOR

Printed Name (First, MI, Last): James W. Cox
Title/ Division/ Program/ Directorate: Biologist/TEV/TOX

PHONE: 436-7762 EMAIL: james.w.cox160.civ@mail.mil

2018-04-26 (*Date*)
COX.JAMES.W.II.1472168696 (*Signature*) Digitally signed by COX.JAMES.W.II.1472168696 Date: 2018.04.26 14:31:01 -04'00'
(SD/PI will sign here before submitting protocol to the IACUC office)

2. SCIENTIFIC/ PEER REVIEW

Printed Name (First, MI, Last): Michael J. Quiinn
Title/ Division/ Program/ Directorate: Supervisory Biologist/HEF/TOX

PHONE: 436-1064 EMAIL: michael.j.quinn104.civ@mail.mil

2018-05-14 (*Date*)
QUINN.MICHAEL.J.JR.1282372092 (*Signature*) Digitally signed by QUINN.MICHAEL.J.JR.1282372092 Date: 2018.05.14 11:24:51 -04'00'

3. STATISTICAL REVIEW

Printed Name (First, MI, Last): Robyn Lee-Stubbs
Title/ Division/ Program/ Directorate: Statistician/ USAMRICD

PHONE: 410-436-5322 EMAIL: robyn.b.lee2.civ@mail.mil

2018-04-27 (*Date*)
LEE.ROBYN.BELLEK.1267390289 (*Signature*) Digitally signed by LEE.ROBYN.BELLEK.1267390289 Date: 2018.04.27 14:43:51 -04'00'

4. ATTENDING VETERINARIAN REVIEW

Printed Name (First, MI, Last): Michael, Robert, Bonhage
Title/ Division/ Program/ Directorate: AV/VMO/QSARC

PHONE: 410-436-8863 EMAIL: michael.r.bonhage.mil@mail.mil

2018-04-26 (*Date*)
BONHAGE.MICHAEL.ROBERT.1014029881 (*Signature*) Digitally signed by BONHAGE.MICHAEL.ROBERT.1014029881 Date: 2018.04.26 14:38:02 -04'00'

5. IACUC APPROVAL

Printed Name (First, MI, Last) *Date:*
Signature

6. INSTITUTIONAL OFFICIAL REVIEW

Printed Name (First, MI, Last) *Signature*

APHC IACUC Protocol Modification Review/Approval

Study Director/ Principal Investigator: Lee Crouse

Phone No.: 410-436-5088 *FAX No.:* 410-436-6710

Email: lee.crouse.civ@mail.mil

PROTOCOL #: **38-18-12-01** *Protocol Approval Date:* 6 December 2018

PROTOCOL TITLE: **The Subchronic Oral Toxicity of 1,1-diamino-2,2-dinitroethene (FOX-7) in Rats (Rattus norvegicus)**

Modification Request #: **1** *Submission Date:* Oct 16, 2020

Study Director/ Principal Investigator Signature: CROUSE.LEE.1239523265 Digitally signed by CROUSE.LEE.1239523265 Date: 2020.10.16 13:13:40 -04'00'

For review use only: Review Process: ADMIN ☐ FCR ☐ DMR ☒

Received Date: 16 October 2020 AURO receipt: SEYFERT.ALLISON.MARIE.1473772210 Digitally signed by SEYFERT.ALLISON.MARIE.1473772210 Date: 2020.10.16 14:20:46 -04'00'

IACUC Designated Member Reviewer(s) (*Sign when review is completed. AV and IC doing DM review for minor modifications IAW IACUC LGD will just sign in lower section on their respective signature lines.*):

GEHLING.ALICIA.MARIE.1364571689 Digitally signed by GEHLING.ALICIA.MARIE.1364571689 Date: 2020.10.23 06:49:54 -04'00'

Attending/ Alternate Veterinarian Review Signature:

23-Oct-2020
Date

GEHLING.ALICIA.MARIE.1364571689 Digitally signed by GEHLING.ALICIA.MARIE.1364571689 Date: 2020.10.23 06:50:14 -04'00'

Safety Review Signature (*if applicable*):

Date

LTACO/GLP Review Signature (*if applicable*):

Date

IACUC Chair Review Signature:

23-Oct-2020
Date

NEWKIRK.KRISTIN.TORELL.1014786895 Digitally signed by NEWKIRK.KRISTIN.TORELL.1014786895 Date: 2020.10.23 12:31:00 -04'00'

Modification IACUC APPROVED ☒ GLP REVIEWED ☐ Date: 23-Oct-2020

APHC IACUC Animal Use Protocol Modification

Study Director/ Principal Investigator: **Lee Crouse**

PROTOCOL #: **38-18-12-01** Protocol Approval Date: 6 Dec 2018

PROTOCOL TITLE: **The Subchronic Oral Toxicity of 1,1-diamino-2,2-dinitroethene (FOX-7) in Rats (Rattus norvegicus)**

Phone No.: 410-436-5088 FAX No.: 410-436-6710

Email: lee.crouse.civ@mail.mil

Modification Request #: 1 Submission Date: 16 October 2020

1. Brief non-technical synopsis of existing protocol or background information pertaining to the modification request.

There are 3 requests associated with this modification. I am requesting the addition of Blas Guigni and Meredith Bohannon to the study staff table with duties of general rat handling only. I am also requesting the addition of 12 male rats to the 14-day phase of the study so that the micronucleus genotoxicity assay can be added to the overall FOX-7 toxicity evaluation. The micronucleus genotoxicity assay requires the collection of a small amount of blood via saphenous blood collection which is the third request.

2. Type(s) of Modification Requested: (check all that apply)

	Type Of Change (See LGD 010 for more details)	X
ADMINISTRATIVE – AURO/GLP REVIEW	Administrative Modifications	
	GLP Modifications	
	Addition or deletion of a qualified technician, co-investigator, or study staff	**X**
MINOR Modifications *(examples)*	Change in animal usage [*e.g., vendor, sex, age, weight, strain, small increase in # of animals used (less than 10% of overall number of approved animals)*]	**X**
	Need to repeat an experiment without the addition of animals	
	Addition/change of sample collection times	
	Addition/change of sample collection volumes	
	Additional noninvasive sampling	
	Changes in acclimation or recovery period	
	Special housing request or change in husbandry procedures that do not deviate from the *Guide*	
	Changes in dosing procedures (e.g., dose, volume, or timing)	
	Other: Addition of saphenous blood collection	**X**
MAJOR Modification	Change in SD/PI	
	Change in objectives of the study	
	Addition of a test article to be evaluated	

	Change that results in greater pain, distress, or degree of invasiveness (changes to pain categories D or E from C require a literature search for alternatives to be completed)	
	Addition of animals to pain Category E (literature search for alternatives required)	
	Addition of or change in Species	
	Addition of more than 10% of the total # of animals originally approved	
	Addition of blood sampling	
	Change in frequency of observations for morbidity	
	Change in study endpoint	
	Change in euthanasia method	
	Changes in feeding, housing, care, or use of animals that is not standard for the species or IAW *The Guide*	
	Changes from nonsurvival to survival surgery	
	Change that impacts personnel safety	
	Other change that relates to the specific experimental design and aims of the original protocol	
	Other: _____	

3. PREVIOUSLY APPROVED MODIFICATIONS: (*Hit 'Enter' after description of each modification to list all individually.*)

Mod #	Short Description of the Amendment(s) (Include pain category breakdown of animal usage if changes were made from the original protocol)	No. & Species of Animal Requested	Approval Date

4. CURRENT APPROVED ANIMAL USAGE ON PROTOCOL:

Species/Total: Rat/264 **B:** 0 **C:** 38 **D:** 120 **E:** 106

5. FOR ITEMS A-H BELOW: Describe the requested changes to be implemented and the justification(s) for each. ***Please include section numbers of protocol for reference.***

A. Administrative change: Editorial (typographical, grammar, contact info update, etc.), GLP compliance changes, or change in personnel (not change of study director/principal investigator):

Requesting the addition of Blas Guigni and Meredith Bohannon to the study staff table for general rat handling only. Blas and Meredith were not employees in the Toxicology Directorate at the time of protocol completion.

B. Specific changes or additions to the experimental design of the protocol (Section V.1. Experimental Design; EIRB Section 9.1 Experimental Design and General Procedures).

For the 14-day phase of the study only, a micronucleus genotoxicity assay will be added to the overall toxicity assessment. The micronucleus genotoxicity assay is only performed on male rats and will require the addition of 12 male rats. Therefore, the total number of animals required for the 14-day study will become 108 (60 male and 48 female). Seven dose groups (N=84) will receive graduated doses of FOX-7 as originally planned, one dose group (N=12) will serve as the original diluent control group receiving corn oil only, one male dose group (N=6) will serve as a untreated control group for the genotoxicity assay, and one male dose group (N=6) will serve as the positive control group for the genotoxicity assay receiving two 200 mg/kg doses of the known genotoxic agent ethyl methanesulfonate (pharmaceutical grade; CAS # 62-50-0) via oral gavage on the two days prior to necropsy.

Performance of the micronucleus assay requires the collection of a small amount of blood (no more than 200 microliters) from the lateral saphenous vein of male rats from the highest 3 FOX-7 dose groups with sufficient survivability as well as the male vehicle (corn oil) controls. Blood collection, using the same method, will also be performed from each rat in the micronucleus negative and positive control groups. Saphenous blood collection will be performed on designated male rats just prior to CO2 anesthesia for the terminal blood sample. The rats will be immobilized with the hindleg extended, the skin surface cleaned and coated with a sterile petroleum-based lubricant (e.g. Puralube® Vet Ointment) to locate the saphenous vein, and the vein punctured with a sterile 20-23 gauge needle. Blood will be collected using a pipette, which has been pre-wetted with anti-coagulant, to capture drops that form at the puncture site and placed into a tube containing anti-coagulant. Hemostasis will be confirmed by compression with a clean paper towel prior to anesthesia for terminal blood sampling. The animals will still be anesthetized with CO2 prior to terminal blood sampling as originally stated in the protocol. Euthanasia following terminal blood sampling will still be done using CO2.

The micronucleus assay allows genotoxicity data to be acquired with the addition of a minimal number of animals and without a significant change in procedures. Collection of blood from the saphenous vein is a fast and reliable method for blood collection and does not require anesthesia. This will enable rapid and humane collection of blood without the repeated use of CO2 to anesthetize the animals.

C. Change in sample size evaluation, data analysis plan, archiving of data, (Section V.2.; EIRB Section 9.3).

For the micronucleus assay, a one-way analysis of variance (ANOVA) will be used to test for significant differences in %MN-RET for male rats only. The Tukey multiple comparison test will be used to evaluate the differences between dose groups. Results will be considered statistically significant at $p < 0.05$. All other data analyses outlined in the protocol will remain unchanged.

D. Change in the animals used, (Section V.3.; EIRB Sections 5.0, 9.4-9.6, 10.0).
(Include any changes in amount used, sex, age/weight, vendor/source, refinement, reduction, and replacement [3Rs]).

The micronucleus assay requires the addition of 12 male rats to the 14-day phase of this study. They will be ordered from the same vendor when the remaining 14-day rats are ordered and will be of the same age and weight. Although the micronucleus assay requires the addition of 12 male rats, the increase in animal numbers is minimal and is significantly less than those required if the assay were to be performed separately from the 14-day study.

E. Changes to technical methods (Section V.4.; EIRB Sections 11.0-17.0). *(Include changes in USDA pain category classifications [section V.4.1.1.1.1 thru V.4.1.1.1.4.], changes in anesthesia, analgesia, restraint, injections, identification, behavior studies, 'other procedures', study endpoint, euthanasia, etc. Include reference source for basis of dose/treatment change.).*
**** * * * If the modification requested will be adding animals to <u>COLUMN D or E</u> and <u>the protocol did not previously have animals in those categories</u>, a <u>LITERATURE SEARCH</u> FOR ALTERNATIVES TO PAINFUL OR DISTRESSFUL PROCEDURES <u>must be completed and submitted</u> with this modification request.***

Other than the saphenous vein bleed from the male animals in the highest 3 surviving dose groups and vehicle control group, as well as the male negative and positive micronucleus controls, no additional change in procedures is requested with this modification. Saphenous vein sticks are not considered a painful procedure so the micronucleus controls (N=12) will be placed in Column C since they do not receive a terminal blood collection. The numbers for all other pain categories described in the protocol will not change as a result of this modification.

F. Changes to the Husbandry and Veterinary Care procedures (Section V.5.; EIRB Sections 18.0, 19.0). *(Changes in husbandry considerations, special provisions, exceptions to the Guide, AWAR, or IACUC Policy that have an impact on animal care and use; any changes to the veterinary medical care or environmental enrichment.)*

None. The additional rats requested for the micronucleus assay will receive the same environmental enrichment as the remaining rats on the 14-day study.

G. Changes to the personnel conducting this protocol (Section VI.; EIRB Section 3.0). *(Include record of completed training for any animal handling or use procedures assigned to new personnel. Signed assurance page(s) must be included with the modification if changing SD/PI, Primary Co-investigator, or adding a co-investigator.)*

Requesting the addition of the following study personnel for general rat handling only:
Meredith Bohannon: PhD Biology; 10+ years animal research experience; general rat handling training at MRICD on 9/5/19
Blas Guigni: PhD Molecular Physiology; 6+ years animal research experience; general rat handling training at MRICD on 9/5/19

H. Changes in Biohazard/ Safety (Section VII.; EIRB Section 21.0).

None

APHC IACUC Protocol Modification Review/Approval

Study Director/ Principal Investigator: Lee Crouse

Phone No.: 410-436-5088 *FAX No.:* 410-

Email: lee.crouse.civ@mail.mil

PROTOCOL #: **38-18-12-01** *Protocol Approval Date:* 6 December 2018

PROTOCOL TITLE: **The Subchronic Oral Toxicity of 1,1-diamino-2,2-dinitroethene (FOX-7) in Rats (Rattus norvegicus)**

Modification Request #: **2** *Submission Date:* Feb 10, 2021

Study Director/ Principal Investigator Signature: CROUSE.LEE.1239523265 Digitally signed by CROUSE.LEE.1239523265 Date: 2021.02.10 13:36:49 -05'00'

For review use only: Review Process: ADMIN ☐ FCR ☐ DMR ☒

Received Date: 10-Feb-2021 AURO receipt: SEYFERT.ALLISON.MARIE.1473772210 Digitally signed by SEYFERT.ALLISON.MARIE.1473772210 Date: 2021.02.10 14:11:45 -05'00'

IACUC Designated Member Reviewer(s) (*Sign when review is completed. AV and IC doing DM review for minor modifications IAW IACUC LGD will just sign in lower section on their respective signature lines.*):

GEHLING.ALICIA.MARIE.1364571689 Digitally signed by GEHLING.ALICIA.MARIE.1364571689 Date: 2021.02.11 09:34:10 -05'00'

Attending/ Alternate Veterinarian Review Signature:

11-Feb-2021 GEHLING.ALICIA.MARIE.1364571689 Digitally signed by GEHLING.ALICIA.MARIE.1364571689 Date: 2021.02.11 09:31:55 -05'00'

Date

Safety Review Signature (*if applicable*):

Date

LTACO/GLP Review Signature (*if applicable*):

Date

IACUC Chair Review Signature:

11-Feb-2021 NEWKIRK.KRISTIN.TORELL.1014786895 Digitally signed by NEWKIRK.KRISTIN.TORELL.1014786895 Date: 2021.02.11 15:19:30 -05'00'

Date

Modification IACUC APPROVED ☒ GLP REVIEWED ☐ Date: 11-Feb-2021

APHC IACUC Animal Use Protocol Modification

Study Director/ Principal Investigator: **Lee Crouse**

PROTOCOL #: **38-18-12-01** Protocol Approval Date: 6 Dec 2018

PROTOCOL TITLE: **The Subchronic Oral Toxicity of 1,1-diamino-2,2-dinitroethene (FOX-7) in Rats (Rattus norvegicus)**

Phone No.: 410-436-5088 FAX No.: 410-436-6710

Email: lee.crouse.civ@mail.mil

Modification Request #: 2 Submission Date: 10 February 2021

1. Brief non-technical synopsis of existing protocol or background information pertaining to the modification request.

The protocol originally stated that terminal blood collection would be in accordance with QSARC 805. It was subsequently discovered that this SOP specifically states that a 3-5 milliliter syringe will be used for the cardiac puncture in rats. This modification is requesting the use of a 6-10 milliter syringe for the reasons described in 5.E.

2. Type(s) of Modification Requested: (check all that apply)

	Type Of Change (See LGD 010 for more details)	X
ADMINISTRATIVE – AURO/GLP REVIEW	Administrative Modifications	
	GLP Modifications	
	Addition or deletion of a qualified technician, co-investigator, or study staff	
MINOR Modifications *(examples)*	Change in animal usage [*e.g., vendor, sex, age, weight, strain, small increase in # of animals used (less than 10% of overall number of approved animals)*]	
	Need to repeat an experiment without the addition of animals	
	Addition/change of sample collection times	
	Addition/change of sample collection volumes	**X**
	Additional noninvasive sampling	
	Changes in acclimation or recovery period	
	Special housing request or change in husbandry procedures that do not deviate from the *Guide*	
	Changes in dosing procedures (e.g., dose, volume, or timing)	
	Other: _____	
MAJOR Modification	Change in SD/PI	
	Change in objectives of the study	
	Addition of a test article to be evaluated	

	Change that results in greater pain, distress, or degree of invasiveness (changes to pain categories D or E from C require a literature search for alternatives to be completed)	
	Addition of animals to pain Category E (literature search for alternatives required)	
	Addition of or change in Species	
	Addition of more than 10% of the total # of animals originally approved	
	Addition of blood sampling	
	Change in frequency of observations for morbidity	
	Change in study endpoint	
	Change in euthanasia method	
	Changes in feeding, housing, care, or use of animals that is not standard for the species or IAW *The Guide*	
	Changes from nonsurvival to survival surgery	
	Change that impacts personnel safety	
	Other change that relates to the specific experimental design and aims of the original protocol	
	Other: _____	

3. PREVIOUSLY APPROVED MODIFICATIONS: (*Hit 'Enter' after description of each modification to list all individually.*)

Mod #	Short Description of the Amendment(s) (Include pain category breakdown of animal usage if changes were made from the original protocol)	No. & Species of Animal Requested	Approval Date
1	Addition of Blas Guigni and Meredith Bohannon to the study staff table with duties of general rat handling only. Requested the addition of 12 male rats to the 14-day phase of the study so that the micronucleus genotoxicity assay could be added to the overall FOX-7 toxicity evaluation. The micronucleus genotoxicity assay required the collection of a small amount of blood via saphenous blood collection which was the third request. This changed the total number of rats to 276 with the pain category breakdown shown in section 4.	Rat/12	23 Oct 2020

4. CURRENT APPROVED ANIMAL USAGE ON PROTOCOL:

Species/Total: Rat/276 **B:** 0 **C:** 50 **D:** 120 **E:** 106

5. FOR ITEMS A-H BELOW: Describe the requested changes to be implemented and the justification(s) for each. ***Please include section numbers of protocol for reference.***

A. Administrative change: Editorial (typographical, grammar, contact info update, etc.), GLP compliance changes, or change in personnel (not change of study director/principal investigator):

N/A

B. Specific changes or additions to the experimental design of the protocol (Section V.1. Experimental Design; EIRB Section 9.1 Experimental Design and General Procedures).

N/A

C. Change in sample size evaluation, data analysis plan, archiving of data, (Section V.2.; EIRB Section 9.3).

N/A

D. Change in the animals used, (Section V.3.; EIRB Sections 5.0, 9.4-9.6, 10.0). *(Include any changes in amount used, sex, age/weight, vendor/source, refinement, reduction, and replacement [3Rs]).*

N/A

E. Changes to technical methods (Section V.4.; EIRB Sections 11.0-17.0). *(Include changes in USDA pain category classifications [section V.4.1.1.1.1 thru V.4.1.1.1.4.], changes in anesthesia, analgesia, restraint, injections, identification, behavior studies, 'other procedures', study endpoint, euthanasia, etc. Include reference source for basis of dose/treatment change.).*
**** * * * If the modification requested will be adding animals to COLUMN D or E and the protocol did not previously have animals in those categories, a LITERATURE SEARCH FOR ALTERNATIVES TO PAINFUL OR DISTRESSFUL PROCEDURES must be completed and submitted with this modification request.***

Section V.4.4.3.1. (Blood Collection and Analysis) of the protocol states that terminal blood collection will be via cardiac puncture in accordance with QSARC 805 for the 14- and 90-day studies. QSARC 805 specifically states that a 3-5 milliliter syringe will be used for cardiac puncture in rats. The total blood analysis for these phases of the study require a minimum of three 1.2 milliliter microtubes so a 3 milliliter syringe is not sufficient for the volume required. Five milliliter syringes are not typically stocked by the Pathology Division due to their lack of use in the past and are also difficult to use since they tend to lose suction as the maximum volume is approached. Since the cardiac puncture is a terminal procedure, obtaining a specific volume of blood above the minimum is not required. I am requesting the use of 6-10 milliliter syringes for the 14- and 90-day studies based on the volumes required for analysis, the age/size of the rats undergoing cardiac puncture, and the success associated with using this size syringe in the past.

F. Changes to the Husbandry and Veterinary Care procedures (Section V.5.; EIRB Sections 18.0, 19.0). *(Changes in husbandry considerations, special provisions, exceptions*

to the Guide, AWAR, or IACUC Policy that have an impact on animal care and use; any changes to the veterinary medical care or environmental enrichment.)

N/A

G. Changes to the personnel conducting this protocol (Section VI.; EIRB Section 3.0). *(Include record of completed training for any animal handling or use procedures assigned to new personnel. Signed assurance page(s) must be included with the modification if changing SD/PI, Primary Co-investigator, or adding a co-investigator.)*

N/A

H. Changes in Biohazard/ Safety (Section VII.; EIRB Section 21.0).

N/A

APHC IACUC Protocol Modification Review/Approval

Study Director/ Principal Investigator: Lee Crouse

Phone No.: 410-436-5088 *FAX No.:* 410-436-6710

Email: lee.crouse.civ@mail.mil

PROTOCOL #: **38-18-12-01** *Protocol Approval Date:* 6 December 2018

PROTOCOL TITLE: The Subchronic Oral Toxicity of 1,1-diamino-2,2-dinitroethene (FOX-7) in Rats (Rattus norvegicus)

Modification Request #: **3** *Submission Date:* May 25, 2021

Study Director/ Principal Investigator Signature: CROUSE.LEE.1239523265 Digitally signed by CROUSE.LEE.1239523265 Date: 2021.05.25 11:16:51 -04'00'

For review use only: Review Process: ADMIN ☐ FCR ☐ DMR ☒

Received Date: 27 May 2021 AURO receipt: SEYFERT.ALLISON.MARIE.1473772210 Digitally signed by SEYFERT.ALLISON.MARIE.1473772210 Date: 2021.05.27 15:19:41 -04'00'

IACUC Designated Member Reviewer(s) (*Sign when review is completed. AV and IC doing DM review for minor modifications IAW IACUC LGD will just sign in lower section on their respective signature lines.*):

Attending/ Alternate Veterinarian Review Signature:

GEHLING.ALICIA.MARIE.1364571689 Digitally signed by GEHLING.ALICIA.MARIE.1364571689 Date: 2021.06.23 15:03:01 -04'00'

Date

Safety Review Signature (*if applicable*):

Date

LTACO/GLP Review Signature (*if applicable*):

Date

IACUC Chair Review Signature:

28-Jun-2021 NEWKIRK.KRISTIN.TORELL.1014786895 Digitally signed by NEWKIRK.KRISTIN.TORELL.1014786895 Date: 2021.06.28 16:01:10 -04'00'

Date

Modification IACUC APPROVED ☒ GLP REVIEWED ☐ Date: 28-Jun-2021

APHC IACUC Animal Use Protocol Modification

Study Director/ Principal Investigator: **Lee Crouse**

PROTOCOL #: **38-18-12-01** Protocol Approval Date: 6 Dec 2018

PROTOCOL TITLE: **The Subchronic Oral Toxicity of 1,1-diamino-2,2-dinitroethene (FOX-7) in Rats (Rattus norvegicus)**

Phone No.: 410-436-5088 FAX No.: 410-436-6710

Email: lee.crouse.civ@mail.mil

Modification Request #: 3_ Submission Date: 25 May 2021

1. Brief non-technical synopsis of existing protocol or background information pertaining to the modification request.

This modification has multiple parts associated with it, but none of the changes are considered major modifications. Briefly, this modification is requesting a change in the primary co-investigator, a change in one of the co-investigators, addition of training/proficiency of oral gavage, the addition of hormone analysis following terminal blood collection, the addition of sperm analysis as part of the necropsy, the addition of a single vaginal swab sample immediately following euthanasia at necropsy for the female rats, and a decrease in the total number of rats required due to recent changes in the health monitoring procedures. Details regarding each of these requests is provided below.

2. Type(s) of Modification Requested: (check all that apply)

	Type Of Change (See LGD 010 for more details)	X
ADMINISTRATIVE – AURO/GLP REVIEW	Administrative Modifications	**X**
	GLP Modifications	
	Addition or deletion of a qualified technician, co-investigator, or study staff	**X**
MINOR Modifications (*examples*)	Change in animal usage [*e.g., vendor, sex, age, weight, strain, small increase in # of animals used (less than 10% of overall number of approved animals)*]	**X**
	Need to repeat an experiment without the addition of animals	
	Addition/change of sample collection times	
	Addition/change of sample collection volumes	**X**
	Additional noninvasive sampling	**X**
	Changes in acclimation or recovery period	
	Special housing request or change in husbandry procedures that do not deviate from the *Guide*	
	Changes in dosing procedures (e.g., dose, volume, or timing)	
	Other: Addition of sperm analysis at necropsy.	**X**
MAJOR	Change in SD/PI	

	Change in objectives of the study	
	Addition of a test article to be evaluated	
	Change that results in greater pain, distress, or degree of invasiveness (changes to pain categories D or E from C require a literature search for alternatives to be completed)	
	Addition of animals to pain Category E (literature search for alternatives required)	
	Addition of or change in Species	
	Addition of more than 10% of the total # of animals originally approved	
	Addition of blood sampling	
	Change in frequency of observations for morbidity	
	Change in study endpoint	
	Change in euthanasia method	
	Changes in feeding, housing, care, or use of animals that is not standard for the species or IAW *The Guide*	
	Changes from nonsurvival to survival surgery	
	Change that impacts personnel safety	
	Other change that relates to the specific experimental design and aims of the original protocol	
	Other: _____	

3. PREVIOUSLY APPROVED MODIFICATIONS: (*Hit 'Enter' after description of each modification to list all individually.*)

Mod #	Short Description of the Amendment(s) (Include pain category breakdown of animal usage if changes were made from the original protocol)	No. & Species of Animal Requested	Approval Date
1	Addition of Blas Guigni and Meredith Bohannon to the study staff table with duties of general rat handling only. Requested the addition of 12 male rats to the 14-day phase of the study so that the micronucleus genotoxicity assay could be added to the overall FOX-7 toxicity evaluation. The micronucleus genotoxicity assay required the collection of a small amount of blood via saphenous blood collection which was the third request. This changed the total number of rats to 276 with the pain category breakdown shown in section 4.	Rat/12	23 Oct 2020
2	Increased the syringe size for terminal blood sampling from 3-5 ml syringe to a 6-10 ml syringe to accommodate the necessary clinical pathology parameters.	No change	11 Feb 2021

4. CURRENT APPROVED ANIMAL USAGE ON PROTOCOL:

Species/Total: Rat/276 **B:** 0 **C:** 50 **D:** 120 **E:** 106

5. FOR ITEMS A-H BELOW: Describe the requested changes to be implemented and the justification(s) for each. ***Please include section numbers of protocol for reference.***

A. Administrative change: Editorial (typographical, grammar, contact info update, etc.), GLP compliance changes, or change in personnel (not change of study director/principal investigator):

Drs. Blas Guigni and Meredith Bohannon will be replacing Dr. Emily Lent as the primary co-investigator(s). This change was requested by TOX management. They are both familiar with the study design and could answer questions in the study director's absence. Taryn Brown will be an addition to the study staff table to replace Theresa Hanna as a co-investigator responsible for the neurotoxicity screening and functional observation battery (FOB). This change is requested because Theresa will be retiring the end of June 2021. Refer to section 5.G. for completed training records regarding these personnel changes.

Section V.1.5. Experiment 3: 90-Day Subchronic Study. This section references SOP QSARC 706, Animal Quality Assurance and Quality Control/Health Monitoring Procedures approved in 2017. Recent changes in the health monitoring procedures, described in 5.B. and 5.D., are outlined in the 2021 version of QSARC 706, Health Monitoring Program.

B. Specific changes or additions to the experimental design of the protocol (Section V.1. Experimental Design; EIRB Section 9.1 Experimental Design and General Procedures).

Section V.1.5. Experiment 3: 90-Day Subchronic Study, Table 1, and Table 3. The protocol originally requested 2 animals of each sex be sent to an approved vendor at the beginning and end of the 90-day study (N=8) for an indicator of the colony's health status. Due to recent changes in the health monitoring procedures detailed in 5.D., no live animals will be required to evaluate the colony's health status and the total number of animals required for the 90-day study will be reduced to 100.

C. Change in sample size evaluation, data analysis plan, archiving of data, (Section V.2.; EIRB Section 9.3).

N/A

D. Change in the animals used, (Section V.3.; EIRB Sections 5.0, 9.4-9.6, 10.0). *(Include any changes in amount used, sex, age/weight, vendor/source, refinement, reduction, and replacement [3Rs]).*

Sections V.3.4. and V.4.1.1.1.2. The total number of animals requested on this protocol will be reduced from 276 to 268. Recent changes to the animal health monitoring program (QSARC VSO SOP 706) eliminates the requirement for animals to be purchased specifically for this

purpose. A combination of non-invasive direct animal sampling and environmental sampling will now be used to replace these 4 male and 4 female column C rats.

E. Changes to technical methods (Section V.4.; EIRB Sections 11.0-17.0). *(Include changes in USDA pain category classifications [section V.4.1.1.1.1 thru V.4.1.1.1.4.], changes in anesthesia, analgesia, restraint, injections, identification, behavior studies, 'other procedures', study endpoint, euthanasia, etc. Include reference source for basis of dose/treatment change.).*
**** * * * If the modification requested will be adding animals to COLUMN D or E and the protocol did not previously have animals in those categories, a LITERATURE SEARCH FOR ALTERNATIVES TO PAINFUL OR DISTRESSFUL PROCEDURES must be completed and submitted with this modification request.***

Section V.4.4.3.1. Blood Collection and Analysis. A relatively recent addition to OECD Health Effects Test Guideline 408 is the recommendation for thyroid hormone analysis at the end of the study. The hormone analysis requires an additional 500 ul of serum or 1 ml of whole blood collected during terminal blood sampling. The additional blood volume will not be problematic given the age of these rats and will not involve any changes in the terminal blood collection procedure. The 1 ml of whole blood will be placed in a separate serum or serum-gel microtube or microvette, held for at least 20 minutes, and centrifuged to separate the serum. The serum can then be frozen at ≤ 20ºC. Serum samples will be analyzed using the EMD Millipore Milliplex® Rat Thyroid Hormone Magnetic Bead Panel. TOX did not have the capability to perform this assay at the time of protocol completion.

Section V.4.4.3.3. Sperm Analysis. Cauda epididymal sperm counts will be determined on all surviving male rats at necropsy using a computer assisted sperm analyzer (TOX IVOS-CASA). After removal, trimming, and weighing, one epididymis will be further trimmed to select the cauda portion and re-weighed. The cauda will be placed in a well of a petri dish containing approximately 10 ml of medium at 34-37ºC and the surface minced using a scalpel to release sperm. A chamber of a rat toxicology slide (Leja® or Hamilton Thorne) will be loaded with the sperm suspension and analyzed by the sperm analyzer.

Section V.4.4.3.4. Vaginal Swabs. A second recent addition to OECD Guideline 408 is that of vaginal smears on all surviving female rats at necropsy for an estrus cycle determination. This will be accomplished by a vaginal swab taken immediately after terminal blood sampling/euthanasia. The procedure will not be performed on live animals for this study although the technique will remain the same. Immediately after confirmation of euthanasia (no respiration and toe pinch), rats will be placed on the counter, ventral surface facing up. The tail will be lifted and a cotton swab, wetted with saline, is inserted approximately 1 cm into the vagina. The swab should be at an angle of about 45º to the rat's body and is continually rotated in the same direction during the swab procedure. The swab is then held horizontally and the tip is gently rolled onto a clean, pre-labeled slide. Swab smears can be held and read by the Pathologist at the time of tissue histopathological evaluation.

F. Changes to the Husbandry and Veterinary Care procedures (Section V.5.; EIRB Sections 18.0, 19.0). *(Changes in husbandry considerations, special provisions, exceptions*

to the Guide, AWAR, or IACUC Policy that have an impact on animal care and use; any changes to the veterinary medical care or environmental enrichment.)

N/A

G. Changes to the personnel conducting this protocol (Section VI.; EIRB Section 3.0). *(Include record of completed training for any animal handling or use procedures assigned to new personnel. Signed assurance page(s) must be included with the modification if changing SD/PI, Primary Co-investigator, or adding a co-investigator.)*

As described in section 5.A. of this modification, Drs. Blas Guigni and Meredith Bohannon will be replacing Dr. Emily Lent as Primary Co-investigators and Taryn Brown will be replacing Terry Hanna as a co-investigator.

Drs. Blas Guigni and Meredith Bohannon were already approved study staff as of modification #1, but for general rat handling only.
This modification adds training/proficiency of oral gavage for Blas.
Formal training on rat oral gavage: 22-26 March 2021

Requesting the addition of the following study personnel and training/proficiencies:
Taryn Brown: AS Business Administration; 3+ years animal research experience
Formal training on rat handling & observations: 27 October 2020 (MRICD Small Animal Handling Course), 18 October 2018
Formal training on neurotoxicity screen and FOB: 5 May 2021 (weeks 1-10 neurotoxicity screen), 12 May 2021 (week 11 FOB), 19 May 2021 (week 1-10 and 11)

H. Changes in Biohazard/ Safety (Section VII.; EIRB Section 21.0).

N/A

APHC IACUC Protocol Modification Review/Approval

Study Director/ Principal Investigator: Lee Crouse

Phone No.: 410-436-5088 *FAX No.:* 410-436-6710

Email: lee.crouse.civ@mail.mil

PROTOCOL #: **38-18-12-01** *Protocol Approval Date:* 6 December 2018

PROTOCOL TITLE: The Subchronic Oral Toxicity of 1,1-diamino-2,2-dinitroethene (FOX-7) in Rats (Rattus norvegicus)

Modification Request #: **4** *Submission Date:* Aug 13, 2021

Study Director/ Principal Investigator Signature: CROUSE.LEE.1239523265 Digitally signed by CROUSE.LEE.1239523265 Date: 2021.08.13 13:02:17 -04'00'

For review use only: Review Process: ADMIN ☒ FCR ☐ DMR ☐

Received Date: 13 Aug 2021 AURO receipt: SEYFERT.ALLISON.MARIE.1473772210 Digitally signed by SEYFERT.ALLISON.MARIE.1473772210 Date: 2021.08.13 13:37:31 -04'00'

IACUC Designated Member Reviewer(s) (*Sign when review is completed. AV and IC doing DM review for minor modifications IAW IACUC LGD will just sign in lower section on their respective signature lines.*):

Attending/ Alternate Veterinarian Review Signature:

Date

Safety Review Signature (*if applicable*):

Date

LTACO/GLP Review Signature (*if applicable*):

Date

IACUC Chair Review Signature:

16-Aug-2021 NEWKIRK.KRISTIN.TORELL.1014786895 Digitally signed by NEWKIRK.KRISTIN.TORELL.1014786895 Date: 2021.08.16 15:45:49 -04'00'

Date

Modification IACUC APPROVED ☒ GLP REVIEWED ☐ Date: 16-Aug-2021

APHC IACUC Animal Use Protocol Modification

Study Director/ Principal Investigator: **Lee Crouse**

PROTOCOL #: **38-18-12-01**

Protocol Approval Date: 6 December 2018

PROTOCOL TITLE: The Subchronic Oral Toxicity of 1,1-diamino-2,2-dinitroethene (FOX-7) in Rats (*Rattus norvegicus*)

Phone No.: 410-436-5088

FAX No.: 410-436-6710

Email: lee.crouse.civ@mail.mil

Modification Request #: 4

Submission Date: 13 August 2021

1. Brief non-technical synopsis of existing protocol or background information pertaining to the modification request.

Previously submitted modifications to this protocol have added Dr. Meredith Bohannon to the study staff and as a co-investigator for general rat handling only. She has recently completed several rounds of gavage training and was signed off to perform oral gavage by the Attending Veterinarian. This modification serves to document that she can begin dosing rats for this protocol.

2. Type(s) of Modification Requested: (check all that apply)

	Type Of Change (See LGD 010 for more details)	X
ADMINISTRATIVE – AURO/GLP REVIEW	Administrative Modifications	
	GLP Modifications	
	Addition or deletion of a qualified technician, co-investigator, or study staff	X
MINOR Modifications *(examples)*	Change in animal usage [*e.g., vendor, sex, age, weight, strain, small increase in # of animals used (less than 10% of overall number of approved animals)*]	
	Need to repeat an experiment without the addition of animals	
	Addition/change of sample collection times	
	Addition/change of sample collection volumes	
	Additional noninvasive sampling	
	Changes in acclimation or recovery period	
	Special housing request or change in husbandry procedures that do not deviate from the *Guide*	
	Changes in dosing procedures (e.g., dose, volume, or timing)	
	Other: _____	
MAJOR Modification	Change in SD/PI	
	Change in objectives of the study	
	Addition of a test article to be evaluated	

	Change that results in greater pain, distress, or degree of invasiveness (changes to pain categories D or E from C require a literature search for alternatives to be completed)	
	Addition of animals to pain Category E (literature search for alternatives required)	
	Addition of or change in Species	
	Addition of more than 10% of the total # of animals originally approved	
	Addition of blood sampling	
	Change in frequency of observations for morbidity	
	Change in study endpoint	
	Change in euthanasia method	
	Changes in feeding, housing, care, or use of animals that is not standard for the species or IAW *The Guide*	
	Changes from nonsurvival to survival surgery	
	Change that impacts personnel safety	
	Other change that relates to the specific experimental design and aims of the original protocol	
	Other: _____	

3. PREVIOUSLY APPROVED MODIFICATIONS: (*Hit 'Enter' after description of each modification to list all individually.*)

Mod #	Short Description of the Amendment(s) (Include pain category breakdown of animal usage if changes were made from the original protocol)	No. & Species of Animal Requested	Approval Date
1	Addition of Blas Guigni and Meredith Bohannon to the study staff table with duties of general rat handling only. Requested the addition of 12 male rats to the 14-day phase of the study so that the micronucleus genotoxicity assay could be added to the overall FOX-7 toxicity evaluation. The micronucleus genotoxicity assay required the collection of a small amount of blood via saphenous blood collection which was the third request. This changed the total number of rats to 276 with the pain category breakdown shown in section 4.	Rat/12	23 Oct 2020
2	Increased the syringe size for terminal blood sampling from 3-5 ml syringe to a 6-10 ml syringe to accommodate the necessary clinical pathology parameters.	No change	11 Feb 2021

Mod #	Short Description of the Amendment(s) (Include pain category breakdown of animal usage if changes were made from the original protocol)	No. & Species of Animal Requested	Approval Date
3	Added Drs. Blas Guigni and Meredith Bohannon as primary coinvestigators, removed Dr. Emily Lent as primary co-investigator, replaced Theresa Hanna with Taryn Brown as a co-investigator, added training/proficiency of oral gavage for Dr. Blas Guigni, added hormone analysis following terminal blood collection, added sperm analysis as part of the necropsy, added a single vaginal swab sample immediately following euthanasia at necropsy for the female rats, and decreased the total number of rats required due to recent changes in the health monitoring procedures	Rat/-8	28 June 2021

4. CURRENT APPROVED ANIMAL USAGE ON PROTOCOL:

Species/Total: Rat/268 **B:** 0 **C:** 42 **D:** 120 **E:** 106

5. FOR ITEMS A-H BELOW: Describe the requested changes to be implemented and the justification(s) for each. ***Please include section numbers of protocol for reference.***

A. Administrative change: Editorial (typographical, grammar, contact info update, etc.), GLP compliance changes, or change in personnel (not change of study director/principal investigator):

See section G. for details.

B. Specific changes or additions to the experimental design of the protocol (Section V.1. Experimental Design; EIRB Section 9.1 Experimental Design and General Procedures).

N/A

C. Change in sample size evaluation, data analysis plan, archiving of data, (Section V.2.; EIRB Section 9.3).

N/A

D. Change in the animals used, (Section V.3.; EIRB Sections 5.0, 9.4-9.6, 10.0). *(Include any changes in amount used, sex, age/weight, vendor/source, refinement, reduction, and replacement [3Rs]).*

N/A

E. Changes to technical methods (Section V.4.; EIRB Sections 11.0-17.0). *(Include changes in USDA pain category classifications [section V.4.1.1.1.1 thru V.4.1.1.1.4.], changes in anesthesia, analgesia, restraint, injections, identification, behavior studies, 'other procedures', study endpoint, euthanasia, etc. Include reference source for basis of dose/treatment change.).*
**** * * * If the modification requested will be adding animals to COLUMN D or E and the protocol did not previously have animals in those categories, a LITERATURE SEARCH FOR ALTERNATIVES TO PAINFUL OR DISTRESSFUL PROCEDURES must be completed and submitted with this modification request.***

N/A

F. Changes to the Husbandry and Veterinary Care procedures (Section V.5.; EIRB Sections 18.0, 19.0). *(Changes in husbandry considerations, special provisions, exceptions to the Guide, AWAR, or IACUC Policy that have an impact on animal care and use; any changes to the veterinary medical care or environmental enrichment.)*

N/A

G. Changes to the personnel conducting this protocol (Section VI.; EIRB Section 3.0). *(Include record of completed training for any animal handling or use procedures assigned to new personnel. Signed assurance page(s) must be included with the modification if changing SD/PI, Primary Co-investigator, or adding a co-investigator.)*

This modification adds training/proficiency of oral gavage for Dr. Meredith Bohannon. Formal training on rat oral gavage: 22-26 March 2021, 15 June 2021, 29-30 June 2021, 1-2 July 2021, 6 July 2021, and 4-6 August 2021.

H. Changes in Biohazard/ Safety (Section VII.; EIRB Section 21.0).

N/A

APHC IACUC Protocol Modification Review/Approval

Study Director/ Principal Investigator: Lee Crouse

Phone No.: 410-436-5088 *FAX No.:* 410-436-6710

Email: lee.crouse.civ@mail.mil

PROTOCOL #: **38-18-12-01** *Protocol Approval Date:* 6 December 2018

PROTOCOL TITLE: The Subchronic Oral Toxicity of 1,1-diamino-2,2-dinitroethene (FOX-7) in Rats (Rattus norvegicus)

Modification Request #: **5** *Submission Date:* Sep 8, 2021

Study Director/ Principal Investigator Signature: CROUSE.LEE.1239523265 Digitally signed by CROUSE.LEE.1239523265 Date: 2021.09.10 13:06:29 -04'00'

For review use only: Review Process: ADMIN ☐ FCR ☐ DMR ☒

Received Date: 8 Sep 21 AURO receipt: SEYFERT.ALLISON.MARIE.1473772210 Digitally signed by SEYFERT.ALLISON.MARIE.1473772210 Date: 2021.09.10 13:22:15 -04'00'

IACUC Designated Member Reviewer(s) (*Sign when review is completed. AV and IC doing DM review for minor modifications IAW IACUC LGD will just sign in lower section on their respective signature lines.*):

TAYLOR.BONNIE.JOYCE.1362334213 Digitally signed by TAYLOR.BONNIE.JOYCE.1362334213 Date: 2021.10.01 13:27:26 -04'00'

Attending/ Alternate Veterinarian Review Signature:

12-Oct-2021
Date

GEHLING.ALICIA.MARIE.1364571689 Digitally signed by GEHLING.ALICIA.MARIE.1364571689 Date: 2021.10.12 12:15:17 -04'00'

Safety Review Signature (*if applicable*):

Date

LTACO/GLP Review Signature (*if applicable*):

Date

IACUC Chair Review Signature:

12-Oct-2021
Date

NEWKIRK.KRISTIN.TORELL.1014786895 Digitally signed by NEWKIRK.KRISTIN.TORELL.1014786895 Date: 2021.10.12 12:39:31 -04'00'

Modification IACUC APPROVED ☒ GLP REVIEWED ☐ Date: 12-Oct-2021

APHC IACUC Animal Use Protocol Modification

Study Director/ Principal Investigator: **Lee Crouse**

PROTOCOL #: **38-18-12-01**

Protocol Approval Date: 6 December 2018

PROTOCOL TITLE: The Subchronic Oral Toxicity of 1,1-diamino-2,2-dinitroethene (FOX-7) in Rats（*Rattus norvegicus*）

Phone No.: 410-436-5088

FAX No.: 410-436-6710

Email: lee.crouse.civ@mail.mil

Modification Request #: 5

Submission Date: 8 September 2021

1. Brief non-technical synopsis of existing protocol or background information pertaining to the modification request.

In the process of beginning to evaluate a number of animals for reduced weight gain compared to the average control animal body weight, it was discovered that one sentence in the study endpoint section of the protocol was written incorrectly. This modification will serve to clarify the intent of additional monitoring and assessment for animals exhibiting >20% reduced weight gain compared to the average control animal weight.

2. Type(s) of Modification Requested: (check all that apply)

	Type Of Change (See LGD 010 for more details)	X
ADMINISTRATIVE – AURO/GLP REVIEW	Administrative Modifications	
	GLP Modifications	
	Addition or deletion of a qualified technician, co-investigator, or study staff	
MINOR Modifications (*examples*)	Change in animal usage [*e.g., vendor, sex, age, weight, strain, small increase in # of animals used (less than 10% of overall number of approved animals)*]	
	Need to repeat an experiment without the addition of animals	
	Addition/change of sample collection times	
	Addition/change of sample collection volumes	
	Additional noninvasive sampling	
	Changes in acclimation or recovery period	
	Special housing request or change in husbandry procedures that do not deviate from the *Guide*	
	Changes in dosing procedures (e.g., dose, volume, or timing)	
	Other: _____	
MAJOR Mo	Change in SD/PI	
	Change in objectives of the study	

	Addition of a test article to be evaluated	
	Change that results in greater pain, distress, or degree of invasiveness (changes to pain categories D or E from C require a literature search for alternatives to be completed)	
	Addition of animals to pain Category E (literature search for alternatives required)	
	Addition of or change in Species	
	Addition of more than 10% of the total # of animals originally approved	
	Addition of blood sampling	
	Change in frequency of observations for morbidity	
	Change in study endpoint	
	Change in euthanasia method	
	Changes in feeding, housing, care, or use of animals that is not standard for the species or IAW *The Guide*	
	Changes from nonsurvival to survival surgery	
	Change that impacts personnel safety	
	Other change that relates to the specific experimental design and aims of the original protocol	
	Other: Morbidity assessment for early euthanasia clarification (specifically body mass)	**X**

3. PREVIOUSLY APPROVED MODIFICATIONS: (*Hit 'Enter' after description of each modification to list all individually.*)

Mod #	Short Description of the Amendment(s) (Include pain category breakdown of animal usage if changes were made from the original protocol)	No. & Species of Animal Requested	Approval Date
1	Addition of Blas Guigni and Meredith Bohannon to the study staff table with duties of general rat handling only. Requested the addition of 12 male rats to the 14-day phase of the study so that the micronucleus genotoxicity assay could be added to the overall FOX-7 toxicity evaluation. The micronucleus genotoxicity assay required the collection of a small amount of blood via saphenous blood collection which was the third request. This changed the total number of rats to 276 with the pain category breakdown shown in section 4.	Rat/12	23 Oct 2020
2	Increased the syringe size for terminal blood sampling from 3-5 ml syringe to a 6-10 ml syringe to accommodate the necessary clinical pathology parameters.	No change	11 Feb 2021

Mod #	Short Description of the Amendment(s) (Include pain category breakdown of animal usage if changes were made from the original protocol)	No. & Species of Animal Requested	Approval Date
3	Added Drs. Blas Guigni and Meredith Bohannon as primary coinvestigators, removed Dr. Emily Lent as primary co-investigator, replaced Theresa Hanna with Taryn Brown as a co-investigator, added training/proficiency of oral gavage for Dr. Blas Guigni, added hormone analysis following terminal blood collection, added sperm analysis as part of the necropsy, added a single vaginal swab sample immediately following euthanasia at necropsy for the female rats, and decreased the total number of rats required due to recent changes in the health monitoring procedures.	Rat/-8	28 June 2021
4	Added dosing proficiency information to the training table for Dr. Meredith Bohannon.	No change	16 Aug 2021

4. CURRENT APPROVED ANIMAL USAGE ON PROTOCOL:

Species/Total: Rat/268 **B:** 0 **C:** 42 **D:** 120 **E:** 106

5. FOR ITEMS A-H BELOW: Describe the requested changes to be implemented and the justification(s) for each. ***Please include section numbers of protocol for reference.***

A. Administrative change: Editorial (typographical, grammar, contact info update, etc.), GLP compliance changes, or change in personnel (not change of study director/principal investigator):

N/A

B. Specific changes or additions to the experimental design of the protocol (Section V.1. Experimental Design; EIRB Section 9.1 Experimental Design and General Procedures).

N/A

C. Change in sample size evaluation, data analysis plan, archiving of data, (Section V.2.; EIRB Section 9.3).

N/A

D. Change in the animals used, (Section V.3.; EIRB Sections 5.0, 9.4-9.6, 10.0). *(Include any changes in amount used, sex, age/weight, vendor/source, refinement, reduction, and replacement [3Rs]).*

N/A

E. Changes to technical methods (Section V.4.; EIRB Sections 11.0-17.0). *(Include changes in USDA pain category classifications [section V.4.1.1.1.1 thru V.4.1.1.1.4.], changes in anesthesia, analgesia, restraint, injections, identification, behavior studies, 'other procedures', study endpoint, euthanasia, etc. Include reference source for basis of dose/treatment change.).*

**** * * * If the modification requested will be adding animals to COLUMN D or E and the protocol did not previously have animals in those categories, a LITERATURE SEARCH FOR ALTERNATIVES TO PAINFUL OR DISTRESSFUL PROCEDURES must be completed and submitted with this modification request.***

The morbidity assessment description of section V.4.5 currently states:

Animals will be assessed for morbidity on a case by case basis and assessed for early euthanasia according to the following criteria:
1. Impaired ambulation (which prevents the animal from reaching food/water)
2. Weight loss or failure to gain weight (> 20% body mass loss as compared to controls)
3. Lack of physical activity or mental alertness
4. Prolonged labored breathing (lasting longer than 8 hours and accompanied by lethargy)
5. Unabated seizure activity (lasting longer than 1 hour)
6. Inability to urinate or defecate longer than 24 hours
7. Prolonged inability to remain upright (lasting more than 2 hours)

The AV may be consulted, if needed, to evaluate potentially moribund animals, unless the SD/PI plans to immediately euthanize the animal. Intervention euthanasia will be conducted on animals determined to be moribund. Euthanasia of moribund animals will be performed IAW section V.4.6.
If body weight of dosed animals is observed to decrease relative to controls, measurements may be done more frequently. Animals that exhibit an excessive decrease in weight, defined as > 20% body mass difference as compared to controls (due to either weight loss or failure to gain weight) compared to controls, as described above, will be euthanized IAW section V.4.6.

The last sentence of this description indicates that animals will automatically be euthanized when they reach the >20% body mass difference compared to controls. The intent, as stated in the first sentence, was that animals would begin to be assessed for possible early euthanasia once they reach the reduced weight gain threshold. This modification is requesting that this section read as follows:

Animals will be assessed for morbidity on a case by case basis and assessed for early euthanasia according to the following criteria:
1. Impaired ambulation (which prevents the animal from reaching food/water)

2. Weight loss or failure to gain weight (> 20% body mass difference (loss) as compared to median control mass)
3. Lack of physical activity or mental alertness
4. Prolonged labored breathing (lasting longer than 8 hours and accompanied by lethargy)
5. Unabated seizure activity (lasting longer than 1 hour)
6. Inability to urinate or defecate longer than 24 hours
7. Prolonged inability to remain upright (lasting more than 2 hours)
Potentially moribund animals will be monitored, in consultation with the AV, for possible reversal and recovery of toxic signs. Body Condition Score as described in Hickman et al. article (reference listed below); assessments may be conducted to assist AV in making a determination about if an animal should remain on study or be euthanized. Animals being assessed for morbidity will be subjected to increased monitoring. Intervention euthanasia will be conducted on animals determined to be moribund. Euthanasia of moribund animals will be performed IAW section V.4.6.

Hickman DL, Swan M. Use of a body condition score technique to assess health status in a rat model of polycystic kidney disease. J Am Assoc Lab Anim Sci. 2010 Mar;49(2):155-9. PMID: 20353688; PMCID: PMC2846001.

F. Changes to the Husbandry and Veterinary Care procedures (Section V.5.; EIRB Sections 18.0, 19.0). *(Changes in husbandry considerations, special provisions, exceptions to the Guide, AWAR, or IACUC Policy that have an impact on animal care and use; any changes to the veterinary medical care or environmental enrichment.)*

N/A

G. Changes to the personnel conducting this protocol (Section VI.; EIRB Section 3.0). *(Include record of completed training for any animal handling or use procedures assigned to new personnel. Signed assurance page(s) must be included with the modification if changing SD/PI, Primary Co-investigator, or adding a co-investigator.)*

N/A

H. Changes in Biohazard/ Safety (Section VII.; EIRB Section 21.0).

N/A

Appendix E

Sequential Stagewise Probit Results

Abbreviations:

mg/ml: milligrams per milliliter
kg: kilogram
mg/kg: milligrams per kilogram
ml: milliliter
LD_{50}: median lethal dose
SSWP: Sequential Stagewise Probit
(f): animal died on study

Table E-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

SEQUENTIAL STAGEWISE PROBIT (SSWP); ORAL, RAT

Protocol No.: 38-18-12-01
Chemical Substance: FOX-7
Route: Oral **Species:** Sprague-Dawley Rat **Sex:** Male
Concentration of Test Substance: 17.5 mg/ml[A], 55 mg/ml[B], 200 mg/ml[C], 104.7 mg/ml[D], 169.8 mg/ml[E], 75.9 mg/ml[F], 89.1 mg/ml[G], and 96.6 mg/ml[H].
Diluent: Corn Oil

MALE INDIVIDUAL ANIMAL EFFECTS

Animal No.	Dosing Stage	Weight kg	Nominal Dose mg/kg	Volume mL	Exposure Day Clinical Signs S* - sign	Exposure Day Morbidity/Mortality
19-0918	1	0.224	55	0.70[A]	N	No
19-0919	1	0.234	175	2.34[A]	N	No
19-0920	1	0.229	550	2.29[B]	N	No
19-0921	1	0.232	2000	2.32[C]	S1; S2	No
19-0922	2	0.231	1047	2.31[D]	S3; S1; S4	No
19-0923	2	0.253	1047	2.52[D]	S1; S4; S5; S6; S9	Yes
19-0924	2	0.233	1445	1.98[E]	S1; S4	No
19-0925	2	0.233	1445	1.98[E]	S1; S4; S7	No
19-0926	2	0.240	1698	2.40[E]	S1; S4	No
19-0927	2	0.251	1698	2.51[E]	S1; S4; S8; S9	Yes
19-0928	3	0.307	550	3.07[B]	N	No
19-0929	3	0.307	550	3.07[B]	S10	No
19-0930	3	0.283	759	2.83[F]	S4; S10; S1	No
19-0931	3	0.312	759	3.12[F]	S7; S10	No
19-0932	3	0.282	1047	2.82[D]	S1; S4	No
19-0933	3	0.305	1047	3.05[D]	S1; S10; S11	No
19-0934	4	0.322	550	1.99[G]	S1; S12; S8	No
19-0935	4	0.282	550	1.74[G]	S12; S1	No
19-0936	4	0.330	550	2.03[G]	N	No
19-0937	4	0.297	550	1.83[G]	S8; S1; S4	No
19-0938	4	0.294	646	2.13[G]	S1; S13; S8	No
19-0939	4	0.292	646	2.12[G]	S8	No
19-0940	4	0.342	646	2.48[G]	S1; S4; S8	No
19-0941	4	0.289	646	2.09[G]	S1; S8	No
19-0942	4	0.312	891	3.12[G]	S7; S8; S4	No
19-0943	4	0.306	891	3.06[G]	S1; S4; S8; S7	No
19-0944	4	0.325	891	3.25[G]	S7; S1; S8; S4; S6	No
19-0945	4	0.318	891	3.18[G]	S6; S13	No
19-0946	5	0.359	966	3.59[H]	S1; S4	No
19-0947	5	0.334	966	3.34[H]	S1; S4; S7	No

* Signs: N - Normal; S1 - Eyes Partially Closed; S2 - Lethargic; S3- Staining Around Anus; S4 - Hunched Posture; S5 - Mouth Breathing; S6 - Head Jerking; S7 - Diarrhea; S8 - Elevated Respiratory Rate; S9 - Mortality; S10 - Depressed Respiratory Rate; S11 - Dark Feces; S12 - Rearing; S13 - Dried Red Material Nose
Doses were based on nominal concentrations of test suspensions.
Study Conclusions: Estimated LD_{50} of 875 mg/kg; 95% Confidence Intervals 708 - 1082 mg/kg

Table E-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

SEQUENTIAL STAGEWISE PROBIT (SSWP); ORAL, RAT

Protocol No.: 38-18-12-01
Chemical Substance: FOX-7
Route: Oral **Species:** Sprague-Dawley Rat **Sex:** Female
Concentration of Test Substance: 17.5 mg/ml[A], 55 mg/ml[B], 200 mg/ml[C], 104.7 mg/ml[D], 169.8 mg/ml[E], 75.9 mg/ml[F], 89.1 mg/ml[G], and 96.6 mg/ml[H].
Diluent: Corn Oil

FEMALE INDIVIDUAL ANIMAL EFFECTS

Animal No.	Dosing Stage	Weight kg	Nominal Dose mg/kg	Volume mL	Exposure Day Clinical Signs S* - sign	Exposure Day Morbidity/Mortality
19-0948	1	0.189	55	0.59[A]	N	No
19-0949	1	0.176	175	1.76[A]	N	No
19-0950	1	0.184	550	1.84[B]	S7	No
19-0951	1	0.192	2000	1.92[C]	S1; S2	No
19-0952	2	0.186	1047	1.86[D]	S1; S4	No
19-0953	2	0.209	1047	2.09[D]	S1;S4	No
19-0954	2	0.173	1445	1.47[E]	S13; S11; S3; S1; S4; S9	Yes
19-0955	2	0.176	1445	1.50[E]	S1; S4	No
19-0956	2	0.198	1698	1.98[E]	S1; S4	No
19-0957	2	0.186	1698	1.86[E]	S1; S4	No
19-0958	3	0.209	550	2.09[B]	S4; S10	No
19-0959	3	0.218	550	2.18[B]	N	No
19-0960	3	0.194	759	1.94[F]	S12; S10	No
19-0961	3	0.217	759	2.17[F]	S11; S10	No
19-0962	3	0.204	1047	2.04[D]	S1; S4; S10	No
19-0963	3	0.206	1047	2.06[D]	S1; S4; S10	No
19-0964	4	0.208	550	1.28[G]	S1; S4	No
19-0965	4	0.208	550	1.28[G]	S4; S1	No
19-0966	4	0.187	550	1.15[G]	S13; S1; S4	No
19-0967	4	0.223	550	1.37[G]	S1; S4	No
19-0968	4	0.196	646	1.42[G]	S1; S4	No
19-0969	4	0.197	646	1.43[G]	S1; S8; S4	No
19-0970	4	0.213	646	1.54[G]	S1; S4; S8	No
19-0971	4	0.207	646	1.50[G]	S1; S4; S8	No
19-0972	4	0.225	891	2.25[G]	S4	No
19-0973	4	0.215	891	2.15[G]	S1; S4	No
19-0974	4	0.223	891	2.23[G]	S1; S4	No
19-0975	4	0.227	891	2.27[G]	S1; S8	No
19-0976	5	0.259	966	2.59[H]	S1; S4	No
19-0977	5	0.237	966	2.37[H]	S1; S4	No

* Signs: N - Normal; S1 - Eyes Partially Closed; S2 - Lethargic; S3- Staining Around Anus; S4 - Hunched Posture; S5 - Mouth Breathing; S6 - Head Jerking; S7 - Diarrhea; S8 - Elevated Respiratory Rate; S9 - Mortality; S10 - Depressed Respiratory Rate; S11 - Soft Stool; S12 - Rearing; S13 - Dried Red Material Nose
Doses were based on nominal concentrations of test suspensions.
Study Conclusions: Estimated LD_{50} of 805 mg/kg; 95% Confidence Intervals 668 - 971 mg/kg

Table E-3
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Acute SSWP Individual Body Weights (grams)

Male Rats

Dosing Stage	Animal ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
1	19-0918	253.1	259.8	270.5	279.7	290.8	300.0	312.9	318.1	325.8	335.7	347.0	356.6	366.7	370.0
1	19-0919	242.8	255.0	268.1	277.4	287.8	299.0	309.2	315.0	317.3	326.6	334.9	344.1	349.0	353.9
1	19-0920	216.9	229.0	240.2	273.4	262.5	270.4	283.5	288.1	297.0	307.4	316.0	323.0	333.6	343.6
1	19-0921	219.3	213.1	203.0	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)

Dosing Stage	Animal ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
2	19-0922	220.6	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
2	19-0923	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
2	09-0924	232.1	236.9	232.5	224.4	223.4	202.0	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
2	19-0925	231.8	221.7	219.0	214.9	213.4	223.2	234.0	242.1	257.4	269.2	283.9	290.5	292.4	301.5
2	19-0926	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
2	19-0927	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)

Dosing Stage	Animal ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 13	Day 14
3	19-0928	303.1	311.0	321.8	335.7	341.2	356.9	369.7	376.6	381.8	389.8	424.4	427.6
3	19-0929	302.9	293.9	301.1	313.0	322.8	331.9	345.9	349.7	363.3	373.8	395.5	403.1
3	19-0930	281.0	279.5	287.4	299.8	307.5	314.8	326.1	331.1	343.4	353.1	372.3	371.5
3	19-0931	294.3	302.0	308.2	318.3	325.3	336.2	345.6	353.6	363.8	371.2	394.7	406.2
3	19-0932	271.4	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
3	19-0933	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)

Dosing Stage	Animal ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 11	Day 12	Day 13	Day 14
4	19-0934	318.7	322.2	316.4	328.2	344.1	357.5	373.6	384.1	412.9	419.8	427.9	420.1
4	19-0935	270.6	281.5	277.9	284.2	289.6	300.7	315.7	322.9	347.9	358.0	364.8	373.0
4	19-0936	331.1	330.6	335.9	339.1	349.1	368.0	381.2	390.8	422.7	434.7	440.8	450.1
4	19-0937	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
4	19-0938	300.8	294.4	292.4	295.1	296.9	307.7	319.4	332.7	350.4	357.2	365.9	371.1
4	19-0939	277.8	285.6	284.2	293.6	298.8	309.0	323.2	329.9	353.9	358.3	369.9	367.5
4	19-0940	313.3	328.3	322.4	321.9	342.0	354.0	370.7	381.3	420.7	435.1	443.7	451.0
4	19-0941	275.7	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
4	19-0942	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
4	19-0943	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
4	19-0944	320.1	319.5	316.9	322.8	333.8	345.3	354.8	363.4	394.5	398.3	409.5	418.3
4	19-0945	314.6	309.1	309.2	295.9	301.2	314.0	326.3	340.6	366.6	379.5	384.2	390.7

Dosing Stage	Animal ID	Day 1	Day 2	Day 3	Day 6	Day 7	Day 8	Day 9	Day 10	Day 13	Day 14
5	19-0946	348.6	350.7	339.8	335.3	347.6	361.6	361.2	376.1	405.9	411.7
5	19-0947	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)

Table E-4
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Acute SSWP Individual Body Weights (grams)

Female Rats

Dosing Stage	Animal ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
1	19-0948	206.5	215.9	218.7	216.2	234.8	239.3	236.9	235.8	250.1	253.7	261.0	256.0	272.5	276.1
1	19-0949	180.4	189.2	194.7	199.1	192.8	203.9	206.8	212.5	209.1	216.5	220.4	227.7	221.9	228.1
1	19-0950	175.4	193.0	187.6	199.6	210.1	220.1	227.5	238.5	240.2	249.4	259.7	262.3	268.1	257.8
1	19-0951	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)

Dosing Stage	Animal ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
2	19-0952	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
2	19-0953	209.9	214.6	212.7	208.4	210.9	223.7	234.8	243.5	254.0	265.9	276.5	276.5	275.4	285.0
2	19-0954	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
2	19-0955	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
2	19-0956	187.9	204.0	194.5	187.9	175.1	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
2	19-0957	184.9	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)

Dosing Stage	Animal ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 13	Day 14
3	19-0958	204.7	214.0	211.9	213.8	218.6	223.0	226.7	223.5	238.5	237.5	247.8	252.2
3	19-0959	222.3	216.6	213.8	230.4	241.5	244.6	260.1	270.0	275.8	284.6	294.3	299.3
3	19-0960	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
3	19-0961	214.6	217.9	222.7	226.1	231.7	237.5	242.7	250.2	255.4	264.0	273.0	280.1
3	19-0962	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
3	19-0963	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)

Dosing Stage	Animal ID	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 11	Day 12	Day 13	Day 14
4	19-0964	213.2	214.7	215.3	221.6	228.5	236.2	245.3	253.3	274.5	284.6	285.3	290.1
4	19-0965	207.9	216.6	225.7	221.7	222.4	228.5	239.8	249.1	262.9	264.9	257.0	262.8
4	19-0966	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
4	19-0967	220.0	224.7	226.1	238.3	226.2	240.2	245.4	242.2	262.5	260.1	255.4	267.6
4	19-0968	197.6	195.4	190.8	196.2	206.4	203.8	221.3	228.9	239.4	238.2	240.9	227.7
4	19-0969	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
4	19-0970	209.4	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
4	19-0971	205.3	212.2	216.1	219.6	225.3	228.8	239.3	250.9	272.9	266.3	262.0	269.5
4	19-0972	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
4	19-0973	211.8	214.5	213.4	206.4	207.4	216.2	229.0	239.0	255.7	265.0	262.8	255.4
4	19-0974	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
4	19-0975	223.4	227.9	227.7	220.9	222.6	233.8	237.7	243.8	255.4	248.5	267.1	267.5

Dosing Stage	Animal ID	Day 1	Day 2	Day 3	Day 6	Day 7	Day 8	Day 9	Day 10	Day 13	Day 14
5	19-0976	257	263.3	260.4	275.6	275.5	277.8	287.7	293	299.9	309.7
5	19-0977	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)

Table E-5
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Acute SSWP Clinical Signs

Male Rats

Dosing Stage	Animal ID	Observation	First Day[a]	Last Day[b]
1	19-0918	Normal	0	14
1	19-0919	Normal	0	14
		Hair loss - back of neck	9	9
1	19-0920	Normal	0	14
		Stains around anus	2	2
		Hair loss - left hind limb	4	9
1	19-0921	Eyes partially closed	0	0
		Slightly lethargic	0	1
		Jerky, non-fluid movement	1	3
		Soft stool	1	1
		Hunched posture	1	1
		Stains around anus	2	3
		Dried red material around nose	3	3
		Moribund euthanasia	3	3
2	19-0922	Staining around anus	0	1
		Eyes partially closed	0	0
		Hunched posture	0	0
		Tremors/shaking	1	1
		Dried red material - nose	1	1
		Reduced body temperature	1	1
		Moribund euthanasia	1	1
2	19-0923	Eyes partially closed	0	0
		Hunched posture	0	0
		Mouth breathing	0	0
		Jerky, non-fluid movement	0	0
		Mortality	0	0
2	19-0924	Eyes partially closed	0	0
		Hunched posture	0	0
		Staining around anus	1	1
		Dried red material - nose	2	3
		Normal	4	5
		Hyperactivity	6	6
		Seizures	6	6
		Moribund euthanasia	6	6

[a] Represents the first day the clinical sign was observed.
Day 0 is the day the dose was administered.
[b] Represents the last day the clinical sign was observed.

Table E-5 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Acute SSWP Clinical Signs

Male Rats

Dosing Stage	Animal ID	Observation	First Day[a]	Last Day[b]
2	19-0925	Eyes partially closed	0	0
		Hunched posture	0	0
		Diarrhea	0	0
		Staining around anus	1	2
		Chromodacryorrhea- both eyes	2	2
		Dried red material - nose	2	3
		Lethargic	3	5
		Normal	6	14
2	19-0926	Eyes partially closed	0	0
		Hunched posture	0	0
		Mortality	1	1
2	19-0927	Eyes partially closed	0	0
		Hunched posture	0	0
		Increased respiratory effort	0	0
		Mortality	0	0
3	19-0928	Normal	0	14
		Staining around anus	1	1
		Dried red material - nose	2	2
3	19-0929	Increased respiratory effort	0	0
		Staining around anus	1	2
		Rough haircoat	1	1
		Dried red material - nose	1	2
		Lethargic	3	3
		Normal	4	14
3	19-0930	Hunched posture	0	0
		Increased respiratory effort	0	0
		Eyes partially closed	0	0
		Staining around anus	1	1
		Rough haircoat	1	1
		Dried red material - nose	1	2
		Dried red material - front limbs	1	1
		Elevated respiratory rate	1	1
		Normal	3	14

[a] Represents the first day the clinical sign was observed.
Day 0 is the day the dose was administered.
[b] Represents the last day the clinical sign was observed.

Table E-5 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Acute SSWP Clinical Signs

Male Rats

Dosing Stage	Animal ID	Observation	First Day[a]	Last Day[b]
3	19-0931	Diarrhea	0	0
		Increased respiratory effort	0	0
		Staining around anus	1	1
		Rough haircoat	1	1
		Dried red material - nose	1	1
		Normal	2	14
3	19-0932	Eyes partially closed	0	1
		Hunched posture	0	1
		Dried red material - nose	1	1
		Dried red material - front limbs	1	1
		Lethargic	1	1
		Staining around anus	1	1
		Reduced body temperature	1	1
		Moribund euthanasia	1	1
3	19-0933	Eyes partially closed	0	0
		Increased respiratory effort	0	0
		Dark feces	0	0
		Mortality	1	1
4	19-0934	Eyes partially closed	0	0
		Rearing	0	0
		Increased respiratory effort	0	0
		Normal	1	14
		Hyperactivity	13	13
4	19-0935	Rearing/loss of coordination	0	0
		Eyes partially closed	0	0
		Lethargic	1	1
		Staining around anus	1	2
		Normal	3	14
		Hyperactivity	4	5
		Dried red material - nose	8	8
4	19-0936	Normal	0	14
		Staining around anus	1	1
4	19-0937	Increased respiratory effort	0	0
		Eyes partially closed	0	0
		Hunched posture	0	0
		Mortality	1	1
4	19-0938	Eyes partially closed	0	0
		Dried red material - nose	0	0
		Increased respiratory effort	0	0
		Normal	1	14
		Lethargic	2	2
		Staining around anus	3	3
		Hyperactivity	8	12

[a] Represents the first day the clinical sign was observed.
Day 0 is the day the dose was administered.
[b] Represents the last day the clinical sign was observed.

Table E-5 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Acute SSWP Clinical Signs

Male Rats

Dosing Stage	Animal ID	Observation	First Day[a]	Last Day[b]
4	19-0939	Increased respiratory effort	0	0
		Staining around anus	1	2
		Dried red material - nose	2	2
		Normal	3	14
4	19-0940	Eyes partially closed	0	0
		Hunched posture	0	0
		Increased respiratory effort	0	0
		Normal	1	14
4	19-0941	Eyes partially closed	0	0
		Increased respiratory effort	0	0
		Lethargic	1	1
		Tremors/shaking	1	1
		Moribund euthanasia	1	1
4	19-0942	Diarrhea	0	0
		Increased respiratory effort	0	0
		Hunched posture	0	0
		Mortality	1	1
4	19-0943	Eyes partially closed	0	0
		Hunched posture	0	0
		Increased respiratory effort	0	0
		Diarrhea	0	0
		Mortality	1	1
4	19-0944	Diarrhea	0	0
		Eyes partially closed	0	0
		Increased respiratory effort	0	0
		Hunched posture	0	0
		Tremors/shaking	0	0
		Lethargic	1	1
		Staining around anus	1	2
		Urine stains	1	1
		Hyperactivity	3	6
		Normal	5	14
		Dried red material - nose	8	8
4	19-0945	Tremors/shaking	0	0
		Dried red material - nose	0	0
		Lethargic	1	1
		Normal	2	14
		Hyperactivity	3	8
5	19-0946	Eyes partially closed	0	0
		Hunched posture	0	0
		Staining around anus	1	3
		Dried red material - nose	1	3
		Hyperactivity	6	7
		Normal	8	14
5	19-0947	Eyes partially closed	0	0
		Hunched posture	0	0
		Diarrhea	0	0
		Mortality	1	1

[a] Represents the first day the clinical sign was observed.
Day 0 is the day the dose was administered.
[b] Represents the last day the clinical sign was observed.

Table E-6
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Acute SSWP Clinical Signs

Female Rats

Dosing Stage	Animal ID	Observation	First Day[a]	Last Day[b]
1	19-0948	Normal	0	7
		Jerky, non-fluid movement	8	14
1	19-0949	Normal	0	5
		Slight jerky, non-fluid movement	6	14
		Slight hyperactivity	8	9
1	19-0950	Diarrhea	0	0
		Lethargic	1	1
		Dried red material - nose	1	1
		Dried red material - mouth	1	1
		Urine stains	1	2
		Stains around anus	2	3
		Normal	4	14
1	19-0951	Eyes partially closed	0	0
		Slightly lethargic	0	0
		Mortality	1	1
2	19-0952	Eyes partially closed	0	0
		Hunched posture	0	0
		Mortality	1	1
2	19-0953	Eyes partially closed	0	0
		Hunched posture	0	0
		Dried red material - nose	1	4
		Staining around anus	1	4
		Lethargic	4	4
		Normal	5	14
		Jerky, non-fluid movement	7	7
2	19-0954	Dried red material - nose	0	0
		Soft stool	0	0
		Staining around anus	0	0
		Eyes partially closed	0	0
		Hunched posture	0	0
		Mortality	0	0
2	19-0955	Eyes partially closed	0	0
		Hunched posture	0	0
		Mortality	1	1

[a] Represents the first day the clinical sign was observed.
Day 0 is the day the dose was administered.
[b] Represents the last day the clinical sign was observed.

Table E-6 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Acute SSWP Clinical Signs

Female Rats

Dosing Stage	Animal ID	Observation	First Day[a]	Last Day[b]
2	19-0956	Eyes partially closed	0	0
		Hunched posture	0	0
		Dried red material - face	1	1
		Staining around anus	1	5
		Dried red material - nose	2	5
		Lethargic	4	5
		Dried red material - front limbs	5	5
		Moribund euthanasia	5	5
2	19-0957	Eyes partially closed	0	0
		Hunched posture	0	0
		Dried red material - nose	1	1
		Dried red material - front limbs	1	1
		Staining around anus	1	1
		Moribund euthanasia	1	1
3	19-0958	Hunched posture	0	0
		Increased respiratory effort	0	0
		Staining around anus	1	1
		Dried red material - nose	2	2
		Normal	3	14
		Jerky, non-fluid movement	4	4
3	19-0959	Normal	0	14
		Dried red material - nose	1	3
		Hyperactivity	3	3
3	19-0960	Small amount of dose on chin	0	0
		Rearing/loss of balance	0	0
		Increased respiratory effort	0	0
		Mortality	1	1
3	19-0961	Soft stool	0	0
		Increased respiratory effort	0	0
		Hyperactivity	1	14
		Dried red material - nose	1	2
		Dried red material - front limbs	1	1
		Staining around anus	1	3
		Lethargic	2	2
3	19-0962	Squinting	0	0
		Hunched posture	0	0
		Increased respiratory effort	0	0
		Mortality	1	1

[a] Represents the first day the clinical sign was observed.
Day 0 is the day the dose was administered.
[b] Represents the last day the clinical sign was observed.

Table E-6 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Acute SSWP Clinical Signs

Female Rats

Dosing Stage	Animal ID	Observation	First Day[a]	Last Day[b]
3	19-0963	Eyes partially closed	0	0
		Hunched posture	0	0
		Increased respiratory effort	0	0
		Mortality	1	1
4	19-0964	Hunched posture	0	0
		Eyes partially closed	0	0
		Dried red material - nose	1	3
		Hyperactivity	1	6
		Staining around anus	1	1
		Normal	5	14
4	19-0965	Hunched posture	0	0
		Eyes partially closed	0	0
		Dried red material - nose	1	1
		Lethargic	1	1
		Normal	2	14
4	19-0966	Dried red material - nose	0	0
		Squinting	0	0
		Hunched posture	0	0
		Mortality	1	1
4	19-0967	Eyes partially closed	0	0
		Hunched posture	0	0
		Lethargic	1	3
		Dried red material - nose	1	1
		Hyperactivity	2	2
		Normal	4	14
4	19-0968	Eyes partially closed	0	0
		Hunched posture	0	0
		Normal	1	14
		Lethargic	2	4
		Hyperactivity	5	6
4	19-0969	Eyes partially closed	0	0
		Increased respiratory effort	0	0
		Hunched posture	0	0
		Mortality	1	1

[a] Represents the first day the clinical sign was observed.
Day 0 is the day the dose was administered.
[b] Represents the last day the clinical sign was observed.

Table E-6 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Acute SSWP Clinical Signs

Female Rats

Dosing Stage	Animal ID	Observation	First Day[a]	Last Day[b]
4	19-0970	Increased respiratory effort	0	0
		Eyes partially closed	0	0
		Hunched posture	0	0
		Tremors/shaking	1	1
		Hyperactivity	1	1
		Moribund euthanasia	1	1
4	19-0971	Increased respiratory effort	0	0
		Eyes partially closed	0	0
		Hunched posture	0	0
		Lethargic	1	4
		Staining around anus	1	3
		Dried red material - nose	2	2
		Normal	5	14
4	19-0972	Hunched posture	0	0
		Mortality	1	1
4	19-0973	Eyes partially closed	0	0
		Hunched posture	0	0
		Staining around anus	1	2
		Lethargic	1	2
		Dried red material - nose	2	4
		Hyperactivity	3	3
		Normal	5	14
4	19-0974	Eyes partially closed	0	0
		Hunched posture	0	0
		Mortality	1	1
4	19-0975	Eyes partially closed	0	0
		Increased respiratory effort	0	0
		Staining around anus	1	4
		Lethargic	1	5
		Normal	6	14
5	19-0976	Eyes partially closed	0	0
		Hunched posture	0	0
		Lethargic	1	3
		Staining around anus	1	3
		Dried red material - nose	1	3
		Hyperactivity	2	6
		Normal	7	14
5	19-0977	Eyes partially closed	0	0
		Hunched posture	0	0
		Mortality	1	1

[a] Represents the first day the clinical sign was observed.
Day 0 is the day the dose was administered.
[b] Represents the last day the clinical sign was observed.

Table E-7
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Acute SSWP Gross Necropsy Observations

Male Rats

Dosing Stage	Animal ID	Observation
1	19-0918	Stomach ingesta more firm than normal
1	19-0919	Mild congestion of meningeal vessels
1	19-0920	Minimal congestion of subcutaneous vessels
		Mild congestion of meningeal vessels
1	19-0921	Moderate diarrheal staining
		Diffuse congestion of mesenteric vessels
		Stomach contains semi-firm ball of ingesta
		Stomach moderately distended - possibly impacted
		Cecum is distended and flaccid
		Mild congestion of meningeal vessels
2	19-0922	Mild diarrheal staining with bedding
		Dried red material - nose
		Congestion of gastrointestinal tract and mesenteric vessels
		Minimal distension of stomach
		Red discoloration of glandular stomach
		Small amount of blood in stomach contents
		Mild congestion of meningeal vessels
2	19-0923	Diarrheal staining around anus
		Distended stomach
		Mild congestion of meningeal vessels
2	19-0924	Active seizure activity at euthanasia
		Severe chromodacryorrhea - both eyes
		Salivation
		Congestion of meningeal vessels
		Very little stomach and intestinal contents
		Stomach lining very red and inflamed
		Blood in intestines

Table E-7 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Acute SSWP Gross Necropsy Observations

Male Rats

Dosing Stage	Animal ID	Observation
2	19-0925	Stomach contents firm and less watery than normal
		Stomach contents form compressable ball when removed
		Slight congestion of meningeal vessels
2	19-0926	Corneal opacity - left eye
		Moderate diarrheal staining
		Head in bent back position (opisthotonos)
		Plug attached to tip of penis
		Red coloration in end of toes
		Severely distended stomach
		Fluid in ingesta
		Hemorrhagic red foci in thymus
		Hemorrhage in stomach
		Ulcerative foci in glandular mucosa
		Moderate congestion of meningeal vessels
2	19-0927	Diarrheal staining
		Yellow ingesta/fluid in stomach
		Severely distended stomach
		Moderate congestion of meningeal vessels
3	19-0928	Minimal congestion of meningeal vessels
3	19-0929	Increased firmness of adhesion between skin and subcutaneous layer
		Mild congestion of subcutaneous, mesenteric, and meningeal vessels
3	19-0930	Increased firmness of adhesion between skin and subcutaneous layer
		Subdermal vessels have increased prominence with white discoloration
		Minimal congestion of meningeal vessels

Table E-7 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Acute SSWP Gross Necropsy Observations

Male Rats

Dosing Stage	Animal ID	Observation
3	19-0931	Increased firmness of adhesion between skin and subcutaneous layer
		Subdermal vessels have increased prominence with white discoloration
		Dilation of renal pelvis (hydronephrosis)
		Congestion of mesenteric and meningeal vessels
3	19-0932	Dried red material on front paws and nose
		Diarrheal staining
		Stomach distended with liquid ingesta and test material
		Minimal contents in intestine
		Congestion of subcutaneous and meningeal vessels
		Ingesta remaining in mouth
3	19-0933	Diarrheal staining
		Congestion of subcutaneous and meningeal vessels
		Stomach contained liquid ingesta, gas, and test material
		Minimal test material and blood throughout intestine
4	19-0934	No gross lesions recognized
4	19-0935	Skin has slightly increased adhesion to body wall
		Minimal congestion of meningeal vessels
4	19-0936	Stomach slightly distended with slightly dry contents
		Mesenteric and meningeal vessels mildly congested
4	19-0937	Congestion of subcutaneous and meningeal vessels
		Semi-solid ingesta and test material in stomach with no inflammation
		Blood and liquid ingesta in intestines
		Minimal pale areas in liver
4	19-0938	Right kidney shrunken by 1/2 normal size and mildly dilated pelvis
		Stomach mildly distended and contents have increased firmness

Table E-7 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Acute SSWP Gross Necropsy Observations

Male Rats

Dosing Stage	Animal ID	Observation
4	19-0939	Stomach slightly distended with ingesta that is more dry than normal
		Slight congestion of meningeal vessels
4	19-0940	Skin has increased firmness of adhesion to subcutaneous layer
4	19-0941	Congestion of subcutaneous and meningeal vessels
		Distended stomach with solid ingesta and test material
		Cecum contained liquid ingesta
		Blood in stomach and intestines
4	19-0942	Bedding in mouth and diarrheal staining
		Congestion of subcutaneous and meningeal vessels
		Distended stomach with gas and liquid ingesta with test material
		Blood and liquid ingesta in intestines
		Pale areas throughout liver
4	19-0943	Congestion of subcutaneous and meningeal vessels
		Diarrheal staining
		Distended stomach with liquid ingesta, test material, and gas
		Blood in stomach and intestines
		Minimal pale areas in liver
4	19-0944	Increased firmness of adhesion between skin and body wall
4	19-0945	Left kidney has mass in caudal pole (white, firm, 1/2 cm diameter)
		Increased firmness of adhesion between skin and body wall
5	19-0946	Increased firmness of adhesion between skin and body wall
		Slight congestion of meningeal and mesenteric vessels
		Stomach contents sticky and dryer than normal
5	19-0947	Moderate to severe congestion of subcutaneous and meningeal vessels
		Fluid in diaphragm
		Liquid ingesta and test material in stomach with small amount of blood
		Semi-solid ingesta and test material in intestine
		Tips of toes and nose are red

Table E-8
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Acute SSWP Gross Necropsy Observations

Female Rats

Dosing Stage	Animal ID	Observation
1	19-0948	Mild congestion of meningeal vessels
1	19-0949	Mild congestion of meningeal vessels
1	19-0950	Mild congestion of subcutaneous vessels
		Mild congestion of meningeal vessels
1	19-0951	Pale liver
		Distended stomach with appearance of blood
		Distended small intestine (slight)
2	19-0952	Red discoloration of all 4 paws (congestion)
		Minimal congestion of subcutaneous vessels
		Pleural mediastinal clear tan fluid
		Mildly distended stomach with fluid and ingesta
		Lungs slightly firm and fail to collapse
		Small amount of blood in stomach
		Moderate congestion of meningeal vessels
		Few superficial ulcerations in glandular mucosa
2	19-0953	No gross lesions recognized
2	19-0954	Multifocal to coalescing hepatic palor
		Diffusely pale liver
		Distended and taught stomach with ingesta
		Minor diarrheal staining
		Meningeal vessels mildly congested
2	19-0955	Red discoloration of all 4 paws (congestion)
		Congestion of subcutaneous vessels throughout body
		Mild pale liver discoloration
		Hemorrhage in stomach with pinpoint ulcerations
		Moderate congestion of meningeal vessels

Table E-8 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Acute SSWP Gross Necropsy Observations

Female Rats

Dosing Stage	Animal ID	Observation
2	19-0956	Blood in stomach with ulcerations of glandular mucosa
		Remainder of gastrointestinal tract has decreased content with dark material (hemorrhage)
		Small amount of dried material in stomach
		Congestion of subcutaneous, gastrointestinal, and meningeal vessels
2	19-0957	Moderate diarrheal staining
		Mild congestion of subcutaneous vessels
		Markedly distended stomach with mild gas
		Ingesta mildly firm
		Ingesta remaining in mouth
		Mild congestion of meningeal vessels
		Glandular mucosa has purple discoloration
		Blood in cecum
3	19-0958	Stomach empty
		Congestion of mesenteric and meningeal vessels
3	19-0959	Ingesta is firm/sticky in consistency
		Congestion of mesenteric, metrial, and mesenteric vessels
3	19-0960	Diarrheal staining
		Congestion of subcutaneous and meningeal vessels
		Distended stomach with semi-solid ingesta and test material
		Blood in stomach and intestine
3	19-0961	Congestion of mesenteric and meningeal vessels
3	19-0962	Minimal dried red material around nose
		Minimal congestion of subcutaneous vessels
		Distended stomach with semi-solid ingesta and test material
		Small amount of blood in intestine
		Minimal ingesta and test material in intestine

Table E-8 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Acute SSWP Gross Necropsy Observations

Female Rats

Dosing Stage	Animal ID	Observation
3	19-0963	Dried red material - nose and front paws
		Distended stomach with semi-solid ingesta and test material
		Small amount of blood in intestines
		Congested subcutaneous and meningeal vessels
		Patchy discoloration of liver
4	19-0964	Coronary vessels slightly congested and prominent with elliptical streaks of localized bulging
4	19-0965	Increased firmness of adhesion between skin and body wall
		Stomach is empty
		Mild congestion of meningeal vessels
4	19-0966	Diarrheal staining
		Congested subcutaneous and meningeal vessels
		Semi-solid ingesta, blood, and test material in stomach
		Moderate inflammation of stomach lining
		Blood and liquid ingesta in intestine
		Pale areas throughout liver
4	19-0967	No gross lesions recognized
4	19-0968	No gross lesions recognized
4	19-0969	Diarrheal staining
		Congested subcutaneous and meningeal vessels
		Stomach contained semi-solid ingesta and test material
		Blood and liquid ingesta in intestine

Table E-8 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Acute SSWP Gross Necropsy Observations

Female Rats

Dosing Stage	Animal ID	Observation
4	19-0970	Fluid inside diaphragm
		Congested meningeal and subcutaneous vessels
		Stomach contained solid ingesta and test material
		Blood in intestines
		Cecum contained liquid ingesta
4	19-0971	Coronary vessels congested and prominent
		Right ventricle has dark purple streaks that appear to be thinning of the vessel wall
		Mild congestion of meningeal vessels
4	19-0972	Congested meningeal and subcutaneous vessels
		Liquid ingesta and test material in stomach
		Stomach lining slightly red and inflamed
		Liquid ingesta and test material in stomach
		Stomach lining slightly red and inflamed
		Liquid ingesta, test material, and blood in intestines
		Stomach distended
		Pale areas throughout liver
4	19-0973	Minimal congestion of meningeal vessels
4	19-0974	Diarrheal staining
		Congestion of subcutaneous and meningeal vessels
		Semi-solid ingesta and test material in stomach
		Blood and liquid ingesta in intestines
		Pale areas throughout liver
4	19-0975	Stomach nearly empty with small amount of ingesta and hair
5	19-0976	Increased adhesion between skin and subcutaneous tissue
		Slight congestion of meningeal and mesenteric vessels
		Stomach contents sticky and dryer than normal
5	19-0977	Moderate-severe congestion of subcutaneous and meningeal vessels
		Fluid inside diaphragm
		Liquid ingesta and test material in stomach with small amount of blood
		Semi-solid ingesta and test material in intestine
		Tips of toes and nose are red

Appendix F

Subacute Individual and Summary of Body Mass

Abbreviations:

mg/kg-d: milligrams per kilogram per day
(f): animal died on study
ND: no data
SD: standard deviation

Table F-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Body Mass (grams)
Male Rats

Group	Animal ID	Day 0	Day 1	Day 3	Day 7	Day 13	Day 14[1]
Corn Oil Control	21-0391	261	268	276	302	335	326
	21-0392	231	240	247	264	292	285
	21-0431	220	226	240	263	294	284
	21-0432	237	245	261	292	337	324
	21-0435	264	269	281	308	336	324
	21-0436	268	272	281	305	333	322
	Mean	**246.8**	**253.3**	**264.3**	**289.0**	**321.2**	**310.8**
	SD	**20.05**	**18.99**	**17.86**	**20.47**	**21.87**	**20.44**
6.25 mg/kg-d	21-0405	253	264	271	305	340	330
	21-0406	281	285	289	311	338	328
	21-0415	213	221	233	257	292	279
	21-0416	230	238	251	278	313	303
	21-0445	230	232	248	291	311	311
	21-0446	243	241	257	294	315	311
	Mean	**241.7**	**246.8**	**258.2**	**289.3**	**318.2**	**310.3**
	SD	**23.54**	**23.46**	**19.52**	**19.56**	**18.13**	**18.63**
12.5 mg/kg-d	21-0393	236	242	261	285	322	313
	21-0394	234	239	253	283	324	318
	21-0441	304	313	332	359	392	381
	21-0442	272	279	293	316	359	348
	21-0447	236	247	265	294	331	320
	21-0448	223	230	241	272	301	294
	Mean	**250.8**	**258.3**	**274.2**	**301.5**	**338.2**	**329.0**
	SD	**30.90**	**31.58**	**33.18**	**31.80**	**32.33**	**30.82**
25 mg/kg-d	21-0395	292	294	305	329	364	358
	21-0396	284	289	303	331	366	352
	21-0397	231	236	249	281	312	303
	21-0398	243	246	259	285	315	306
	21-0409	256	261	277	316	350	339
	21-0410	219	223	232	261	281	276
	Mean	**254.2**	**258.2**	**270.8**	**300.5**	**331.3**	**322.3**
	SD	**29.06**	**28.70**	**29.55**	**28.86**	**34.03**	**32.30**
50 mg/kg-d	21-0407	239	245	253	280	308	301
	21-0408	238	240	253	274	301	291
	21-0413	232	237	248	268	301	291
	21-0414	238	246	259	288	322	314
	21-0429	305	304	322	341	370	360
	21-0430	280	281	295	325	357	342
	Mean	**255.3**	**258.8**	**271.7**	**296.0**	**326.5**	**316.5**
	SD	**29.96**	**27.27**	**29.98**	**29.85**	**29.95**	**28.60**
100 mg/kg-d	21-0421	309	307	309	288	315	298
	21-0422	252	253	261	259	286	271
	21-0433	242	242	246	246	284	276
	21-0434	258	261	262	262	274	266
	21-0443	268	270	271	283	301	292
	21-0444	226	229	235	245	275	265
	Mean	**259.2**	**260.3**	**264.0**	**263.8**	**289.2**	**278.0**
	SD	**28.32**	**26.99**	**25.50**	**18.17**	**15.97**	**13.87**
200 mg/kg-d	21-0403	221	224	215	181	(f)	(f)
	21-0404	281	274	260	(f)	(f)	(f)
	21-0423	257	248	227	(f)	(f)	(f)
	21-0424	243	242	232	(f)	(f)	(f)
	21-0427	306	299	297	242	(f)	(f)
	21-0428	295	288	269	248	(f)	(f)
	Mean	**267.2**	**262.5**	**250.0**	**223.7**	**ND**	**ND**
	SD	**32.54**	**29.08**	**30.82**	**37.07**	**ND**	**ND**
400 mg/kg-d	21-0399	256	249	240	(f)	(f)	(f)
	21-0400	284	276	264	(f)	(f)	(f)
	21-0401	245	234	219	(f)	(f)	(f)
	21-0402	236	232	210	(f)	(f)	(f)
	21-0419	229	223	208	(f)	(f)	(f)
	21-0420	249	251	222	(f)	(f)	(f)
	Mean	**249.8**	**244.2**	**227.2**	**ND**	**ND**	**ND**
	SD	**19.26**	**18.88**	**21.34**	**ND**	**ND**	**ND**

[1] Fasted Day 14 body weights

Table F-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Body Mass (grams)
Female Rats

Group	Animal ID	Day 0	Day 1	Day 3	Day 7	Day 13	Day 14[1]
Corn Oil Control	21-0467	191	198	203	217	231	221
	21-0468	191	198	206	225	242	231
	21-0471	187	196	198	216	228	220
	21-0472	182	184	194	213	225	220
	21-0481	213	214	227	237	256	246
	21-0482	225	227	242	260	274	264
	Mean	**198.2**	**202.8**	**211.7**	**228.0**	**242.7**	**233.7**
	SD	**16.90**	**15.21**	**18.77**	**17.91**	**19.10**	**17.96**
6.25 mg/kg-d	21-0453	191	197	203	224	247	237
	21-0454	190	186	194	209	217	209
	21-0485	199	208	211	220	228	223
	21-0486	196	208	224	251	279	269
	21-0495	196	206	218	234	236	231
	21-0496	179	186	194	207	236	233
	Mean	**191.8**	**198.5**	**207.3**	**224.2**	**240.5**	**233.7**
	SD	**7.14**	**10.50**	**12.48**	**16.49**	**21.32**	**19.95**
12.5 mg/kg-d	21-0451	191	195	204	222	247	237
	21-0452	179	179	196	207	217	209
	21-0465	188	187	202	217	228	223
	21-0466	190	188	194	212	279	269
	21-0469	207	214	220	228	236	231
	21-0470	204	210	220	231	236	233
	Mean	**193.2**	**195.5**	**206.0**	**219.5**	**240.5**	**233.7**
	SD	**10.50**	**13.81**	**11.45**	**9.27**	**21.32**	**19.95**
25 mg/kg-d	21-0455	192	203	210	228	238	229
	21-0456	217	221	226	243	263	257
	21-0459	199	208	213	230	245	236
	21-0460	174	188	198	209	217	210
	21-0461	189	194	200	211	226	221
	21-0462	175	179	184	192	209	200
	Mean	**191.0**	**198.8**	**205.2**	**218.8**	**233.0**	**225.5**
	SD	**16.06**	**15.01**	**14.46**	**18.28**	**19.75**	**20.13**
50 mg/kg-d	21-0463	175	187	195	210	223	214
	21-0464	195	194	212	225	234	227
	21-0473	206	208	217	228	244	238
	21-0474	221	227	233	248	267	258
	21-0487	198	206	219	241	254	251
	21-0488	195	199	209	224	231	227
	Mean	**198.3**	**203.5**	**214.2**	**229.3**	**242.2**	**235.8**
	SD	**15.10**	**13.87**	**12.53**	**13.47**	**16.24**	**16.49**
100 mg/kg-d	21-0449	166	173	182	191	197	188
	21-0450	200	208	214	217	227	215
	21-0483	198	196	208	200	215	203
	21-0484	211	213	209	225	235	225
	21-0493	216	225	227	246	253	239
	21-0494	215	219	226	217	219	209
	Mean	**201.0**	**205.7**	**211.0**	**216.0**	**224.3**	**213.2**
	SD	**18.74**	**18.82**	**16.40**	**19.31**	**19.00**	**17.69**
200 mg/kg-d	21-0475	190	200	192	(f)	(f)	(f)
	21-0476	200	202	191	198	(f)	(f)
	21-0479	195	200	195	(f)	(f)	(f)
	21-0480	216	211	200	189	(f)	(f)
	21-0491	209	208	198	(f)	(f)	(f)
	21-0492	181	181	171	(f)	(f)	(f)
	Mean	**198.5**	**200.3**	**191.2**	**193.5**	**ND**	**ND**
	SD	**12.72**	**10.48**	**10.46**	**6.36**	**ND**	**ND**
400 mg/kg-d	21-0457	205	199	190	(f)	(f)	(f)
	21-0458	170	174	167	(f)	(f)	(f)
	21-0477	206	201	197	(f)	(f)	(f)
	21-0478	209	205	205	(f)	(f)	(f)
	21-0489	206	211	205	(f)	(f)	(f)
	21-0490	204	206	205	(f)	(f)	(f)
	Mean	**200.0**	**199.3**	**194.8**	**ND**	**ND**	**ND**
	SD	**14.79**	**13.09**	**14.92**	**ND**	**ND**	**ND**

[1] Fasted Day 14 body weights

Table F-3
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Summary of 14-Day Body Mass (grams)
Male Rats

Group		Day 0	Day 1	Day 3	Day 7	Day 13	Day 14[1]
Corn Oil Control	Mean	246.8	253.3	264.3	289.0	321.2	310.8
	S.D.	20.05	18.99	17.86	20.47	21.87	20.44
	N	6	6	6	6	6	6
6.25 mg/kg-d	Mean	241.7	246.8	258.2	289.3	318.2	310.3
	S.D.	23.54	23.46	19.52	19.56	18.13	18.63
	N	6	6	6	6	6	6
12.5 mg/kg-d	Mean	250.8	258.3	274.2	301.5	338.2	329.0
	S.D.	30.90	31.58	33.18	31.80	32.33	30.82
	N	6	6	6	6	6	6
25 mg/kg-d	Mean	254.2	258.2	270.8	300.5	331.3	322.3
	S.D.	29.06	28.70	29.55	28.86	34.03	32.30
	N	6	6	6	6	6	6
50 mg/kg-d	Mean	255.3	258.8	271.7	296.0	326.5	316.5
	S.D.	29.96	27.27	29.98	29.85	29.95	28.60
	N	6	6	6	6	6	6
100 mg/kg-d	Mean	259.2	260.3	264.0	263.8	289.2	278.0
	S.D.	28.32	26.99	25.50	18.17	15.97	13.87
	N	6	6	6	6	6	6
200 mg/kg-d	Mean	267.2	262.5	250.0	223.7	ND	ND
	S.D.	32.54	29.08	30.82	37.07	ND	ND
	N	6	6	6	3	0	0
400 mg/kg-d	Mean	249.8	244.2	227.2	ND	ND	ND
	S.D.	19.26	18.88	21.34	ND	ND	ND
	N	6	6	6	0	0	0

[1] Fasted day 14 body mass

Table F-4
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Summary of 14-Day Body Mass (grams)
Female Rats

Group		Day 0	Day 1	Day 3	Day 7	Day 13	Day 14[1]
Corn Oil Control	Mean	198.2	202.8	211.7	228.0	242.7	233.7
	S.D.	16.90	15.21	18.77	17.91	19.10	17.96
	N	6	6	6	6	6	6
6.25 mg/kg-d	Mean	191.8	198.5	207.3	224.2	240.5	233.7
	S.D.	7.14	10.50	12.48	16.49	21.32	19.95
	N	6	6	6	6	6	6
12.5 mg/kg-d	Mean	193.2	195.5	206.0	219.5	240.5	233.7
	S.D.	10.50	13.81	11.45	9.27	21.32	19.95
	N	6	6	6	6	6	6
25 mg/kg-d	Mean	191.0	198.8	205.2	218.8	233.0	225.5
	S.D.	16.06	15.01	14.46	18.28	19.75	20.13
	N	6	6	6	6	6	6
50 mg/kg-d	Mean	198.3	203.5	214.2	229.3	242.2	235.8
	S.D.	15.10	13.87	12.53	13.47	16.24	16.49
	N	6	6	6	6	6	6
100 mg/kg-d	Mean	201.0	205.7	211.0	216.0	224.3	213.2
	S.D.	18.74	18.82	16.40	19.31	19.00	17.69
	N	6	6	6	6	6	6
200 mg/kg-d	Mean	198.5	200.3	191.2	193.5	ND	ND
	S.D.	12.72	10.48	10.46	6.36	ND	ND
	N	6	6	6	2	0	0
400 mg/kg-d	Mean	200.0	199.3	194.8	ND	ND	ND
	S.D.	14.79	13.09	14.92	ND	ND	ND
	N	6	6	6	0	0	0

[1] Fasted day 14 body mass

Appendix G

Subacute Individual and Summary of Body Mass Change

Abbreviations:

mg/kg-d: milligrams per kilogram per day
(f): animal died on study
ND: no data
SD: standard deviation

Table G-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Body Mass Change (grams)
Male Rats

Group	Animal ID	Days 0-1	Days 1-3	Days 3-7	Days 7-13	Final
Corn Oil Control	21-0391	7	8	26	33	74
	21-0392	9	7	17	28	61
	21-0431	6	14	23	31	74
	21-0432	8	16	31	45	100
	21-0435	5	12	27	28	72
	21-0436	4	9	24	28	65
	Mean	**6.5**	**11.0**	**24.7**	**32.2**	**74.3**
	SD	**1.87**	**3.58**	**4.68**	**6.62**	**13.63**
6.25 mg/kg-d	21-0405	11	7	34	35	87
	21-0406	4	4	22	27	57
	21-0415	8	12	24	35	79
	21-0416	8	13	27	35	83
	21-0445	2	16	43	20	81
	21-0446	-2	16	37	21	72
	Mean	**5.2**	**11.3**	**31.2**	**28.8**	**76.5**
	SD	**4.75**	**4.89**	**8.18**	**7.17**	**10.77**
12.5 mg/kg-d	21-0393	6	19	24	37	86
	21-0394	5	14	30	41	90
	21-0441	9	19	27	33	88
	21-0442	7	14	23	43	87
	21-0447	11	18	29	37	95
	21-0448	7	11	31	29	78
	Mean	**7.5**	**15.8**	**27.3**	**36.7**	**87.3**
	SD	**2.17**	**3.31**	**3.27**	**5.13**	**5.57**
25 mg/kg-d	21-0395	2	11	24	35	72
	21-0396	5	14	28	35	82
	21-0397	5	13	32	31	81
	21-0398	3	13	26	30	72
	21-0409	5	16	39	34	94
	21-0410	4	9	29	20	62
	Mean	**4.0**	**12.7**	**29.7**	**30.8**	**77.2**
	SD	**1.26**	**2.42**	**5.32**	**5.71**	**11.00**
50 mg/kg-d	21-0407	6	8	27	28	69
	21-0408	2	13	21	27	63
	21-0413	5	11	20	33	69
	21-0414	8	13	29	34	84
	21-0429	-1	18	19	29	65
	21-0430	1	14	30	32	77
	Mean	**3.5**	**12.8**	**24.3**	**30.5**	**71.2**
	SD	**3.39**	**3.31**	**4.89**	**2.88**	**7.91**
100 mg/kg-d	21-0421	-2	2	-21	27	6
	21-0422	1	8	-2	27	34
	21-0433	0	4	0	38	42
	21-0434	3	1	0	12	16
	21-0443	2	1	12	18	33
	21-0444	3	6	10	30	49
	Mean	**1.2**	**3.7**	**-0.2**	**25.3**	**30.0**
	SD	**1.94**	**2.88**	**11.74**	**9.16**	**16.14**
200 mg/kg-d	21-0403	3	-9	-34	(f)	-40
	21-0404	-7	-14	(f)	(f)	-21
	21-0423	-9	-21	(f)	(f)	-30
	21-0424	-1	-10	(f)	(f)	-11
	21-0427	-7	-2	-55	(f)	-64
	21-0428	-7	-19	-21	(f)	-47
	Mean	**-4.7**	**-12.5**	**-36.7**	**ND**	**-35.5**
	SD	**4.63**	**7.01**	**17.16**	**ND**	**19.00**
400 mg/kg-d	21-0399	-7	-9	(f)	(f)	-16
	21-0400	-8	-12	(f)	(f)	-20
	21-0401	-11	-15	(f)	(f)	-26
	21-0402	-4	-22	(f)	(f)	-26
	21-0419	-6	-15	(f)	(f)	-21
	21-0420	2	-29	(f)	(f)	-27
	Mean	**-5.7**	**-17.0**	**ND**	**ND**	**-22.7**
	SD	**4.41**	**7.29**	**ND**	**ND**	**4.37**

Table G-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Body Mass Change (grams)
Female Rats

Group	Animal ID	Days 0-1	Days 1-3	Days 3-7	Days 7-13
	21-0467	7	5	14	14
Corn Oil	21-0468	7	8	19	17
Control	21-0471	9	2	18	12
	21-0472	2	10	19	12
	21-0481	1	13	10	19
	21-0482	2	15	18	14
	Mean	**4.7**	**8.8**	**16.3**	**14.7**
	SD	**3.39**	**4.88**	**3.61**	**2.80**
	21-0453	6	6	21	23
6.25 mg/kg-d	21-0454	-4	8	15	8
	21-0485	9	3	9	8
	21-0486	12	16	27	28
	21-0495	10	12	16	2
	21-0496	7	8	13	29
	Mean	**6.7**	**8.8**	**16.8**	**16.3**
	SD	**5.65**	**4.58**	**6.34**	**11.71**
	21-0451	4	9	18	25
12.5 mg/kg-d	21-0452	0	17	11	10
	21-0465	-1	15	15	11
	21-0466	-2	6	18	67
	21-0469	7	6	8	8
	21-0470	6	10	11	5
	Mean	**2.3**	**10.5**	**13.5**	**21.0**
	SD	**3.83**	**4.59**	**4.14**	**23.57**
	21-0455	11	7	18	10
25 mg/kg-d	21-0456	4	5	17	20
	21-0459	9	5	17	15
	21-0460	14	10	11	8
	21-0461	5	6	11	15
	21-0462	4	5	8	17
	Mean	**7.8**	**6.3**	**13.7**	**14.2**
	SD	**4.17**	**1.97**	**4.18**	**4.45**
	21-0463	12	8	15	13
50 mg/kg-d	21-0464	-1	18	13	9
	21-0473	2	9	11	16
	21-0474	6	6	15	19
	21-0487	8	13	22	13
	21-0488	4	10	15	7
	Mean	**5.2**	**10.7**	**15.2**	**12.8**
	SD	**4.58**	**4.27**	**3.71**	**4.40**
	21-0449	7	9	9	6
100 mg/kg-d	21-0450	8	6	3	10
	21-0483	-2	12	-8	15
	21-0484	2	-4	16	10
	21-0493	9	2	19	7
	21-0494	4	7	-9	2
	Mean	**4.7**	**5.3**	**5.0**	**8.3**
	SD	**4.18**	**5.65**	**11.85**	**4.41**
	21-0475	10	-8	(f)	(f)
200 mg/kg-d	21-0476	2	-11	7	(f)
	21-0479	5	-5	(f)	(f)
	21-0480	-5	-11	-11	(f)
	21-0491	-1	-10	(f)	(f)
	21-0492	0	-10	(f)	(f)
	Mean	**1.8**	**-9.2**	**-2.0**	**ND**
	SD	**5.19**	**2.32**	**12.73**	**ND**
	21-0457	-6	-9	(f)	(f)
400 mg/kg-d	21-0458	4	-7	(f)	(f)
	21-0477	-5	-4	(f)	(f)
	21-0478	-4	0	(f)	(f)
	21-0489	5	-6	(f)	(f)
	21-0490	2	-1	(f)	(f)
	Mean	**-0.7**	**-4.5**	**ND**	**ND**
	SD	**4.89**	**3.51**	**ND**	**ND**

Table G-3
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Summary of 14-Day Body Mass Change (grams)
Male Rats

Group		Days 0-1	Days 1-3	Days 3-7	Days 7-13	Final
Corn Oil Control	Mean	6.5	11.0	24.7	32.2	74.3
	S.D.	1.87	3.58	4.68	6.62	13.63
	N	6	6	6	6	6
6.25 mg/kg-d	Mean	5.2	11.3	31.2	28.8	76.5
	S.D.	4.75	4.89	8.18	7.17	10.77
	N	6	6	6	6	6
12.5 mg/kg-d	Mean	7.5	15.8	27.3	36.7	87.3
	S.D.	2.17	3.31	3.27	5.13	5.57
	N	6	6	6	6	6
25 mg/kg-d	Mean	4.0	12.7	29.7	30.8	77.2
	S.D.	1.26	2.42	5.32	5.71	11.00
	N	6	6	6	6	6
50 mg/kg-d	Mean	3.5	12.8	24.3	30.5	71.2
	S.D.	3.39	3.31	4.89	2.88	7.91
	N	6	6	6	6	6
100 mg/kg-d	Mean	1.2*	3.7	-0.2	25.3	30.0*
	S.D.	1.94	2.88	11.74	9.16	16.14
	N	6	6	6	6	6
200 mg/kg-d	Mean	-4.7*	-12.5*	-36.7a	ND	-35.5a
	S.D.	4.63	7.01	17.16	ND	19.00
	N	6	6	3	0	6
400 mg/kg-d	Mean	-5.7*	-17.0*	ND	ND	-22.7a
	S.D.	4.41	7.29	ND	ND	4.37
	N	6	6	0	0	6

* $p<0.05$ compared to controls
a = not included in data analysis due to pre-term mortality

Table G-4
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Summary of 14-Day Body Mass Change (grams)
Female Rats

Group		Days 0-1	Days 1-3	Days 3-7	Days 7-13	Final
Corn Oil Control	Mean	4.7	8.8	16.3	14.7	44.5
	S.D.	3.39	4.88	3.61	2.80	4.46
	N	6	6	6	6	6
6.25 mg/kg-d	Mean	6.7	8.8	16.8	16.3	48.7
	S.D.	5.65	4.58	6.34	11.71	21.13
	N	6	6	6	6	6
12.5 mg/kg-d	Mean	2.3	10.5	13.5	21.0	47.3
	S.D.	3.83	4.59	4.14	23.57	22.46
	N	6	6	6	6	6
25 mg/kg-d	Mean	7.8	6.3	13.7	14.2	42.0
	S.D.	4.17	1.97	4.18	4.45	5.25
	N	6	6	6	6	6
50 mg/kg-d	Mean	5.2	10.7	15.2	12.8	43.8
	S.D.	4.58	4.27	3.71	4.40	7.60
	N	6	6	6	6	6
100 mg/kg-d	Mean	4.7	5.3	5.0	8.3	23.3*
	S.D.	4.18	5.65	11.85	4.41	11.60
	N	6	6	6	6	6
200 mg/kg-d	Mean	1.8	-9.2*	-2.0	ND	-8.0a
	S.D.	5.19	2.32	12.73	ND	10.71
	N	6	6	2	0	6
400 mg/kg-d	Mean	-0.7	-4.5*	ND	ND	-5.2a
	S.D.	4.89	3.51	ND	ND	5.88
	N	6	6	0	0	6

* $p<0.05$ compared to controls
a = not included in data analysis due to pre-term mortality

Appendix H

Subacute Individual and Summary of Paired Food Consumption

Abbreviations:

mg/kg-d: milligrams per kilogram per day
(f): animal died on study
ND: no data
SD: standard deviation

Table H-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Paired Food Consumption (grams)
Male Rats

Group	Animal ID	Days 0-7	Days 7-13	Final
Corn Oil Control	21-0391/21-0392	267	236	503
	21-0431/21-0432	330	285	615
	21-0435/21-0436	294	249	543
	Mean	**297.0**	**256.7**	**553.7**
	SD	**31.61**	**25.38**	**56.76**
6.25 mg/kg-d	21-0405/21-0406	302	259	561
	21-0415/21-0416	309	254	563
	21-0445/21-0446	329	260	589
	Mean	**313.3**	**257.7**	**571.0**
	SD	**14.01**	**3.21**	**15.62**
12.5 mg/kg-d	21-0393/21-0394	317	279	596
	21-0441/21-0442	330	302	632
	21-0447/21-0448	327	284	611
	Mean	**324.7**	**288.3**	**613.0**
	SD	**6.81**	**12.10**	**18.08**
25 mg/kg-d	21-0395/21-0396	295	274	569
	21-0397/21-0398	297	260	557
	21-0409/21-0410	303	261	564
	Mean	**298.3**	**265.0**	**563.3**
	SD	**4.16**	**7.81**	**6.03**
50 mg/kg-d	21-0407/21-0408	283	249	532
	21-0413/21-0414	293	274	567
	21-0429/21-0430	299	254	553
	Mean	**291.7**	**259.0**	**550.7**
	SD	**8.08**	**13.23**	**17.62**
100 mg/kg	21-0421/21-0422	176	183	359
	21-0433/21-0434	170	205	375
	21-0443/21-0444	232	327	559
	Mean	**192.7**	**238.3**	**431.0**
	SD	**34.20**	**77.57**	**111.14**
200 mg/kg-d	21-0403/21-0404	(f)	(f)	(f)
	21-0423/21-0424	(f)	(f)	(f)
	21-0427/21-0428	71	(f)	(f)
	Mean	**71.0**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**
400 mg/kg-d	21-0399/21-0400	(f)	(f)	(f)
	21-0401/21-0402	(f)	(f)	(f)
	21-0419/21-0420	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**

Table H-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Paired Food Consumption (grams)
Female Rats

Group	Animal ID	Days 0-7	Days 7-13	Final
Corn Oil Control	21-0467/21-0468	247	213	460
	21-0471/21-0472	234	203	437
	21-0481/21-0482	270	226	496
	Mean	**250.3**	**214.0**	**464.3**
	SD	**18.23**	**11.53**	**29.74**
6.25 mg/kg-d	21-0453/21-0454	228	186	414
	21-0485/21-0486	261	223	484
	21-0495/21-0496	249	206	455
	Mean	**246.0**	**205.0**	**451.0**
	SD	**16.70**	**18.52**	**35.17**
12.5 mg/kg-d	21-0451/21-0452	229	196	425
	21-0465/21-0466	221	187	408
	21-0469/21-0470	253	208	461
	Mean	**234.3**	**197.0**	**431.3**
	SD	**16.65**	**10.54**	**27.06**
25 mg/kg-d	21-0455/21-0456	265	228	493
	21-0459/21-0460	253	196	449
	21-0461/21-0462	222	190	412
	Mean	**246.7**	**204.7**	**451.3**
	SD	**22.19**	**20.43**	**40.55**
50 mg/kg-d	21-0463/21-0464	238	200	438
	21-0473/21-0474	256	225	481
	21-0487/21-0488	256	222	478
	Mean	**250.0**	**215.7**	**465.7**
	SD	**10.39**	**13.65**	**24.01**
100 mg/kg-d	21-0449/21-0450	203	180	383
	21-0483/21-0484	191	187	378
	21-0493/21-0494	238	190	428
	Mean	**210.7**	**185.7**	**396.3**
	SD	**24.42**	**5.13**	**27.54**
200 mg/kg-d	21-0475/21-0476	(f)	(f)	(f)
	21-0479/21-0480	(f)	(f)	(f)
	21-0491/21-0492	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**
400 mg/kg-d	21-0457/21-0458	(f)	(f)	(f)
	21-0477/21-0478	(f)	(f)	(f)
	21-0489/21-0490	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**

Table H-3
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Summary of 14-Day Paired Food Consumption (grams)
Male Rats

Group		Days 0-7	Days 7-13	Final
Corn Oil Control	Mean	297.0	256.7	553.7
	S.D.	31.61	25.38	56.76
	N	6	6	6
6.25 mg/kg-d	Mean	313.3	257.7	571.0
	S.D.	14.01	3.21	15.62
	N	6	6	6
12.5 mg/kg-d	Mean	324.7	288.3	613.0
	S.D.	6.81	12.10	18.08
	N	6	6	6
25 mg/kg-d	Mean	298.3	265.0	563.3
	S.D.	4.16	7.81	6.03
	N	6	6	6
50 mg/kg-d	Mean	291.7	259.0	550.7
	S.D.	8.08	13.23	17.62
	N	6	6	6
100 mg/kg-d	Mean	192.7	238.3	431.0
	S.D.	34.20	77.57	111.14
	N	6	6	6
200 mg/kg-d	Mean	71.0a	NDa	NDa
	S.D.	ND	ND	ND
	N	1	0	0
400 mg/kg-d	Mean	NDa	NDa	NDa
	S.D.	ND	ND	ND
	N	0	0	0

a = not included in data analysis due to pre-term mortality

Table H-4
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Summary of 14-Day Paired Food Consumption (grams)
Female Rats

Group		Days 0-7	Days 7-13	Final
Corn Oil Control	Mean	250.3	214.0	464.3
	S.D.	18.23	11.53	29.74
	N	6	6	6
6.25 mg/kg-d	Mean	246.0	205.0	451.0
	S.D.	16.70	18.52	35.17
	N	6	6	6
12.5 mg/kg-d	Mean	234.3	197.0	431.3
	S.D.	16.65	10.54	27.06
	N	6	6	6
25 mg/kg-d	Mean	246.7	204.7	451.3
	S.D.	22.19	20.43	40.55
	N	6	6	6
50 mg/kg-d	Mean	250.0	215.7	465.7
	S.D.	10.39	13.65	24.01
	N	6	6	6
100 mg/kg-d	Mean	210.7	185.7	396.3
	S.D.	24.42	5.13	27.54
	N	6	6	6
200 mg/kg-d	Mean	NDa	NDa	NDa
	S.D.	ND	ND	ND
	N	0	0	0
400 mg/kg-d	Mean	NDa	NDa	NDa
	S.D.	ND	ND	ND
	N	0	0	0

a = not included in data analysis due to pre-term mortality

Appendix I

Subacute Individual and Summary of Hematology

Abbreviations:

mg/kg-d: milligrams per kilogram per day
(f): animal died on study
ND: no data
K/uL: thousands per microliter
M/uL: million per microliter
g/dL: grams per deciliter
%: percent
fL: femtoliter
pg: picogram
WBC: white blood cell
RBC: red blood cell
HGB: hemoglobin
HCT: hematocrit
MCV: mean corpuscular volume
MCH: mean corpuscular hemoglobin
MCHC: mean corpuscular hemoglobin concentration
PLT: platelet
RDW-SD: red blood cell distribution width-standard deviation
RDW-CV: red blood cell distribution width-coefficient of variation
MPV: mean platelet volume
NRBC: nucleated red blood cells
NEUT: neutrophils
LYMPH: lymphocytes
MONO: monophils
EO: eosinophils
BASO: basophils
RET: reticulocytes
IRF: immature red blood cell fraction
RET-He: reticulocyte hemoglobin concentration
PLT-F: platelet count fluorescent
SD: standard deviation

Table I-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Hematology
Male Rats

Group	Animal ID	WBC (K/uL)	RBC (M/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT (K/uL)	RDW-SD (fL)	RDW-CV (%)	MPV (fL)	NRBC (K/uL)	NRBC (%)	NEUT (K/uL)	NEUT (%)	LYMPH (K/uL)	LYMPH (%)	MONO (K/uL)	MONO (%)	EO (K/uL)	EO (%)	BASO (K/uL)	BASO (%)	RET (K/uL)	RET (%)	IRF (%)	RET-He (pg)	PLT-F (K/uL)
Corn Oil Control	21-0391	14.33	8.38	16.3	49.1	58.6	19.5	33.2	1146	26.0	13.8	8.4	0.00	0.0	1.57	10.9	11.76	82.1	0.94	6.6	0.02	0.1	0.04	0.3	4.82	0.4039	59.3	21.7	1146
	21-0392	14.40	10.51	20.0	59.6	56.7	19.0	33.6	1435	24.6	16.7	7.6	0.05	0.3	2.00	13.8	11.33	78.7	0.91	6.3	0.08	0.6	0.08	0.6	3.87	0.4067	52.6	21.2	1435
	21-0431	4.19	8.06	15.3	46.6	57.8	19.0	32.8	1144	25.3	13.1	7.7	0.00	0.0	0.74	17.7	3.23	77.1	0.20	4.8	0.01	0.2	0.01	0.2	3.98	0.3208	55.0	21.0	1144
	21-0432	2.38	7.69	15.4	46.9	61.0	20.0	32.8	1417	27.8	13.0	8.3	0.00	0.0	0.33	13.9	1.95	81.9	0.09	3.8	0.01	0.4	0.00	0.0	4.88	0.3753	65.5	21.9	1417
	21-0435	12.85	8.36	17.0	51.5	61.6	20.3	33.0	1250	26.5	13.1	8.1	0.00	0.0	1.01	7.9	11.00	85.6	0.77	6.0	0.03	0.2	0.04	0.3	4.52	0.3779	57.2	22.3	1250
	21-0436	13.30	7.67	16.4	49.1	64.0	21.4	33.4	1192	26.3	11.5	7.5	0.00	0.0	2.28	17.2	10.24	77.0	0.71	5.3	0.03	0.2	0.04	0.3	3.99	0.3060	53.1	23.1	1192
	Mean	**10.24**	**8.45**	**16.7**	**50.5**	**60.0**	**19.9**	**33.1**	**1264**	**26.1**	**13.5**	**7.9**	**0.01**	**0.1**	**1.32**	**13.6**	**8.25**	**80.4**	**0.60**	**5.5**	**0.03**	**0.3**	**0.04**	**0.3**	**4.34**	**0.3651**	**57.1**	**21.9**	**1264**
	SD	**5.451**	**1.058**	**1.72**	**4.81**	**2.73**	**0.92**	**0.33**	**131.4**	**1.09**	**1.73**	**0.38**	**0.020**	**0.12**	**0.756**	**3.73**	**4.432**	**3.39**	**0.367**	**1.05**	**0.026**	**0.183**	**0.028**	**0.194**	**0.453**	**0.04233**	**4.82**	**0.77**	**131.4**
6.25 mg/kg-d	21-0405	14.99	7.82	15.8	47.4	60.6	20.2	33.3	1435	25.7	11.9	7.4	0.00	0.0	0.99	6.5	13.29	88.7	0.63	4.2	0.04	0.3	0.04	0.3	3.73	0.2917	56.7	21.8	1435
	21-0406	5.81	7.84	16.3	46.3	59.1	20.8	35.2	1039	25.2	12.3	8.1	0.02	0.3	1.11	19.1	4.51	77.6	0.17	2.9	0.01	0.2	0.01	0.2	3.62	0.2838	55.0	23.3	1039
	21-0415	8.77	7.79	16.0	48.4	62.1	20.5	33.1	130	28.6	13.2	8.0	0.00	0.0	1.28	14.7	6.95	79.2	0.50	5.7	0.02	0.2	0.02	0.2	5.53	0.4308	59.5	23.2	130
	21-0416	4.02	9.24	17.4	51.8	56.1	18.8	33.6	799	24.4	15.1	8.0	0.03	0.7	0.74	18.5	3.00	74.6	0.25	6.2	0.02	0.5	0.01	0.2	4.20	0.3881	55.1	21.2	799
	21-0445	7.28	8.42	16.6	50.8	60.3	19.7	32.7	1215	27.3	13.8	8.3	0.00	0.0	0.61	8.4	6.14	84.3	0.47	6.5	0.03	0.4	0.03	0.4	4.09	0.3444	53.2	21.6	1215
	21-0446	13.07	8.60	16.5	50.6	58.8	19.2	32.6	1368	26.9	13.8	8.3	0.03	0.2	1.02	7.8	10.96	83.9	1.03	7.9	0.03	0.2	0.03	0.2	4.03	0.3466	56.8	21.4	1368
	Mean	**8.99**	**8.29**	**16.4**	**49.2**	**59.5**	**19.9**	**33.4**	**998**	**26.4**	**13.4**	**8.0**	**0.01**	**0.2**	**0.96**	**12.5**	**7.48**	**81.4**	**0.51**	**5.6**	**0.03**	**0.3**	**0.02**	**0.3**	**4.20**	**0.3476**	**56.1**	**22.1**	**998**
	SD	**4.253**	**0.581**	**0.56**	**2.17**	**2.04**	**0.77**	**0.95**	**483.7**	**1.54**	**1.16**	**0.33**	**0.015**	**0.28**	**0.245**	**5.64**	**3.920**	**5.17**	**0.306**	**1.77**	**0.010**	**0.126**	**0.012**	**0.084**	**0.688**	**0.05616**	**2.15**	**0.93**	**483.7**
12.5 mg/kg-d	21-0393	11.34	7.92	15.7	47.8	60.4	19.8	32.8	1348	25.8	12.2	7.9	0.02	0.2	2.10	18.5	8.65	76.3	0.50	4.4	0.05	0.4	0.04	0.4	4.77	0.3778	57.5	21.7	1348
	21-0394	20.01	7.90	16.4	49.2	62.3	20.8	33.3	1069	27.8	12.8	7.7	0.05	0.2	5.13	25.7	13.50	67.5	1.22	6.1	0.09	0.4	0.07	0.3	5.50	0.4345	62.0	22.3	1069
	21-0441	9.38	8.19	16.3	49.0	59.8	19.9	33.3	1489	25.8	13.0	7.9	0.00	0.0	1.67	17.8	7.26	77.4	0.38	4.1	0.05	0.5	0.02	0.2	3.93	0.3219	57.6	22.3	1489
	21-0442	7.13	7.75	15.5	45.3	58.5	20.0	34.2	1152	25.2	12.1	8.2	0.00	0.0	1.16	16.3	5.46	76.6	0.45	6.3	0.03	0.4	0.03	0.4	3.97	0.3077	56.6	21.9	1152
	21-0447	10.19	9.43	17.9	54.3	57.6	19.0	33.0	1730	25.4	15.6	7.8	0.00	0.0	1.28	12.5	8.13	79.8	0.71	7.0	0.03	0.3	0.04	0.4	3.96	0.3734	52.4	20.6	1730
	21-0448	8.99	8.20	16.1	49.2	60.0	19.6	32.7	1336	26.1	13.0	8.3	0.03	0.3	0.56	6.3	7.96	88.5	0.41	4.6	0.03	0.3	0.03	0.3	3.84	0.3149	52.9	20.9	1336
	Mean	**11.17**	**8.23**	**16.3**	**49.1**	**59.8**	**19.9**	**33.2**	**1354**	**26.0**	**13.1**	**8.0**	**0.02**	**0.1**	**1.98**	**16.2**	**8.49**	**77.7**	**0.61**	**5.4**	**0.05**	**0.4**	**0.04**	**0.3**	**4.33**	**0.3550**	**56.5**	**21.6**	**1354**
	SD	**4.548**	**0.613**	**0.85**	**2.94**	**1.62**	**0.59**	**0.54**	**237.5**	**0.93**	**1.28**	**0.23**	**0.021**	**0.13**	**1.626**	**6.48**	**2.692**	**6.76**	**0.320**	**1.20**	**0.023**	**0.075**	**0.017**	**0.082**	**0.668**	**0.04923**	**3.53**	**0.72**	**237.5**
25 mg/kg-d	21-0395	12.85	8.16	15.7	46.9	57.5	19.2	33.5	1287	25.7	13.2	7.6	0.02	0.2	1.61	12.6	10.35	80.5	0.80	6.2	0.04	0.3	0.05	0.4	4.40	0.3590	57.7	20.6	1287
	21-0396	13.41	8.65	16.4	49.4	57.1	19.0	33.2	1122	25.3	14.3	8.1	0.02	0.1	2.52	18.8	9.92	74.0	0.89	6.6	0.03	0.2	0.05	0.4	4.09	0.3538	57.6	21.1	1122
	21-0397	11.19	8.46	17.3	51.3	60.6	20.4	33.7	1486	25.7	12.8	7.4	0.03	0.3	1.95	17.4	8.45	75.5	0.72	6.4	0.04	0.4	0.03	0.3	5.01	0.4238	56.2	22.8	1486
	21-0398	10.09	8.17	16.5	49.1	60.1	20.2	33.6	1190	27.3	13.6	8.0	0.00	0.0	0.93	9.2	8.59	85.1	0.53	5.3	0.02	0.2	0.02	0.2	4.24	0.3464	57.1	22.1	1190
	21-0409	17.81	7.90	16.0	49.3	62.4	20.3	32.5	1319	28.9	13.2	8.5	0.05	0.3	2.48	14.0	14.27	80.1	0.93	5.2	0.09	0.5	0.04	0.2	4.85	0.3832	62.3	21.1	1319
	21-0410	7.72	7.92	15.6	47.7	60.2	19.7	32.7	1298	26.6	13.0	8.3	0.02	0.3	1.36	17.6	5.97	77.3	0.33	4.3	0.04	0.5	0.02	0.3	4.02	0.3184	58.3	21.4	1298
	Mean	**12.18**	**8.21**	**16.3**	**49.0**	**59.7**	**19.8**	**33.2**	**1284**	**26.6**	**13.4**	**8.0**	**0.02**	**0.2**	**1.81**	**14.9**	**9.59**	**78.8**	**0.70**	**5.7**	**0.04**	**0.4**	**0.04**	**0.3**	**4.44**	**0.3641**	**58.2**	**21.5**	**1284**
	SD	**3.432**	**0.297**	**0.63**	**1.53**	**2.00**	**0.60**	**0.50**	**124.3**	**1.35**	**0.54**	**0.42**	**0.016**	**0.13**	**0.631**	**3.67**	**2.757**	**4.01**	**0.230**	**0.88**	**0.024**	**0.138**	**0.014**	**0.089**	**0.408**	**0.03595**	**2.13**	**0.80**	**124.3**
50 mg/kg-d	21-0407	18.66	8.20	16.2	47.4	57.8	19.8	34.2	1078	26.8	14.6	7.9	0.03	0.2	1.37	7.3	16.29	87.3	0.95	5.1	0.01	0.1	0.04	0.2	4.45	0.3649	54.1	21.3	1078
	21-0408	12.38	7.65	15.1	45.1	59.0	19.7	33.5	994	26.6	13.0	8.8	0.00	0.0	0.90	7.4	10.54	85.1	0.88	7.1	0.03	0.2	0.03	0.2	3.78	0.2892	56.4	20.8	994
	21-0413	20.05	7.86	15.8	47.4	60.3	20.1	33.3	985	26.4	13.2	8.0	0.05	0.2	4.17	20.9	14.78	73.7	0.99	4.9	0.05	0.2	0.06	0.3	4.48	0.3521	58.9	21.9	985
	21-0414	13.36	8.35	16.9	51.0	61.1	20.2	33.1	1127	26.3	13.3	8.5	0.07	0.5	2.03	15.2	10.30	77.1	0.93	7.0	0.06	0.4	0.04	0.3	5.61	0.4684	59.6	22.3	1127
	21-0429	17.37	7.58	14.5	44.3	58.4	19.1	32.7	1065	25.1	12.2	8.0	0.03	0.2	3.78	21.9	12.81	73.7	0.72	4.1	0.02	0.1	0.04	0.2	4.76	0.3608	59.4	20.9	1065
	21-0430	16.17	8.73	16.7	50.6	58.0	19.1	33.0	952	27.8	15.9	8.2	0.04	0.2	2.20	13.6	12.95	80.1	0.95	5.9	0.03	0.2	0.04	0.2	4.62	0.4033	59.3	20.5	952
	Mean	**16.33**	**8.06**	**15.9**	**47.6**	**59.1**	**19.7**	**33.3**	**1034**	**26.5**	**13.7**	**8.2**	**0.04**	**0.2**	**2.41**	**14.4**	**12.95**	**79.5**	**0.90**	**5.7**	**0.03**	**0.2**	**0.04**	**0.2**	**4.62**	**0.3731**	**58.0**	**21.3**	**1034**
	SD	**2.993**	**0.445**	**0.93**	**2.75**	**1.33**	**0.48**	**0.52**	**66.7**	**0.87**	**1.33**	**0.35**	**0.023**	**0.16**	**1.306**	**6.31**	**2.339**	**5.75**	**0.097**	**1.20**	**0.019**	**0.110**	**0.010**	**0.052**	**0.592**	**0.05949**	**2.23**	**0.69**	**66.7**
100 mg/kg-d	21-0421	27.26	8.13	15.7	46.3	56.9	19.3	33.9	829	28.5	15.6	10.1	0.02	0.1	4.29	15.7	20.55	75.4	2.29	8.4	0.05	0.2	0.08	0.3	3.35	0.2724	59.8	20.1	829
	21-0422	17.55	7.30	13.5	39.6	54.2	18.5	34.1	695	26.1	14.3	8.7	0.03	0.2	5.08	28.9	11.58	66.0	0.86	4.9	0.01	0.1	0.02	0.1	3.32	0.2424	59.1	.19.4	695
	21-0433	23.33	8.05	15.7	47.3	58.8	19.5	33.2	786	28.1	14.8	8.9	0.07	0.3	4.51	19.3	17.50	75.0	1.20	5.1	0.06	0.3	0.06	0.3	4.95	0.3985	60.2	20.5	786
	21-0434	10.72	7.93	15.4	46.2	58.3	19.4	33.3	447	29.4	15.8	9.9	0.00	0.0	0.85	7.9	8.44	78.7	1.34	12.5	0.02	0.2	0.07	0.7	2.25	0.1784	50.1	20.4	447
	21-0443	9.42	6.74	12.7	37.3	55.3	18.8	34.0	505	25.3	13.0	9.0	0.04	0.4	0.80	8.5	7.43	78.9	1.12	11.9	0.03	0.3	0.04	0.4	4.82	0.3249	68.3	21.3	505
	21-0444	11.47	8.28	16.7	49.9	60.3	20.2	33.5	799	32.7	17.1	9.7	0.10	0.9	1.96	17.1	7.93	69.1	1.50	13.1	0.01	0.1	0.07	0.6	5.92	0.4902	62.9	20.3	799
	Mean	**16.63**	**7.74**	**15.0**	**44.4**	**57.3**	**19.3**	**33.7**	**677**	**28.4**	**15.1**	**9.4**	**0.04**	**0.3**	**2.92**	**16.2**	**12.24**	**73.9**	**1.39**	**9.3**	**0.03**	**0.2**	**0.06**	**0.4**	**4.10**	**0.3178**	**60.1**	**20.5**	**677**
	SD	**7.379**	**0.595**	**1.52**	**4.88**	**2.28**	**0.59**	**0.38**	**162.9**	**2.63**	**1.41**	**0.59**	**0.036**	**0.32**	**1.938**	**7.75**	**5.537**	**5.23**	**0.493**	**3.72**	**0.021**	**0.089**	**0.023**	**0.219**	**1.353**	**0.11266**	**5.94**	**0.46**	**162.9**
200 mg/kg-d	21-0403	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0404	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0423	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0424	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0427	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0428	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
400 mg/kg	21-0399	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0400	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0401	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0402	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0419	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0420	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**

Table I-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Hematology
Female Rats

Group	Animal ID	WBC (K/uL)	RBC (M/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT (K/uL)	RDW-SD (fL)	RDW-CV (%)	MPV (fL)	NRBC (K/uL)	NRBC (%)	NEUT (K/uL)	NEUT (%)	LYMPH (K/uL)	LYMPH (%)	MONO (K/uL)	MONO (%)	EO (K/uL)	EO (%)	BASO (K/uL)	BASO (%)	RET (K/uL)	RET (%)	IRF (%)	RET-He (pg)	PLT-F (K/uL)
	21-0467	9.18	9.53	18.5	55.2	57.9	19.4	33.5	1786	22.9	13.4	7.7	0.00	0.0	0.52	5.7	7.99	87.0	0.56	6.1	0.08	0.9	0.03	0.3	3.17	0.3021	40.1	22.4	1786
Corn Oil	21-0468	5.93	7.58	16.1	47.2	62.3	21.2	34.1	1004	23.8	10.6	8.5	0.00	0.0	0.37	6.1	5.27	88.9	0.27	4.6	0.01	0.2	0.01	0.2	3.05	0.2312	49.0	23.4	1004
Control	21-0471	9.84	9.53	18.8	55.3	58.0	19.7	34.0	1516	22.6	13.2	7.7	0.00	0.0	0.77	7.8	7.85	79.8	1.10	11.2	0.08	0.8	0.04	0.4	2.79	0.2659	41.3	22.3	1516
	21-0472	4.22	8.49	17.4	51.3	60.4	20.5	33.9	1239	23.6	11.9	7.8	0.00	0.0	0.40	9.4	3.35	79.4	0.43	10.2	0.02	0.5	0.02	0.5	3.78	0.3209	50.4	23.3	1239
	21-0481	11.71	9.43	19.4	57.2	60.7	20.6	33.9	1675	24.1	13.3	7.5	0.02	0.2	0.85	7.3	10.25	87.5	0.52	4.4	0.07	0.6	0.02	0.2	3.80	0.3583	46.6	23.5	1675
	21-0482	10.67	8.25	17.7	50.7	61.5	21.5	34.9	1222	24.3	11.5	8.4	0.00	0.0	0.24	2.2	9.70	90.9	0.66	6.2	0.04	0.4	0.03	0.3	3.63	0.2995	54.4	24.6	1222
	Mean	**8.59**	**8.80**	**18.0**	**52.8**	**60.1**	**20.5**	**34.1**	**1407**	**23.6**	**12.3**	**7.9**	**0.00**	**0.0**	**0.53**	**6.4**	**7.40**	**85.6**	**0.59**	**7.1**	**0.05**	**0.6**	**0.03**	**0.3**	**3.37**	**0.2963**	**47.0**	**23.3**	**1407**
	SD	**2.903**	**0.818**	**1.18**	**3.73**	**1.82**	**0.82**	**0.46**	**300.7**	**0.67**	**1.16**	**0.41**	**0.008**	**0.08**	**0.239**	**2.45**	**2.642**	**4.83**	**0.282**	**2.89**	**0.031**	**0.258**	**0.010**	**0.117**	**0.424**	**0.04394**	**5.49**	**0.84**	**300.7**
	21-0453	9.12	9.59	19.9	58.6	61.1	20.8	34.0	1526	24.7	13.9	8.0	0.02	0.2	0.55	6.1	8.12	89.0	0.40	4.4	0.03	0.3	0.02	0.2	4.08	0.3913	50.7	23.6	1526
6.25 mg/kg-d	21-0454	4.25	8.57	17.2	50.8	59.3	20.1	33.9	1339	22.9	11.6	7.8	0.00	0.0	0.23	5.5	3.78	88.9	0.21	4.9	0.02	0.5	0.01	0.2	2.95	0.2528	49.3	23.5	1339
	21-0485	9.82	8.18	16.3	48.0	58.7	19.9	34.0	1205	22.2	10.9	7.8	0.00	0.0	0.58	6.0	8.40	85.5	0.75	7.6	0.07	0.7	0.02	0.2	2.14	0.1751	36.1	23.2	1205
	21-0486	14.68	9.15	19.1	56.9	62.2	20.9	33.6	1494	24.6	12.5	8.0	0.00	0.0	0.99	6.7	12.61	85.9	0.95	6.5	0.07	0.5	0.06	0.4	3.67	0.3358	47.1	23.7	1494
	21-0495	7.04	8.13	16.5	49.2	60.5	20.3	33.5	1135	23.3	11.1	7.5	0.00	0.0	0.32	4.6	6.21	88.2	0.46	6.5	0.03	0.4	0.02	0.3	3.07	0.2496	38.1	22.8	1135
	21-0496	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	Mean	**8.98**	**8.72**	**17.8**	**52.7**	**60.4**	**20.4**	**33.8**	**1340**	**23.5**	**12.0**	**7.8**	**0.00**	**0.0**	**0.53**	**5.8**	**7.82**	**87.5**	**0.55**	**6.0**	**0.04**	**0.5**	**0.03**	**0.3**	**3.18**	**0.2809**	**44.3**	**23.4**	**1340**
	SD	**3.852**	**0.633**	**1.61**	**4.75**	**1.40**	**0.44**	**0.23**	**172.2**	**1.09**	**1.23**	**0.20**	**0.009**	**0.09**	**0.295**	**0.79**	**3.251**	**1.68**	**0.294**	**1.31**	**0.024**	**0.148**	**0.019**	**0.089**	**0.741**	**0.08391**	**6.70**	**0.36**	**172.2**
	21-0451	8.99	8.75	17.8	52.5	60.0	20.3	33.9	1670	23.6	12.1	7.9	0.00	0.0	1.14	12.7	7.17	79.8	0.61	6.8	0.04	0.4	0.03	0.3	3.01	0.2634	52.7	23.5	1670
12.5 mg/kg-d	21-0452	5.19	7.66	15.7	46.0	60.1	20.5	34.1	1179	23.3	10.6	7.9	0.00	0.0	0.30	5.7	4.52	87.1	0.33	6.4	0.03	0.6	0.01	0.2	2.68	0.2053	43.4	23.5	1179
	21-0465	8.60	7.84	16.3	47.7	60.8	20.8	34.2	1280	23.2	10.8	7.7	0.00	0.0	0.23	2.8	7.94	92.3	0.38	4.4	0.03	0.3	0.02	0.2	2.89	0.2266	48.1	23.5	1280
	21-0466	9.20	8.62	17.3	49.9	57.9	20.1	34.7	1182	21.8	11.9	7.9	0.02	0.2	0.87	9.5	7.63	82.9	0.51	5.5	0.13	1.4	0.06	0.7	3.36	0.2896	46.7	23.1	1182
	21-0469	12.33	8.05	16.0	47.8	59.4	19.9	33.5	1554	22.5	11.2	8.3	0.00	0.0	0.50	4.0	11.34	92.0	0.40	3.2	0.07	0.6	0.02	0.2	2.73	0.2198	41.9	23.0	1554
	21-0470	5.86	8.99	18.1	53.7	59.7	20.1	33.7	1659	23.3	11.9	7.8	0.02	0.3	0.62	10.7	4.90	83.6	0.30	5.1	0.02	0.3	0.02	0.3	3.51	0.3155	41.7	22.7	1659
	Mean	**8.36**	**8.32**	**16.9**	**49.6**	**59.7**	**20.3**	**34.0**	**1421**	**23.0**	**11.4**	**7.9**	**0.01**	**0.1**	**0.61**	**7.6**	**7.25**	**86.3**	**0.42**	**5.2**	**0.05**	**0.6**	**0.03**	**0.3**	**3.03**	**0.2534**	**45.8**	**23.2**	**1421**
	SD	**2.578**	**0.541**	**1.00**	**3.00**	**0.98**	**0.33**	**0.42**	**233.2**	**0.67**	**0.64**	**0.20**	**0.010**	**0.13**	**0.347**	**3.97**	**2.463**	**5.10**	**0.117**	**1.32**	**0.041**	**0.415**	**0.018**	**0.194**	**0.338**	**0.04342**	**4.28**	**0.34**	**233.2**
	21-0455	3.09	8.01	15.9	47.6	59.4	19.9	33.4	943	23.1	11.0	8.1	0.03	1.0	0.35	11.3	2.61	84.5	0.12	3.9	0.01	0.3	0.00	0.0	3.43	0.2747	50.9	23.1	943
25 mg/kg-d	21-0456	15.27	9.39	19.8	56.8	60.5	21.1	34.9	1354	23.5	12.9	7.7	0.00	0.0	0.60	3.9	13.19	86.4	1.31	8.6	0.06	0.4	0.11	0.7	2.97	0.2789	44.7	24.1	1354
	21-0459	11.25	8.48	18.1	52.5	61.9	21.3	34.5	1309	24.8	12.0	8.5	0.00	0.0	1..6	14.2	8.74	77.7	0.82	7.3	0.05	0.4	0.04	0.4	2.27	0.1925	39.0	24.8	1309
	21-0460	7.67	9.23	18.0	53.8	58.3	19.5	33.5	1277	22.9	12.7	8.8	0.00	0.0	0.30	4.0	6.89	89.8	0.44	5.7	0.03	0.4	0.01	0.1	3.11	0.2871	40.9	22.5	1277
	21-0461	5.79	7.67	16.1	47.2	61.5	21.0	34.1	1395	24.3	11.1	8.1	0.00	0.0	0.38	6.6	5.14	88.8	0.22	3.8	0.03	0.5	0.02	0.3	2.68	0.2056	45.6	23.7	1395
	21-0462	6.32	9.20	18.7	55.5	60.3	20.3	33.7	1653	24.3	13.2	7.9	0.00	0.0	0.38	6.0	5.62	88.9	0.26	4.1	0.03	0.5	0.03	0.5	3.86	0.3551	49.2	23.0	1653
	Mean	**8.23**	**8.66**	**17.8**	**52.2**	**60.3**	**20.5**	**34.0**	**1322**	**23.8**	**12.2**	**8.2**	**0.01**	**0.2**	**0.40**	**7.7**	**7.03**	**86.0**	**0.53**	**5.6**	**0.04**	**0.4**	**0.04**	**0.3**	**3.05**	**0.2657**	**45.1**	**23.5**	**1322**
	SD	**4.359**	**0.719**	**1.51**	**4.02**	**1.33**	**0.73**	**0.59**	**228.8**	**0.76**	**0.94**	**0.40**	**0.012**	**0.41**	**0.115**	**4.18**	**3.633**	**4.52**	**0.456**	**2.01**	**0.018**	**0.075**	**0.039**	**0.258**	**0.558**	**0.05946**	**4.60**	**0.84**	**228.8**
	21-0463	12.13	8.40	17.1	50.7	60.4	20.4	33.7	1182	23.6	11.7	8.4	0.02	0.2	1.24	10.2	10.21	84.2	0.59	4.9	0.04	0.3	0.05	0.4	4.14	0.3478	49.7	23.2	1182
50 mg/kg-d	21-0464	8.78	8.46	17.1	50.8	60.0	20.2	33.7	1171	24.7	12.4	8.9	0.00	0.0	0.55	6.3	7.83	89.2	0.36	4.1	0.03	0.3	0.01	0.1	2.72	0.2301	46.8	23.4	1171
	21-0473	9.54	7.80	16.0	47.2	60.5	20.5	33.9	1055	24.7	11.3	8.4	0.00	0.0	0.55	5.8	8.33	87.3	0.58	6.1	0.03	0.3	0.05	0.5	2.75	0.2145	42.9	23.7	1055
	21-0474	5.61	8.83	18.5	53.8	60.9	21.0	34.4	1321	25.8	13.8	8.3	0.02	0.4	0.29	5.2	4.91	87.5	0.33	5.9	0.05	0.9	0.03	0.5	2.89	0.2552	50.3	24.2	1321
	21-0487	11.52	8.15	17.4	50.6	62.1	21.3	34.4	1312	25.0	11.7	8.4	0.02	0.2	0.49	4.3	10.14	88.0	0.68	5.9	0.16	1.4	0.05	0.4	4.09	0.3333	48.3	24.3	1312
	21-0488	7.35	9.57	18.9	55.9	58.4	19.7	33.8	1291	26.0	15.8	8.4	0.00	0.0	0.49	6.6	6.31	85.9	0.49	6.7	0.03	0.4	0.03	0.4	3.19	0.3053	43.4	22.7	1291
	Mean	**9.16**	**8.54**	**17.5**	**51.5**	**60.4**	**20.5**	**34.0**	**1222**	**25.0**	**12.8**	**8.5**	**0.01**	**0.1**	**0.60**	**6.4**	**7.96**	**87.0**	**0.51**	**5.6**	**0.06**	**0.6**	**0.04**	**0.4**	**3.30**	**0.2810**	**46.9**	**23.6**	**1222**
	SD	**2.472**	**0.612**	**1.05**	**3.00**	**1.21**	**0.57**	**0.33**	**104.6**	**0.87**	**1.72**	**0.22**	**0.011**	**0.16**	**0.327**	**2.03**	**2.097**	**1.75**	**0.138**	**0.94**	**0.051**	**0.456**	**0.016**	**0.147**	**0.656**	**0.05562**	**3.15**	**0.61**	**104.6**
	21-0449	14.28	7.32	14.1	42.2	57.7	19.3	33.4	898	23.9	11.2	9.1	0.08	0.6	0.60	4.2	12.74	89.2	0.89	6.2	0.01	0.1	0.04	0.3	2.07	0.1515	41.1	21.0	898
100 mg/kg-d	21-0450	19.81	7.66	15.0	44.2	57.7	19.6	33.9	759	25.2	12.5	10.0	0.00	0.0	0.85	4.2	17.73	89.5	1.18	6.0	0.01	0.1	0.04	0.2	1.82	0.1394	43.1	21.5	759
	21-0483	10.19	6.38	12.9	37.9	59.4	20.2	34.0	673	23.7	10.6	9.6	0.00	0.0	0.77	7.6	7.90	77.5	1.39	13.6	0.07	0.7	0.06	0.6	1.81	0.1155	39.6	22.1	673
	21-0484	15.57	7.37	15.2	45.2	61.3	20.6	33.6	857	24.8	11.2	9.3	0.00	0.0	1.37	8.9	13.25	85.1	0.86	5.5	0.02	0.1	0.07	0.4	3.18	0.2344	51.4	22.3	857
	21-0493	14.55	8.11	16.4	48.8	60.2	20.2	33.6	549	24.9	11.9	10.2	0.00	0.0	0.88	6.1	13.17	90.5	0.45	3.1	0.03	0.2	0.02	0.1	2.73	0.2214	51.0	22.7	549
	21-0494	11.66	9.10	18.0	53.0	58.2	19.8	34.0	581	23.8	13.2	10.0	0.00	0.0	0.15	1.3	10.83	92.9	0.61	5.2	0.02	0.2	0.05	0.4	0.88	0.0801	14.8	25.2	581
	Mean	**14.34**	**7.66**	**15.3**	**45.2**	**59.1**	**20.0**	**33.8**	**720**	**24.4**	**11.8**	**9.7**	**0.01**	**0.1**	**0.77**	**5.4**	**12.60**	**87.5**	**0.90**	**6.6**	**0.03**	**0.2**	**0.05**	**0.3**	**2.08**	**0.1571**	**40.2**	**22.5**	**720**
	SD	**3.343**	**0.907**	**1.78**	**5.24**	**1.47**	**0.47**	**0.25**	**143.3**	**0.66**	**0.96**	**0.44**	**0.033**	**0.24**	**0.398**	**2.73**	**3.234**	**5.49**	**0.348**	**3.60**	**0.023**	**0.234**	**0.018**	**0.175**	**0.802**	**0.06019**	**13.39**	**1.47**	**143.3**
	21-0475	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
200 mg/kg-d	21-0476	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0479	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0480	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0491	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0492	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	21-0457	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
400 mg/kg-d	21-0458	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0477	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0478	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0489	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0490	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**

Table I-3
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Hematology Summary
Male Rats

Group		WBC (K/uL)	RBC (M/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT (K/uL)	RDW-SD (fL)	RDW-CV (%)	MPV (fL)	NRBC (K/uL)	NRBC (%)	NEUT (K/uL)	NEUT (%)	LYMPH (K/uL)	LYMPH (%)	MONO (K/uL)	MONO (%)	EO (K/uL)	EO (%)	BASO (K/uL)	BASO (%)	RET (K/uL)	RET (%)	IRF (%)	RET-He (pg)	PLT-F (K/uL)
Corn Oil	**Mean**	10.24	8.45	16.7	50.5	60.0	19.9	33.1	1264	26.1	13.5	7.9	0.01	0.1	1.32	13.6	8.25	80.4	0.60	5.5	0.03	0.3	0.04	0.3	4.34	0.3651	57.1	21.9	1264
Control	**SD**	5.451	1.058	1.72	4.81	2.73	0.92	0.33	131.4	1.09	1.73	0.38	0.020	0.12	0.756	3.73	4.432	3.39	0.367	1.05	0.026	0.183	0.028	0.194	0.453	0.04233	4.82	0.77	131.4
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
6.25 mg/kg-d	**Mean**	8.99	8.29	16.4	49.2	59.5	19.9	33.4	998	26.4	13.4	8.0	0.01	0.2	0.96	12.5	7.48	81.4	0.51	5.6	0.03	0.3	0.02	0.3	4.20	0.3476	56.1	22.1	998
	SD	4.253	0.581	0.56	2.17	2.04	0.77	0.95	483.7	1.54	1.16	0.33	0.015	0.28	0.245	5.64	3.920	5.17	0.306	1.77	0.010	0.126	0.012	0.084	0.688	0.05616	2.15	0.93	483.7
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
12.5 mg/kg-d	**Mean**	11.17	8.23	16.3	49.1	59.8	19.9	33.2	1354	26.0	13.1	8.0	0.02	0.1	1.98	16.2	8.49	77.7	0.61	5.4	0.05	0.4	0.04	0.3	4.33	0.3550	56.5	21.6	1354
	SD	4.548	0.613	0.85	2.94	1.62	0.59	0.54	237.5	0.93	1.28	0.23	0.021	0.13	1.626	6.48	2.692	6.76	0.320	1.20	0.023	0.075	0.017	0.082	0.668	0.04923	3.53	0.72	237.5
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
25 mg/kg-d	**Mean**	12.18	8.21	16.3	49.0	59.7	19.8	33.2	1284	26.6	13.4	8.0	0.02	0.2	1.81	14.9	9.59	78.8	0.70	5.7	0.04	0.4	0.04	0.3	4.44	0.3641	58.2	21.5	1284
	SD	3.432	0.297	0.63	1.53	2.00	0.60	0.50	124.3	1.35	0.54	0.42	0.016	0.13	0.631	3.67	2.757	4.01	0.230	0.88	0.024	0.138	0.014	0.089	0.408	0.03595	2.13	0.80	124.3
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
50 mg/kg-d	**Mean**	16.33	8.06	15.9	47.6	59.1	19.7	33.3	1034	26.5	13.7	8.2	0.04	0.2	2.41	14.4	12.95	79.5	0.90	5.7	0.03	0.2	0.04	0.2	4.62	0.3731	58.0	21.3	1034
	SD	2.993	0.445	0.93	2.75	1.33	0.48	0.52	66.7	0.87	1.33	0.35	0.023	0.16	1.306	6.31	2.339	5.75	0.097	1.20	0.019	0.110	0.010	0.052	0.592	0.05949	2.23	0.69	66.7
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
100 mg/kg-d	**Mean**	16.63	7.74	15.0	44.4	57.3	19.3	33.7	677*	28.4	15.1	9.4*	0.04	0.3	2.92	16.2	12.24	73.9	1.39*	9.3	0.03	0.2	0.06	0.4	4.10	0.3178	60.1	20.5*	677*
	SD	7.379	0.595	1.52	4.88	2.28	0.59	0.38	162.9	2.63	1.41	0.59	0.036	0.32	1.938	7.75	5.537	5.23	0.493	3.72	0.021	0.089	0.023	0.219	1.353	0.11266	5.94	0.46	162.9
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
200 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
400 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

* p<0.05 compared to controls

Table I-4
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Hematology Summary
Female Rats

Group		WBC (K/uL)	RBC (M/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT (K/uL)	RDW-SD (fL)	RDW-CV (%)	MPV (fL)	NRBC (K/uL)	NRBC (%)	NEUT (K/uL)	NEUT (%)	LYMPH (K/uL)	LYMPH (%)	MONO (K/uL)	MONO (%)	EO (K/uL)	EO (%)	BASO (K/uL)	BASO (%)	RET (K/uL)	RET (%)	IRF (%)	RET-He (pg)	PLT-F (K/uL)
Corn Oil	**Mean**	8.59	8.80	18.0	52.8	60.1	20.5	34.1	1407	23.6	12.3	7.9	0.00	0.0	0.53	6.4	7.40	85.6	0.59	7.1	0.05	0.6	0.03	0.3	3.37	0.2963	47.0	23.3	1407
Control	**SD**	2.903	0.818	1.18	3.73	1.82	0.82	0.46	300.7	0.67	1.16	0.41	0.008	0.08	0.239	2.45	2.642	4.83	0.282	2.89	0.031	0.258	0.010	0.117	0.424	0.04394	5.49	0.84	300.7
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
6.25 mg/kg-d	**Mean**	8.98	8.72	17.8	52.7	60.4	20.4	33.8	1340	23.5	12.0	7.8	0.00	0.0	0.53	5.8	7.82	87.5	0.55	6.0	0.04	0.5	0.03	0.3	3.18	0.2809	44.3	23.4	1340
	SD	3.852	0.633	1.61	4.75	1.40	0.44	0.23	172.2	1.09	1.23	0.20	0.009	0.09	0.295	0.79	3.251	1.68	0.294	1.31	0.024	0.148	0.019	0.089	0.741	0.08391	6.70	0.36	172.2
	N	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
12.5 mg/kg-d	**Mean**	8.36	8.32	16.9	49.6	59.7	20.3	34.0	1421	23.0	11.4	7.9	0.01	0.1	0.61	7.6	7.25	86.3	0.42	5.2	0.05	0.6	0.03	0.3	3.03	0.2534	45.8	23.2	1421
	SD	2.578	0.541	1.00	3.00	0.98	0.33	0.42	233.2	0.67	0.64	0.20	0.010	0.13	0.347	3.97	2.463	5.10	0.117	1.32	0.041	0.415	0.018	0.194	0.338	0.04342	4.28	0.34	233.2
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
25 mg/kg-d	**Mean**	8.23	8.66	17.8	52.2	60.3	20.5	34.0	1322	23.8	12.2	8.2	0.01	0.2	0.40	7.7	7.03	86.0	0.53	5.6	0.04	0.4	0.04	0.3	3.05	0.2657	45.1	23.5	1322
	SD	4.359	0.719	1.51	4.02	1.33	0.73	0.59	228.8	0.76	0.94	0.40	0.012	0.41	0.115	4.18	3.633	4.52	0.456	2.01	0.018	0.075	0.039	0.258	0.558	0.05946	4.60	0.84	228.8
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
50 mg/kg-d	**Mean**	9.16	8.54	17.5	51.5	60.4	20.5	34.0	1222	25.0*	12.8	8.5*	0.01	0.1	0.60	6.4	7.96	87.0	0.51	5.6	0.06	0.6	0.04	0.4	3.30	0.2810	46.9	23.6	1222
	SD	2.472	0.612	1.05	3.00	1.21	0.57	0.33	104.6	0.87	1.72	0.22	0.011	0.16	0.327	2.03	2.097	1.75	0.138	0.94	0.051	0.456	0.016	0.147	0.656	0.05562	3.15	0.61	104.6
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
100 mg/kg-d	**Mean**	14.34*	7.66	15.3*	45.2*	59.1	20.0	33.8	720*	24.4	11.8	9.7*	0.01	0.1	0.77	5.4	12.60*	87.5	0.90	6.6	0.03	0.2	0.05	0.3	2.08	0.1571*	40.2	22.5	720
	SD	3.343	0.907	1.78	5.24	1.47	0.47	0.25	143.3	0.66	0.96	0.44	0.033	0.24	0.398	2.73	3.234	5.49	0.348	3.60	0.023	0.234	0.018	0.175	0.802	0.06019	13.39	1.47	143.3
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
200 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
400 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

* p<0.05 compared to controls

Appendix J

Subacute Individual and Summary of Clinical Chemistry

Abbreviations:

mg/kg-d: milligrams per kilogram per day
(f): animal died on study
ND: no data
g/dL: grams per deciliter
U/L: units per liter
mg/dl: milligrams per deciliter
ALB: albumin
ALB/GLOB ratio: albumin/globulin ratio
ALP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
BUN: blood urea nitrogen
BUN/CREA ratio: blood urea nitrogen/creatinine ratio
CA: calcium
CHOL: cholesterol
CK: creatinine kinase
CREA: creatinine
GLOB calc: globulin calculated
GLU: glucose
PHOS: phosphate
TP: total protein
TRIG: triglycerides
AMY: amylase
LPS: lipase
SD: standard deviation

Table J-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Clinical Chemistry
Male Rats

Group	Animal ID	ALB (g/dL)	ALB / GLOB ratio (g/dL)	ALP (U/L)	ALT (U/L)	AST (U/L)	BUN (mg/dL)	BUN / CREA ratio	CA (mg/dL)	CHOL (mg/dL)	CK (U/L)	CREA (mg/dL)	GLOB calc. (g/dL)	GLU (mg/dL)	PHOS (mg/dL)	TP (g/dL)	TRIG (g/dL)	AMY (U/L)	LPS (U/L)
	21-0391	3.5	1.21	251	54	110	7	7.00	12.5	95	377	1.0	2.9	301	14.5	6.4	23	3431	5.3
Corn Oil	21-0392	3.6	1.24	226	57	115	9	10.00	12.4	75	309	0.9	2.9	179	16.9	6.5	26	3578	6.2
Control	21-0431	3.7	1.37	404	77	100	12	15.00	11.7	80	189	0.8	2.7	223	13.3	6.4	33	3922	6.3
	21-0432	3.9	1.34	307	65	98	10	12.50	13.1	75	303	0.8	2.9	238	17.8	6.8	23	3317	7.1
	21-0435	3.8	1.41	244	63	109	9	11.25	12.3	76	179	0.8	2.7	195	18.7	6.5	21	2308	8.3
	21-0436	3.7	1.42	227	60	95	13	14.44	11.4	75	193	0.9	2.6	164	12.9	6.3	27	4984	7.5
	Mean	**3.7**	**1.33**	**277**	**63**	**105**	**10**	**11.70**	**12.2**	**79**	**258**	**0.9**	**2.8**	**217**	**15.7**	**6.5**	**26**	**3590**	**6.8**
	SD	**0.14**	**0.088**	**69.1**	**8.1**	**7.9**	**2.2**	**2.974**	**0.61**	**7.9**	**82.5**	**0.08**	**0.13**	**49.5**	**2.44**	**0.17**	**4.3**	**871.4**	**1.07**
	21-0405	3.6	1.29	252	56	91	8	11.43	13.2	86	156	0.7	2.8	348	16.7	6.4	35	2698	6.0
6.25 mg/kg-d	21-0406	3.7	1.28	176	36	97	10	11.11	11.3	71	168	0.9	2.9	128	11.7	6.6	12	3559	6.6
	21-0415	3.8	1.73	331	71	95	12	13.33	13.2	75	148	0.9	2.2	407	14.7	6.0	27	3518	6.9
	21-0416	4.0	1.38	363	78	133	10	12.50	12.2	66	341	0.8	2.9	138	18.4	6.9	36	2742	7.1
	21-0445	3.9	1.56	332	61	109	15	15.00	12.9	73	115	1.0	2.5	246	18.4	6.4	32	2186	10.4
	21-0446	3.9	1.56	284	74	105	13	14.44	12.3	71	135	0.9	2.5	148	17.0	6.4	36	2403	8.6
	Mean	**3.8**	**1.47**	**290**	**63**	**105**	**11**	**12.97**	**12.5**	**74**	**177**	**0.9**	**2.6**	**236**	**16.2**	**6.5**	**30**	**2851**	**7.6**
	SD	**0.15**	**0.179**	**68.2**	**15.4**	**15.2**	**2.5**	**1.579**	**0.74**	**6.7**	**82.3**	**0.10**	**0.28**	**119.1**	**2.57**	**0.29**	**9.3**	**570.0**	**1.62**
	21-0393	3.8	1.19	234	56	77	9	11.25	13.2	89	105	0.8	3.2	293	14.9	7.0	31	3891	6.4
12.5 mg/kg-d	21-0394	3.7	1.42	402	77	94	11	12.22	13.2	91	112	0.9	2.6	405	17.1	6.3	34	2891	6.8
	21-0441	3.8	1.41	169	41	86	11	13.75	12.0	82	150	0.8	2.7	234	13.6	6.5	20	2807	5.8
	21-0442	3.8	1.41	249	45	80	12	20.00	11.8	61	120	0.6	2.7	131	12.5	6.5	24	2255	7.6
	21-0447	4.1	1.32	258	51	96	10	12.50	13.1	65	158	0.8	3.1	139	19.0	7.2	35	4016	6.7
	21-0448	3.9	1.50	308	64	83	14	20.00	12.7	70	81	0.7	2.6	314	15.5	6.5	59	2525	7.7
	Mean	**3.9**	**1.38**	**270**	**56**	**86**	**11**	**14.95**	**12.7**	**76**	**121**	**0.8**	**2.8**	**253**	**15.4**	**6.7**	**34**	**3064**	**6.8**
	SD	**0.14**	**0.107**	**78.7**	**13.2**	**7.6**	**1.7**	**3.990**	**0.63**	**12.7**	**28.8**	**0.10**	**0.26**	**106.5**	**2.36**	**0.35**	**13.6**	**725.4**	**0.72**
	21-0395	3.9	1.50	255	72	86	11	12.22	12.5	71	158	0.9	2.6	232	15.0	6.5	12	3382	6.1
25 mg/kg-d	21-0396	3.7	1.12	212	54	185	8	10.00	12.4	71	964	0.8	3.3	133	20.0	7.0	12	3731	8.2
	21-0397	3.9	1.39	318	47	87	9	11.25	13.5	92	211	0.8	2.8	182	19.6	6.7	26	5934	8.4
	21-0398	3.8	1.46	156	46	99	8	8.89	12.1	83	236	0.9	2.6	171	15.1	6.4	10	2413	5.8
	21-0409	3.7	1.32	211	58	100	9	12.86	12.6	73	127	0.7	2.8	264	16.2	6.5	45	2600	8.4
	21-0410	3.9	1.26	219	56	112	11	11.00	13.0	72	192	1.0	3.1	348	15.4	7.0	15	2932	6.6
	Mean	**3.8**	**1.34**	**229**	**56**	**112**	**9**	**11.04**	**12.7**	**77**	**315**	**0.9**	**2.9**	**222**	**16.9**	**6.7**	**20**	**3499**	**7.3**
	SD	**0.10**	**0.140**	**54.1**	**9.4**	**37.3**	**1.4**	**1.446**	**0.50**	**8.6**	**320.4**	**0.10**	**0.28**	**77.3**	**2.30**	**0.26**	**13.5**	**1288.9**	**1.22**
	21-0407	3.9	1.50	219	55	93	12	17.14	12.5	136	465	0.7	2.6	172	17.1	6.5	12	2134	6.7
50 mg/kg-d	21-0408	3.7	1.23	291	42	83	9	18.00	12.3	110	231	0.5	3.0	234	15.3	6.7	17	2193	6.2
	21-0413	3.6	1.38	254	35	79	17	24.29	12.3	125	173	0.7	2.6	334	15.2	6.2	27	2444	6.6
	21-0414	3.8	1.46	249	47	83	17	21.25	12.3	102	270	0.8	2.6	240	16.2	6.4	22	2513	6.5
	21-0429	3.9	1.34	237	46	80	11	13.75	11.9	109	127	0.8	2.9	218	14.5	6.8	25	4462	7.4
	21-0430	3.9	1.50	179	41	109	10	14.29	12.5	92	167	0.7	2.6	152	18.7	6.5	22	3449	6.3
	Mean	**3.8**	**1.40**	**238**	**44**	**88**	**13**	**18.12**	**12.3**	**112**	**239**	**0.7**	**2.7**	**225**	**16.2**	**6.5**	**21**	**2866**	**6.6**
	SD	**0.13**	**0.106**	**37.5**	**6.7**	**11.5**	**3.5**	**4.065**	**0.22**	**15.9**	**121.8**	**0.11**	**0.18**	**63.8**	**1.53**	**0.21**	**5.5**	**914.2**	**0.43**
	21-0421	3.9	1.34	170	53	86	13	16.25	13.1	123	281	0.8	2.9	164	18.2	6.8	33	2255	8.4
100 mg/kg-d	21-0422	3.9	1.22	193	54	75	27	27.00	12.3	121	160	1.0	3.2	155	13.4	7.1	14	2053	5.3
	21-0433	3.9	1.39	228	55	92	20	25.00	12.7	125	213	0.8	2.8	281	17.0	6.7	27	2488	6.8
	21-0434	4.1	1.37	150	46	129	15	13.64	12.8	145	234	1.1	3.0	129	16.3	7.1	17	2127	7.9
	21-0443	4.0	1.08	214	60	116	18	18.00	11.7	98	404	1.0	3.7	115	13.9	7.7	16	2528	7.6
	21-0444	4.1	1.52	250	36	98	18	20.00	12.5	127	164	0.9	2.7	125	18.7	6.8	17	2231	8.3
	Mean	**4.0**	**1.32**	**201**	**51**	**99**	**19**	**19.98**	**12.5**	**123**	**243**	**0.9**	**3.1**	**162**	**16.3**	**7.0**	**21**	**2280**	**7.4**
	SD	**0.10**	**0.152**	**37.2**	**8.5**	**19.9**	**4.8**	**5.148**	**0.48**	**15.1**	**91.1**	**0.12**	**0.36**	**61.4**	**2.19**	**0.37**	**7.6**	**191.2**	**1.17**
	21-0403	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
200 mg/kg-d	21-0404	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0423	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0424	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0427	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0428	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	21-0399	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
400 mg/kg-d	21-0400	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0401	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0402	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0419	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0420	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**

Table J-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Clinical Chemistry
Female Rats

Group	Animal ID	ALB (g/dL)	ALB / GLOB ratio (g/dL)	ALP (U/L)	ALT (U/L)	AST (U/L)	BUN (mg/dL)	BUN / CREA ratio	CA (mg/dL)	CHOL (mg/dL)	CK (U/L)	CREA (mg/dL)	GLOB calc. (g/dL)	GLU (mg/dL)	PHOS (mg/dL)	TP (g/dL)	TRIG (g/dL)	AMY (U/L)	LPS (U/L)
	21-0467	4.5	1.50	189	63	97	24	26.67	13.2	95	145	0.9	3.0	259	18.4	7.5	29	1124	10.3
Corn Oil	21-0468	4.5	1.36	145	68	470	13	11.82	12.5	105	2522	1.1	3.3	154	19.3	7.8	31	1231	7.9
Control	21-0471	4.6	1.59	139	57	109	17	15.45	12.9	101	446	1.1	2.9	79	18.6	7.5	24	1143	9.1
	21-0472	4.2	1.35	141	44	91	13	13.00	12.4	110	133	1.0	3.1	83	20.8	7.3	38	1327	13.1
	21-0481	5.0	1.52	176	58	84	18	20.00	12.9	94	138	0.9	3.3	107	16.1	8.3	37	2027	8.4
	21-0482	4.6	1.44	131	39	94	21	21.00	13.0	77	209	1.0	3.2	83	19.3	7.8	42	1433	8.4
	Mean	**4.6**	**1.46**	**154**	**55**	**158**	**18**	**17.99**	**12.8**	**97**	**599**	**1.0**	**3.1**	**128**	**18.8**	**7.7**	**34**	**1381**	**9.5**
	SD	**0.26**	**0.094**	**23.3**	**11.2**	**153.3**	**4.4**	**5.619**	**0.31**	**11.5**	**949.7**	**0.09**	**0.16**	**70.3**	**1.55**	**0.35**	**6.7**	**337.1**	**1.94**
	21-0453	4.7	1.68	90	55	110	16	20.00	12.7	83	223	0.8	2.8	99	16.0	7.5	32	1267	7.8
6.25 mg/kg-d	21-0454	5.0	1.56	101	41	110	12	10.91	12.8	87	341	1.1	3.2	87	16.7	8.2	30	1369	6.3
	21-0485	4.3	1.72	202	49	90	14	14.00	12.4	71	90	1.0	2.5	187	15.8	6.8	25	1123	7.2
	21-0486	4.1	1.21	185	66	101	15	16.67	13.3	143	170	0.9	3.4	267	17.0	7.5	38	1390	7.3
	21-0495	4.2	1.56	142	48	71	17	17.00	12.4	80	79	1.0	2.7	100	17.3	6.9	15	1517	12.2
	21-0496	4.3	1.79	139	62	113	17	21.25	12.6	88	259	0.8	2.4	77	19.3	6.7	26	1341	4.0
	Mean	**4.4**	**1.59**	**143**	**54**	**99**	**15**	**16.64**	**12.7**	**92**	**194**	**0.9**	**2.8**	**136**	**17.0**	**7.3**	**28**	**1335**	**7.5**
	SD	**0.34**	**0.205**	**44.4**	**9.4**	**16.2**	**1.9**	**3.807**	**0.33**	**25.7**	**101.3**	**0.12**	**0.39**	**75.2**	**1.26**	**0.58**	**7.8**	**131.8**	**2.68**
	21-0451	4.2	1.50	133	61	106	15	16.67	13.1	85	208	0.9	2.8	66	16.9	7.0	25	1084	9.3
12.5 mg/kg-d	21-0452	4.8	1.55	96	41	96	11	12.22	12.7	92	206	0.9	3.1	112	15.9	7.9	17	1374	7.8
	21-0465	4.6	1.44	180	54	101	15	18.75	12.1	83	217	0.8	3.2	81	17.9	7.8	16	1197	8.9
	21-0466	4.3	1.65	150	49	95	14	15.56	12.1	92	152	0.9	2.6	98	11.4	6.9	23	1205	6.8
	21-0469	4.1	1.14	224	56	93	19	15.83	12.4	63	129	1.2	3.6	115	15.1	7.7	22	1533	8.2
	21-0470	4.3	1.48	166	45	94	16	16.00	12.2	79	137	1.0	2.9	89	17.0	7.2	15	1451	8.4
	Mean	**4.4**	**1.46**	**158**	**51**	**98**	**15**	**15.84**	**12.4**	**82**	**175**	**1.0**	**3.0**	**94**	**15.7**	**7.4**	**20**	**1307**	**8.2**
	SD	**0.26**	**0.173**	**43.4**	**7.4**	**5.0**	**2.6**	**2.115**	**0.40**	**10.8**	**39.8**	**0.14**	**0.35**	**18.7**	**2.32**	**0.44**	**4.2**	**172.4**	**0.88**
	21-0455	4.4	1.69	126	37	112	15	18.75	12.3	91	271	0.8	2.6	95	19.1	7.0	25	1329	7.6
25 mg/kg-d	21-0456	4.7	1.52	154	61	86	21	21.00	12.9	79	141	1.0	3.1	111	16.6	7.8	28	1523	9.4
	21-0459	4.9	1.44	116	49	80	14	15.56	12.7	120	85	0.9	3.4	139	17.3	8.3	30	1569	8.7
	21-0460	4.1	1.52	145	59	109	19	17.27	12.6	85	213	1.1	2.7	73	15.9	6.8	17	1069	8.8
	21-0461	4.9	1.75	138	52	92	14	15.56	12.2	105	101	0.9	2.8	120	15.5	7.7	23	2003	8.2
	21-0462	4.8	1.92	106	38	79	13	14.44	13.0	102	163	0.9	2.5	155	20.0	7.3	25	1568	8.6
	Mean	**4.6**	**1.64**	**131**	**49**	**93**	**16**	**17.10**	**12.6**	**97**	**162**	**0.9**	**2.9**	**116**	**17.4**	**7.5**	**25**	**1510**	**8.6**
	SD	**0.32**	**0.180**	**18.2**	**10.2**	**14.4**	**3.2**	**2.440**	**0.32**	**15.0**	**70.1**	**0.10**	**0.34**	**29.6**	**1.80**	**0.56**	**4.5**	**309.0**	**0.61**
	21-0463	4.4	1.47	98	41	82	16	20.00	13.0	97	96	0.8	3.0	154	17.7	7.4	21	1125	7.5
50 mg/kg-d	21-0464	5.1	1.65	106	44	84	15	21.43	13.3	130	201	0.7	3.1	209	18.9	8.2	43	1745	8.8
	21-0473	4.4	1.57	95	46	77	17	21.25	12.4	99	131	0.8	2.8	95	15.0	7.2	19	969	7.5
	21-0474	4.9	1.58	176	46	63	20	22.22	12.8	162	78	0.9	3.1	106	16.2	8.0	37	1803	8.1
	21-0487	4.6	1.64	179	37	79	13	14.44	13.1	119	52	0.9	2.8	79	16.9	7.4	25	1307	8.0
	21-0488	5.2	1.63	156	61	84	18	22.50	13.6	110	182	0.8	3.2	79	17.9	8.4	33	1397	8.0
	Mean	**4.8**	**1.59**	**135**	**46**	**78**	**17**	**20.31**	**13.0**	**120**	**123**	**0.8**	**3.0**	**120**	**17.1**	**7.8**	**30**	**1391**	**8.0**
	SD	**0.35**	**0.067**	**39.7**	**8.2**	**7.9**	**2.4**	**3.005**	**0.41**	**24.2**	**59.0**	**0.08**	**0.17**	**51.5**	**1.38**	**0.50**	**9.5**	**332.0**	**0.48**
	21-0449	4.5	1.61	131	66	137	20	25.00	13.0	168	400	0.8	2.8	81	21.4	7.3	26	1741	16.0
100 mg/kg-d	21-0450	5.0	1.43	90	43	65	25	31.25	13.4	141	87	0.8	3.5	98	16.1	8.5	25	1811	7.4
	21-0483	4.9	1.26	94	54	82	27	33.75	13.3	130	182	0.8	3.9	190	13.1	8.8	29	1495	8.0
	21-0484	4.6	1.28	135	40	72	18	22.50	13.4	207	84	0.8	3.6	252	16.4	8.2	30	1435	8.2
	21-0493	4.8	1.60	127	45	70	16	22.86	13.0	239	66	0.7	3.0	158	16.3	7.8	38	1341	7.8
	21-0494	4.5	1.45	217	75	132	24	21.82	13.3	165	453	1.1	3.1	238	16.4	7.6	46	1357	11.0
	Mean	**4.7**	**1.44**	**132**	**54**	**93**	**22**	**26.20**	**13.2**	**175**	**212**	**0.8**	**3.3**	**170**	**16.6**	**8.0**	**32**	**1530**	**9.7**
	SD	**0.21**	**0.150**	**45.8**	**14.0**	**32.7**	**4.3**	**5.059**	**0.19**	**41.1**	**171.8**	**0.14**	**0.42**	**70.7**	**2.67**	**0.57**	**8.1**	**199.7**	**3.33**
	21-0475	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
200 mg/kg-d	21-0476	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0479	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0480	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0491	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0492	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	21-0457	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
400 mg/kg-d	21-0458	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0477	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0478	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0489	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0490	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**

Table J-3
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Clinical Chemistry Summary
Male Rats

Group		ALB (g/dL)	ALB / GLOB ratio (g/dL)	ALP (U/L)	ALT (U/L)	AST (U/L)	BUN (mg/dL)	BUN / CREA ratio	CA (mg/dL)	CHOL (mg/dL)	CK (U/L)	CREA (mg/dL)	GLOB calc. (g/dL)	GLU (mg/dL)	PHOS (mg/dL)	TP (g/dL)	TRIG (g/dL)	AMY (U/L)	LPS (U/L)
Corn Oil Control	**Mean**	3.7	1.33	277	63	105	10	11.70	12.2	79	258	0.9	2.8	217	15.7	6.5	26	3590	6.8
	SD	0.14	0.088	69.1	8.1	7.9	2.2	2.974	0.61	7.9	82.5	0.08	0.13	49.5	2.44	0.17	4.3	871.4	1.07
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
6.25 mg/kg-d	**Mean**	3.8	1.47	290	63	105	11	12.97	12.5	74	177	0.9	2.6	236	16.2	6.5	30	2851	7.6
	SD	0.15	0.179	68.2	15.4	15.2	2.5	1.579	0.74	6.7	82.3	0.10	0.28	119.1	2.57	0.29	9.3	570	1.62
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
12.5 mg/kg-d	**Mean**	3.9	1.38	270	56	86*	11	14.95	12.7	76	121*	0.8	2.8	253	15.4	6.7	34	3064	6.8
	SD	0.14	0.107	78.7	13.2	7.6	1.7	3.990	0.63	12.7	28.8	0.10	0.26	106.5	2.36	0.35	13.6	725.4	0.72
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
25 mg/kg-d	**Mean**	3.8	1.34	229	56	112	9	11.04	12.7	77	315	0.9	2.9	222	16.9	6.7	20	3499	7.3
	SD	0.10	0.140	54.1	9.4	37.3	1.4	1.446	0.50	8.6	320.4	0.10	0.28	77.3	2.30	0.26	13.5	1288.9	1.22
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
50 mg/kg-d	**Mean**	3.8	1.40	238	44*	88*	13	18.12*	12.3	112*	239	0.7*	2.7	225	16.2	6.5	21	2866	6.6
	SD	0.13	0.106	37.5	6.7	11.5	3.5	4.065	0.22	15.9	121.8	0.11	0.18	63.8	1.53	0.21	5.5	914.2	0.43
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
100 mg/kg-d	**Mean**	4.0*	1.32	201	51	99	19*	19.98*	12.5	123*	243	0.9	3.1	162	16.3	7.0*	21	2280*	7.4
	SD	0.10	0.152	37.2	8.5	19.9	4.8	5.148	0.48	15.1	91.1	0.12	0.36	61.4	2.19	0.37	7.6	191.2	1.17
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
200 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
400 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

* p<0.05 compared to controls

Table J-4
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Clinical Chemistry Summary
Female Rats

Group		ALB (g/dL)	ALB / GLOB ratio (g/dL)	ALP (U/L)	ALT (U/L)	AST (U/L)	BUN (mg/dL)	BUN / CREA ratio	CA (mg/dL)	CHOL (mg/dL)	CK (U/L)	CREA (mg/dL)	GLOB calc. (g/dL)	GLU (mg/dL)	PHOS (mg/dL)	TP (g/dL)	TRIG (g/dL)	AMY (U/L)	LPS (U/L)
Corn Oil Control	**Mean**	4.6	1.46	154	55	158	18	17.99	12.8	97	599	1.0	3.1	128	18.8	7.7	34	1381	9.5
	SD	0.26	0.094	23.3	11.2	153.3	4.4	5.619	0.31	11.5	949.7	0.09	0.16	70.3	1.55	0.35	6.7	337.1	1.94
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
6.25 mg/kg-d	**Mean**	4.4	1.59	143	54	99	15	16.64	12.7	92	194	0.9	2.8	136	17.0	7.3	28	1335	7.5
	SD	0.34	0.205	44.4	9.4	16.2	1.9	3.807	0.33	25.7	101.3	0.12	0.39	75.2	1.26	0.58	7.8	131.8	2.68
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
12.5 mg/kg-d	**Mean**	4.4	1.46	158	51	98	15	15.84	12.4	82	175	1.0	3.0	94	15.7	7.4	20*	1307	8.2
	SD	0.26	0.173	43.4	7.4	5.0	2.6	2.115	0.40	10.8	39.8	0.14	0.35	18.7	2.32	0.44	4.2	172.4	0.88
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
25 mg/kg-d	**Mean**	4.6	1.64	131	49	93	16	17.10	12.6	97	162	0.9	2.9	116	17.4	7.5	25	1510	8.6
	SD	0.32	0.180	18.2	10.2	14.4	3.2	2.440	0.32	15.0	70.1	0.10	0.34	29.6	1.80	0.56	4.5	309.0	0.61
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
50 mg/kg-d	**Mean**	4.8	1.59	135	46	78	17	20.31	13.0	120	123	0.8*	3.0	120	17.1	7.8	30	1391	8
	SD	0.35	0.067	39.7	8.2	7.9	2.4	3.005	0.41	24.2	59.0	0.08	0.17	51.5	1.38	0.50	9.5	332	0.48
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
100 mg/kg-d	**Mean**	4.7	1.44	132	54	93	22	26.20*	13.2	175*	212	0.8*	3.3	170	16.6	8.0	32	1530	9.7
	SD	0.21	0.150	45.8	14.0	32.7	4.3	5.059	0.19	41.1	171.8	0.14	0.42	70.7	2.67	0.57	8.1	199.7	3.33
	N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
200 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
400 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

* $p<0.05$ compared to controls

Appendix K

Subacute Individual and Summary of Electrolytes and Prothrombin Time

Abbreviations:

mg/kg-d: milligrams per kilogram per day
(f): animal died on study
ND: no data
mmol/L: millimoles per liter
mg/dl: milligrams per deciliter
sec: second
Na: sodium
K: potassium
Cl: chloride
iCa: ionized calcium
iMg: ionized magnesium
Glu: glucose
Lac: lactate
AVG PT: average prothrombin time
SD: standard deviation

Table K-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Electrolytes and Prothrombin Time
Male Rats

Group	Animal ID	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	iCa (mmol/L)	iMg (mmol/L)	Glu (mg/dL)	Lac (mmol/L)	AVG. PT (sec)
	21-0391	152.9	7.34	106.6	1.59	1.42	248	10.0	10.7
Corn Oil	21-0392	154.5	9.63	106.7	1.63	1.47	165	11.2	11.0
Control	21-0431	156.2	7.56	105.2	1.59	1.26	203	6.0	10.1
	21-0432	159.6	7.54	106.4	1.65	1.30	151	6.2	9.9
	21-0435	153.5	8.70	104.6	1.59	0.89	198	5.9	10.3
	21-0436	152.5	6.80	104.3	1.54	0.84	154	3.9	10.0
	Mean	**154.9**	**7.93**	**105.6**	**1.60**	**1.20**	**187**	**7.2**	**10.3**
	SD	**2.67**	**1.039**	**1.07**	**0.038**	**0.269**	**37.3**	**2.79**	**0.44**
	21-0405	154.3	8.05	105.6	1.66	1.29	267	8.7	10.0
6.25 mg/kg-d	21-0406	150.5	7.32	103.4	1.47	0.95	105	6.6	10.9
	21-0415	151.2	10.01	105.7	1.68	1.42	274	8.3	10.0
	21-0416	151.1	8.95	105.0	1.55	1.31	110	6.6	ND
	21-0445	152.5	9.35	106.7	1.64	1.03	216	7.1	12.2
	21-0446	150.4	8.81	105.5	1.45	1.04	139	4.6	10.2
	Mean	**151.7**	**8.75**	**105.3**	**1.58**	**1.17**	**185**	**7.0**	**10.6**
	SD	**1.49**	**0.951**	**1.09**	**0.100**	**0.190**	**77.1**	**1.46**	**0.91**
	21-0393	157.9	7.83	106.3	1.69	1.35	242	8.8	9.9
12.5 mg/kg-d	21-0394	151.2	10.32	107.6	1.72	1.50	320	9.8	10.6
	21-0441	155.4	6.16	105.4	1.60	1.20	214	4.4	ND
	21-0442	153.5	7.02	101.9	1.49	0.98	114	3.5	11.1
	21-0447	148.9	11.84	105.0	1.38	1.02	162	6.8	9.8
	21-0448	153.1	7.16	104.4	1.68	1.03	283	7.1	10.4
	Mean	**153.3**	**8.39**	**105.1**	**1.59**	**1.18**	**223**	**6.7**	**10.3**
	SD	**3.14**	**2.205**	**1.92**	**0.134**	**0.210**	**76.2**	**2.44**	**0.56**
	21-0395	151.3	9.02	105.5	1.54	1.30	178	6.6	9.9
25 mg/kg-d	21-0396	153.2	7.90	104.8	1.55	1.20	112	8.5	10.3
	21-0397	151.0	10.80	105.4	1.66	1.48	164	9.4	10.4
	21-0398	159.7	7.53	105.1	1.56	1.27	146	7.7	10.8
	21-0409	154.3	7.03	105.7	1.60	0.97	266	6.4	10.9
	21-0410	151.3	8.05	105.8	1.57	1.08	294	8.7	10.4
	Mean	**153.5**	**8.39**	**105.4**	**1.58**	**1.22**	**193**	**7.9**	**10.4**
	SD	**3.32**	**1.353**	**0.38**	**0.044**	**0.178**	**71.2**	**1.20**	**0.36**
	21-0407	151.3	7.52	104.8	1.57	1.09	139	5.6	10.1
50 mg/kg-d	21-0408	153.3	7.45	105.9	1.62	1.19	191	6.2	10.1
	21-0413	150.3	8.75	104.6	1.54	1.03	296	6.9	9.8
	21-0414	152.3	8.09	104.8	1.56	0.92	179	5.6	10.0
	21-0429	153.6	7.04	104.1	1.51	0.90	219	5.1	10.3
	21-0430	152.4	8.98	105.0	1.56	0.88	150	5.5	ND
	Mean	**152.2**	**7.97**	**104.9**	**1.56**	**1.00**	**196**	**5.8**	**10.0**
	SD	**1.24**	**0.772**	**0.59**	**0.036**	**0.123**	**56.9**	**0.64**	**0.18**
	21-0421	153.5	9.87	105.2	1.68	1.13	138	9.6	10.4
100 mg/kg-d	21-0422	145.6	7.57	104.8	1.56	0.95	132	5.1	9.5
	21-0433	152.0	8.46	104.3	1.60	0.95	251	7.2	9.8
	21-0434	151.0	9.50	105.9	1.58	0.84	116	6.4	10.1
	21-0443	144.9	6.47	106.1	1.51	0.80	109	5.9	10.0
	21-0444	152.1	9.77	105.6	1.57	0.85	126	6.3	10.5
	Mean	**149.9**	**8.61**	**105.3**	**1.58**	**0.92**	**145**	**6.8**	**10.0**
	SD	**3.66**	**1.372**	**0.69**	**0.056**	**0.120**	**52.8**	**1.56**	**0.36**
	21-0403	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
200 mg/kg-d	21-0404	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0423	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0424	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0427	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0428	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	21-0399	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
400 mg/kg-d	21-0400	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0401	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0402	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0419	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0420	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**

Table K-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Electrolytes and Prothrombin Time
Female Rats

Group	Animal ID	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	iCa (mmol/L)	iMg (mmol/L)	Glu (mg/dL)	Lac (mmol/L)	AVG. PT (sec)
	21-0467	146.2	12.69	106.1	1.68	1.11	256	6.8	9.3
Corn Oil	21-0468	153.2	5.81	108.6	1.61	0.95	118	4.3	9.9
Control	21-0471	145.2	11.60	105.0	1.64	1.15	78	4.5	9.3
	21-0472	150.9	9.77	107.4	1.60	1.01	78	5.0	9.2
	21-0481	153.3	8.59	103.4	1.65	0.99	102	4.4	8.9
	21-0482	146.3	8.99	104.1	1.54	0.93	76	5.5	8.5
	Mean	**149.2**	**9.58**	**105.8**	**1.62**	**1.02**	**118**	**5.1**	**9.2**
	SD	**3.72**	**2.422**	**1.99**	**0.049**	**0.088**	**69.7**	**0.95**	**0.45**
	21-0453	151.8	8.49	105.4	1.58	0.87	102	4.8	9.2
6.25 mg/kg-d	21-0454	153.5	8.99	107.7	1.63	0.89	88	3.9	9.4
	21-0485	146.4	8.91	107.0	1.55	0.99	170	5.5	9.8
	21-0486	150.3	9.93	102.9	1.72	1.03	276	7.0	9.3
	21-0495	152.1	8.73	106.2	1.55	0.87	91	2.5	9.1
	21-0496	154.2	6.72	104.7	1.60	0.98	71	3.8	ND
	Mean	**151.4**	**8.63**	**105.7**	**1.61**	**0.94**	**133**	**4.6**	**9.4**
	SD	**2.80**	**1.056**	**1.72**	**0.064**	**0.070**	**78.0**	**1.56**	**0.27**
	21-0451	144.5	12.07	105.4	1.64	1.02	73	5.6	9.4
12.5 mg/kg-d	21-0452	152.3	7.00	105.8	1.61	0.81	102	2.9	9.0
	21-0465	145.7	8.32	105.4	1.55	0.94	77	3.3	9.0
	21-0466	146.6	8.52	105.9	1.52	0.77	94	4.3	9.4
	21-0469	150.4	7.05	104.6	1.58	0.87	109	2.6	9.2
	21-0470	154.1	8.61	106.0	1.58	0.87	84	3.7	8.9
	Mean	**148.9**	**8.60**	**105.5**	**1.58**	**0.88**	**90**	**3.7**	**9.1**
	SD	**3.89**	**1.849**	**0.52**	**0.042**	**0.090**	**14.2**	**1.09**	**0.21**
	21-0455	152.9	7.03	108.0	1.54	0.86	82	4.6	9.2
25 mg/kg-d	21-0456	150.4	8.44	104.3	1.63	0.99	108	4.8	9.3
	21-0459	150.4	10.49	106.3	1.67	1.10	159	6.5	9.4
	21-0460	148.8	9.70	104.9	1.58	1.03	72	4.8	9.7
	21-0461	150.0	6.55	105.8	1.54	0.88	117	3.8	8.7
	21-0462	152.6	11.00	105.2	1.66	0.94	169	7.0	9.0
	Mean	**150.9**	**8.87**	**105.8**	**1.60**	**0.97**	**118**	**5.3**	**9.2**
	SD	**1.59**	**1.833**	**1.30**	**0.058**	**0.092**	**39.5**	**1.23**	**0.35**
	21-0463	145.7	11.46	104.2	1.65	0.99	146	6.6	9.4
50 mg/kg-d	21-0464	152.8	10.01	104.6	1.69	0.92	197	8.7	9.1
	21-0473	155.2	6.33	102.8	1.63	0.87	85	4.0	8.9
	21-0474	150.6	8.22	104.3	1.57	0.87	110	5.3	8.8
	21-0487	148.8	9.97	104.8	1.62	1.03	79	4.9	8.7
	21-0488	146.0	12.22	104.9	1.64	1.01	79	6.1	8.3
	Mean	**149.9**	**9.70**	**104.3**	**1.63**	**0.95**	**116**	**5.9**	**8.9**
	SD	**3.77**	**2.152**	**0.77**	**0.039**	**0.071**	**47.3**	**1.63**	**0.37**
	21-0449	148.7	10.86	106.3	1.65	1.02	97	6.0	8.7
100 mg/kg-d	21-0450	152.6	9.49	102.9	1.68	1.00	91	4.1	9.2
	21-0483	147.6	8.72	102.2	1.54	0.86	180	6.8	9.1
	21-0484	148.6	9.98	105.6	1.69	1.01	224	6.6	9.0
	21-0493	152.7	8.33	103.7	1.66	1.10	152	5.8	8.9
	21-0494	153.9	8.98	104.7	1.58	0.98	150	6.4	9.1
	Mean	**150.7**	**9.39**	**104.2**	**1.63**	**1.00**	**149**	**6.0**	**9.0**
	SD	**2.68**	**0.923**	**1.58**	**0.060**	**0.078**	**50.3**	**0.98**	**0.16**
	21-0475	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
200 mg/kg-d	21-0476	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0479	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0480	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0491	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0492	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	21-0457	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
400 mg/kg-d	21-0458	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0477	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0478	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0489	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0490	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**

Table K-3
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Electrolytes and Prothrombin Time Summary
Male Rats

Group	Animal ID	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	iCa (mmol/L)	iMg (mmol/L)	Glu (mg/dL)	Lac (mmol/L)	AVG. PT (sec)
Corn Oil Control	**Mean**	154.9	7.93	105.6	1.60	1.20	187	7.2	10.3
	SD	2.67	1.039	1.07	0.038	0.269	37.3	2.79	0.44
	N	6	6	6	6	6	6	6	6
6.25 mg/kg-d	**Mean**	151.7	8.75	105.3	1.58	1.17	185	7.0	10.6
	SD	1.49	0.951	1.09	0.100	0.190	77.1	1.46	0.91
	N	6	6	6	6	6	6	6	5.00
12.5 mg/kg-d	**Mean**	153.3	8.39	105.1	1.59	1.18	223	6.7	10.3
	SD	3.14	2.205	1.92	0.134	0.210	76.2	2.44	0.56
	N	6	6	6	6	6	6	6	5.00
25 mg/kg-d	**Mean**	153.5	8.39	105.4	1.58	1.22	193	7.9	10.4
	SD	3.32	1.353	0.38	0.044	0.178	71.2	1.20	0.36
	N	6	6	6	6	6	6	6	6
50 mg/kg-d	**Mean**	152.2	7.97	104.9	1.56	1.00	196	5.8	10.0
	SD	1.24	0.772	0.59	0.036	0.123	56.9	0.64	0.18
	N	6	6	6	6	6	6	6	6
100 mg/kg-d	**Mean**	149.9	8.61	105.3	1.58	0.92	145	6.8	10.0
	SD	3.66	1.372	0.69	0.056	0.120	52.8	1.56	0.36
	N	6	6	6	6	6	6	6	6
200 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0
400 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0

Table K-4
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Electrolytes and Prothrombin Time Summary
Female Rats

Group	Animal ID	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	iCa (mmol/L)	iMg (mmol/L)	Glu (mg/dL)	Lac (mmol/L)	AVG. PT (sec)
Corn Oil Control	**Mean**	149.2	9.58	105.8	1.62	1.02	118	5.1	9.2
	SD	3.72	2.422	1.99	0.049	0.088	69.7	0.95	0.45
	N	6	6	6	6	6	6	6	6
6.25 mg/kg-d	**Mean**	151.4	8.63	105.7	1.61	0.94	133	4.6	9.4
	SD	2.80	1.056	1.72	0.064	0.070	78.0	1.56	0.27
	N	6	6	6	6	6	6	6	5
12.5 mg/kg-d	**Mean**	148.9	8.60	105.5	1.58	0.88	90	3.7	9.1
	SD	3.89	1.849	0.52	0.042	0.090	14.2	1.09	0.21
	N	6	6	6	6	6	6	6	6
25 mg/kg-d	**Mean**	150.9	8.87	105.8	1.60	0.97	118	5.3	9.2
	SD	1.59	1.833	1.30	0.058	0.092	39.5	1.23	0.35
	N	6	6	6	6	6	6	6	6
50 mg/kg-d	**Mean**	149.9	9.70	104.3	1.63	0.95	116	5.9	8.9
	SD	3.77	2.152	0.77	0.039	0.071	47.3	1.63	0.37
	N	6	6	6	6	6	6	6	6
100 mg/kg-d	**Mean**	150.7	9.39	104.2	1.63	1.00	149	6.0	9.0
	SD	2.68	0.923	1.58	0.060	0.078	50.3	0.98	0.16
	N	6	6	6	6	6	6	6	6
200 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0
400 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0

Appendix L

Subacute Individual and Summary of Organ Mass and Mass Ratios

Abbreviations:

mg/kg-d: milligrams per kilogram per day
(f): animal died on study
ND: no data
SD: standard deviation

Table L-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Absolute Organ Mass (grams)
Male Rats

Group	Animal ID	Body Weight[1]	Body Weight[2]	Brain	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Testes	Epididymides
	21-0391	335	326	1.989	0.046	2.435	0.669	1.151	0.561	11.871	2.938	0.698
Corn Oil	21-0392	292	285	2.011	0.041	1.851	0.494	1.080	0.425	10.536	3.048	0.778
Control	21-0431	294	284	1.985	0.038	2.029	0.558	1.029	0.564	10.466	2.594	0.564
	21-0432	337	324	2.031	0.051	2.400	0.662	1.275	0.454	12.047	3.204	0.614
	21-0435	336	324	1.941	0.047	2.337	0.702	1.270	0.572	12.409	2.896	0.672
	21-0436	333	322	2.029	0.040	2.061	0.650	1.177	0.610	11.060	3.124	0.710
	Mean	**321**	**311**	**1.998**	**0.044**	**2.186**	**0.623**	**1.164**	**0.531**	**11.398**	**2.967**	**0.673**
	SD	**21.9**	**20.4**	**0.0338**	**0.0050**	**0.2379**	**0.0793**	**0.0992**	**0.0736**	**0.8238**	**0.2156**	**0.0753**
	21-0405	340	330	2.059	0.038	2.495	0.698	1.248	0.574	11.885	3.322	0.715
6.25 mg/kg-d	21-0406	338	328	2.173	0.054	2.568	0.742	1.255	0.473	11.444	2.908	0.865
	21-0415	292	279	1.936	0.039	2.125	0.557	1.217	0.428	9.529	2.670	0.684
	21-0416	313	303	2.066	0.027	2.366	0.657	1.306	0.694	11.862	2.577	0.671
	21-0445	311	311	2.014	0.045	2.281	0.539	1.235	0.525	10.880	3.138	0.635
	21-0446	315	311	2.051	0.038	2.139	0.524	1.227	0.472	11.099	2.621	0.666
	Mean	**318**	**310**	**2.050**	**0.040**	**2.329**	**0.620**	**1.248**	**0.528**	**11.117**	**2.873**	**0.706**
	SD	**18.1**	**18.6**	**0.0771**	**0.0089**	**0.1822**	**0.0917**	**0.0316**	**0.0958**	**0.8752**	**0.3051**	**0.0821**
	21-0393	322	313	1.997	0.040	2.167	0.680	1.216	0.542	10.528	3.014	0.677
12.5 mg/kg-d	21-0394	324	318	2.085	0.041	2.071	0.886	1.192	0.606	1.287*	2.563	0.636
	21-0441	392	381	2.142	0.051	2.860	0.872	1.347	0.501	13.881	3.335	0.767
	21-0442	359	348	1.908	0.047	2.466	0.582	1.445	0.749	11.972	3.373	0.774
	21-0447	331	320	2.062	0.055	2.481	0.671	1.408	0.650	13.039	2.385	0.666
	21-0448	301	294	1.997	0.038	1.954	0.475	1.146	0.601	9.760	2.640	0.654
	Mean	**338**	**329**	**2.032**	**0.045**	**2.333**	**0.694**	**1.292**	**0.608**	**11.836**	**2.885**	**0.696**
	SD	**32.3**	**30.8**	**0.0820**	**0.0068**	**0.3338**	**0.1611**	**0.1241**	**0.0866**	**1.7079**	**0.4174**	**0.0596**
	21-0395	364	358	2.211	0.045	2.668	0.687	1.214	0.428	12.232	3.224	0.926
25 mg/kg-d	21-0396	366	352	2.201	0.043	2.318	0.674	1.316	0.523	12.276	3.147	0.859
	21-0397	312	303	1.991	0.038	2.144	0.702	1.157	0.507	11.211	2.907	0.661
	21-0398	315	306	2.037	0.047	2.396	0.623	1.303	0.549	11.042	3.033	0.684
	21-0409	350	339	2.009	0.042	2.575	0.827	1.439	0.601	12.689	3.031	0.682
	21-0410	281	276	1.982	0.042	2.093	0.438	1.170	0.469	9.397	2.860	0.622
	Mean	**331**	**322**	**2.072**	**0.043**	**2.366**	**0.659**	**1.267**	**0.513**	**11.475**	**3.034**	**0.739**
	SD	**34.0**	**32.3**	**0.1057**	**0.0031**	**0.2289**	**0.1274**	**0.1073**	**0.0606**	**1.2053**	**0.1380**	**0.1228**
	21-0407	308	301	2.060	0.049	2.271	0.711	1.342	0.626	10.167	2.760	0.681
50 mg/kg-d	21-0408	301	291	2.104	0.038	2.347	0.766	1.263	0.645	10.356	2.544	0.582
	21-0413	301	291	2.009	0.033	1.988	0.810	1.011	0.483	10.073	2.972	0.732
	21-0414	322	314	2.046	0.043	2.166	0.797	1.081	0.681	12.466	2.779	0.692
	21-0429	370	360	2.252	0.047	2.781	0.953	1.303	0.598	12.392	3.179	0.854
	21-0430	357	342	2.076	0.052	2.623	0.861	1.318	0.695	14.090	3.329	0.743
	Mean	**327**	**317**	**2.091**	**0.044**	**2.363**	**0.816**	**1.220**	**0.621**	**11.591**	**2.927**	**0.714**
	SD	**30.0**	**28.6**	**0.0849**	**0.0071**	**0.2934**	**0.0833**	**0.1387**	**0.0765**	**1.6437**	**0.2911**	**0.0892**
	21-0421	315	298	2.038	0.052	2.806	0.991	1.159	0.594	12.251	2.979	0.737
100 mg/kg-d	21-0422	286	271	2.027	0.048	2.254	0.866	1.053	0.589	9.765	2.779	0.640
	21-0433	284	276	2.024	0.039	2.225	0.669	1.131	0.584	10.234	2.917	0.595
	21-0434	274	266	2.095	0.052	2.477	0.965	1.111	0.546	10.820	2.684	0.609
	21-0443	301	292	1.991	0.055	2.337	1.250	1.182	0.497	10.924	2.484	0.683
	21-0444	275	265	2.091	0.042	2.197	1.006	1.208	0.675	11.197	2.736	0.553
	Mean	**289**	**278**	**2.044**	**0.048**	**2.383**	**0.958**	**1.141**	**0.581**	**10.865**	**2.763**	**0.636**
	SD	**16.0**	**13.9**	**0.0408**	**0.0063**	**0.2307**	**0.1901**	**0.0552**	**0.0589**	**0.8538**	**0.1763**	**0.0659**
	21-0403	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
200 mg/kg-d	21-0404	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0423	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0424	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0427	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0428	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	21-0399	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
400 mg/kg-d	21-0400	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0401	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0402	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0419	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0420	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**

[1] = Unfasted day 13 body weight
[2] = Fasted day 14 body weight
* = Outlier

Table L-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Organ to Body Mass Ratios
Male Rats

Group	Animal ID	Brain	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Testes	Epididymides
	21-0391	0.0059	0.0001	0.0073	0.0020	0.0034	0.0017	0.0354	0.0088	0.0021
Corn Oil	21-0392	0.0069	0.0001	0.0063	0.0017	0.0037	0.0015	0.0361	0.0104	0.0027
Control	21-0431	0.0068	0.0001	0.0069	0.0019	0.0035	0.0019	0.0356	0.0088	0.0019
	21-0432	0.0060	0.0002	0.0071	0.0020	0.0038	0.0013	0.0357	0.0095	0.0018
	21-0435	0.0058	0.0001	0.0070	0.0021	0.0038	0.0017	0.0369	0.0086	0.0020
	21-0436	0.0061	0.0001	0.0062	0.0020	0.0035	0.0018	0.0332	0.0094	0.0021
	Mean	**0.0062**	**0.0001**	**0.0068**	**0.0019**	**0.0036**	**0.0017**	**0.0355**	**0.0093**	**0.0021**
	SD	**0.00046**	**0.00001**	**0.00043**	**0.00013**	**0.00015**	**0.00022**	**0.00124**	**0.00068**	**0.00030**
	21-0405	0.0061	0.0001	0.0073	0.0021	0.0037	0.0017	0.0350	0.0098	0.0021
6.25 mg/kg-d	21-0406	0.0064	0.0002	0.0076	0.0022	0.0037	0.0014	0.0339	0.0086	0.0026
	21-0415	0.0066	0.0001	0.0073	0.0019	0.0042	0.0015	0.0326	0.0091	0.0023
	21-0416	0.0066	0.0001	0.0076	0.0021	0.0042	0.0022	0.0379	0.0082	0.0021
	21-0445	0.0065	0.0001	0.0073	0.0017	0.0040	0.0017	0.0350	0.0101	0.0020
	21-0446	0.0065	0.0001	0.0068	0.0017	0.0039	0.0015	0.0352	0.0083	0.0021
	Mean	**0.0065**	**0.0001**	**0.0073**	**0.0019**	**0.0039**	**0.0017**	**0.0349**	**0.0090**	**0.0022**
	SD	**0.00021**	**0.00003**	**0.00029**	**0.00021**	**0.00022**	**0.00030**	**0.00175**	**0.00078**	**0.00020**
	21-0393	0.0062	0.0001	0.0067	0.0021	0.0038	0.0017	0.0327	0.0094	0.0021
12.5 mg/kg-d	21-0394	0.0064	0.0001	0.0064	0.0027	0.0037	0.0019	ND	0.0079	0.0020
	21-0441	0.0055	0.0001	0.0073	0.0022	0.0034	0.0013	0.0354	0.0085	0.0020
	21-0442	0.0053	0.0001	0.0069	0.0016	0.0040	0.0021	0.0333	0.0094	0.0022
	21-0447	0.0062	0.0002	0.0075	0.0020	0.0043	0.0020	0.0394	0.0072	0.0020
	21-0448	0.0066	0.0001	0.0065	0.0016	0.0038	0.0020	0.0324	0.0088	0.0022
	Mean	**0.0060**	**0.0001**	**0.0069**	**0.0020**	**0.0038**	**0.0018**	**0.0347**	**0.0085**	**0.0021**
	SD	**0.00053**	**0.00002**	**0.00044**	**0.00043**	**0.00028**	**0.00030**	**0.00290**	**0.00085**	**0.00010**
	21-0395	0.0061	0.0001	0.0073	0.0019	0.0033	0.0012	0.0336	0.0089	0.0025
25 mg/kg-d	21-0396	0.0060	0.0001	0.0063	0.0018	0.0036	0.0014	0.0335	0.0086	0.0023
	21-0397	0.0064	0.0001	0.0069	0.0023	0.0037	0.0016	0.0359	0.0093	0.0021
	21-0398	0.0065	0.0001	0.0076	0.0020	0.0041	0.0017	0.0351	0.0096	0.0022
	21-0409	0.0057	0.0001	0.0074	0.0024	0.0041	0.0017	0.0363	0.0087	0.0019
	21-0410	0.0071	0.0001	0.0074	0.0016	0.0042	0.0017	0.0334	0.0102	0.0022
	Mean	**0.0063**	**0.0001**	**0.0072**	**0.0020**	**0.0038**	**0.0016**	**0.0346**	**0.0092**	**0.0022**
	SD	**0.00046**	**0.00001**	**0.00047**	**0.00029**	**0.00035**	**0.00022**	**0.00128**	**0.00062**	**0.00020**
	21-0407	0.0067	0.0002	0.0074	0.0023	0.0044	0.0020	0.0330	0.0090	0.0022
50 mg/kg-d	21-0408	0.0070	0.0001	0.0078	0.0025	0.0042	0.0021	0.0344	0.0085	0.0019
	21-0413	0.0067	0.0001	0.0066	0.0027	0.0034	0.0016	0.0335	0.0099	0.0024
	21-0414	0.0064	0.0001	0.0067	0.0025	0.0034	0.0021	0.0387	0.0086	0.0021
	21-0429	0.0061	0.0001	0.0075	0.0026	0.0035	0.0016	0.0335	0.0086	0.0023
	21-0430	0.0058	0.0001	0.0073	0.0024	0.0037	0.0019	0.0395	0.0093	0.0021
	Mean	**0.0064**	**0.0001**	**0.0072**	**0.0025**	**0.0037**	**0.0019**	**0.0354**	**0.0090**	**0.0022**
	SD	**0.00043**	**0.00002**	**0.00047**	**0.00013**	**0.00043**	**0.00024**	**0.00289**	**0.00054**	**0.00017**
	21-0421	0.0065	0.0002	0.0089	0.0031	0.0037	0.0019	0.0389	0.0095	0.0023
100 mg/kg-d	21-0422	0.0071	0.0002	0.0079	0.0030	0.0037	0.0021	0.0341	0.0097	0.0022
	21-0433	0.0071	0.0001	0.0078	0.0024	0.0040	0.0021	0.0360	0.0103	0.0021
	21-0434	0.0076	0.0002	0.0090	0.0035	0.0041	0.0020	0.0395	0.0098	0.0022
	21-0443	0.0066	0.0002	0.0078	0.0042	0.0039	0.0017	0.0363	0.0083	0.0023
	21-0444	0.0076	0.0002	0.0080	0.0037	0.0044	0.0025	0.0407	0.0099	0.0020
	Mean	**0.0071**	**0.0002**	**0.0082**	**0.0033**	**0.0040**	**0.0020**	**0.0376**	**0.0096**	**0.0022**
	SD	**0.00049**	**0.00002**	**0.00058**	**0.00062**	**0.00027**	**0.00026**	**0.00249**	**0.00070**	**0.00012**
	21-0403	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
200 mg/kg-d	21-0404	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0423	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0424	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0427	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0428	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	21-0399	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
400 mg/kg-d	21-0400	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0401	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0402	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0419	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0420	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**

Table L-3
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Organ to Brain Mass Ratios
Male Rats

Group	Animal ID	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Testes	Epididymides
	21-0391	0.0231	1.2242	0.3363	0.5787	0.2821	5.9683	1.4771	0.3509
Corn Oil	21-0392	0.0204	0.9204	0.2456	0.5370	0.2113	5.2392	1.5157	0.3869
Control	21-0431	0.0191	1.0222	0.2811	0.5184	0.2841	5.2725	1.3068	0.2841
	21-0432	0.0251	1.1817	0.3259	0.6278	0.2235	5.9316	1.5775	0.3023
	21-0435	0.0242	1.2040	0.3617	0.6543	0.2947	6.3931	1.4920	0.3462
	21-0436	0.0197	1.0158	0.3204	0.5801	0.3006	5.4510	1.5397	0.3499
	Mean	**0.0219**	**1.0947**	**0.3118**	**0.5827**	**0.2661**	**5.7093**	**1.4848**	**0.3367**
	SD	**0.00252**	**0.12502**	**0.04167**	**0.05177**	**0.03847**	**0.46099**	**0.09419**	**0.03723**
	21-0405	0.0185	1.2118	0.3390	0.6061	0.2788	5.7722	1.6134	0.3473
6.25 mg/kg-d	21-0406	0.0249	1.1818	0.3415	0.5775	0.2177	5.2665	1.3382	0.3981
	21-0415	0.0201	1.0976	0.2877	0.6286	0.2211	4.9220	1.3791	0.3533
	21-0416	0.0131	1.1452	0.3180	0.6321	0.3359	5.7415	1.2473	0.3248
	21-0445	0.0223	1.1326	0.2676	0.6132	0.2607	5.4022	1.5581	0.3153
	21-0446	0.0185	1.0429	0.2555	0.5982	0.2301	5.4115	1.2779	0.3247
	Mean	**0.0196**	**1.1353**	**0.3015**	**0.6093**	**0.2574**	**5.4193**	**1.4024**	**0.3439**
	SD	**0.00401**	**0.06011**	**0.03669**	**0.02025**	**0.04533**	**0.31604**	**0.15031**	**0.03028**
	21-0393	0.0200	1.0851	0.3405	0.6089	0.2714	5.2719	1.5093	0.3390
12.5 mg/kg-d	21-0394	0.0197	0.9933	0.4249	0.5717	0.2906	ND	1.2293	0.3050
	21-0441	0.0238	1.3352	0.4071	0.6289	0.2339	6.4804	1.5570	0.3581
	21-0442	0.0246	1.2925	0.3050	0.7573	0.3926	6.2746	1.7678	0.4057
	21-0447	0.0267	1.2032	0.3254	0.6828	0.3152	6.3235	1.1565	0.3230
	21-0448	0.0190	0.9785	0.2379	0.5739	0.3010	4.8873	1.3220	0.3275
	Mean	**0.0223**	**1.1480**	**0.3401**	**0.6372**	**0.3008**	**5.8475**	**1.4236**	**0.3430**
	SD	**0.00315**	**0.15205**	**0.06868**	**0.07168**	**0.05305**	**0.71812**	**0.22936**	**0.03536**
	21-0395	0.0204	1.2067	0.3107	0.5491	0.1936	5.5323	1.4582	0.4188
25 mg/kg-d	21-0396	0.0195	1.0532	0.3062	0.5979	0.2376	5.5775	1.4298	0.3903
	21-0397	0.0191	1.0768	0.3526	0.5811	0.2546	5.6308	1.4601	0.3320
	21-0398	0.0231	1.1762	0.3058	0.6397	0.2695	5.4207	1.4890	0.3358
	21-0409	0.0209	1.2817	0.4116	0.7163	0.2992	6.3161	1.5087	0.3395
	21-0410	0.0212	1.0560	0.2210	0.5903	0.2366	4.7412	1.4430	0.3138
	Mean	**0.0207**	**1.1418**	**0.3180**	**0.6124**	**0.2485**	**5.5364**	**1.4648**	**0.3550**
	SD	**0.00141**	**0.09425**	**0.06280**	**0.05869**	**0.03556**	**0.50285**	**0.02925**	**0.04038**
	21-0407	0.0238	1.1024	0.3451	0.6515	0.3039	4.9354	1.3398	0.3306
50 mg/kg-d	21-0408	0.0181	1.1154	0.3641	0.6003	0.3066	4.9221	1.2091	0.2766
	21-0413	0.0164	0.9895	0.4032	0.5032	0.2404	5.0139	1.4793	0.3644
	21-0414	0.0210	1.0587	0.3895	0.5283	0.3328	6.0929	1.3583	0.3382
	21-0429	0.0209	1.2349	0.4232	0.5786	0.2655	5.5025	1.4116	0.3792
	21-0430	0.0250	1.2635	0.4147	0.6349	0.3348	6.7871	1.6036	0.3579
	Mean	**0.0209**	**1.1274**	**0.3900**	**0.5828**	**0.2973**	**5.5423**	**1.4003**	**0.3411**
	SD	**0.00327**	**0.10447**	**0.03024**	**0.05839**	**0.03753**	**0.75978**	**0.13392**	**0.03620**
	21-0421	0.0255	1.3768	0.4863	0.5687	0.2915	6.0113	1.4617	0.3616
100 mg/kg-d	21-0422	0.0237	1.1120	0.4272	0.5195	0.2906	4.8175	1.3710	0.3157
	21-0433	0.0193	1.0993	0.3305	0.5588	0.2885	5.0563	1.4412	0.2940
	21-0434	0.0248	1.1823	0.4606	0.5303	0.2606	5.1647	1.2811	0.2907
	21-0443	0.0276	1.1738	0.6278	0.5937	0.2496	5.4867	1.2476	0.3430
	21-0444	0.0201	1.0507	0.4811	0.5777	0.3228	5.3549	1.3085	0.2645
	Mean	**0.0235**	**1.1658**	**0.4689**	**0.5581**	**0.2839**	**5.3152**	**1.3519**	**0.3116**
	SD	**0.00324**	**0.11440**	**0.09660**	**0.02838**	**0.02590**	**0.41302**	**0.08737**	**0.03599**
	21-0403	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
200 mg/kg-d	21-0404	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0423	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0424	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0427	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0428	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	21-0399	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
400 mg/kg-d	21-0400	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0401	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0402	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0419	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0420	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**

Table L-4
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Absolute Organ Mass (grams)
Female Rats

Group	Animal ID	Body Weight[1]	Body Weight[2]	Brain	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Uterus	Ovaries
	21-0467	231	221	1.947	0.056	1.377	0.548	0.880	0.661	9.039	0.485	0.119
Corn Oil	21-0468	242	231	1.876	0.060	1.648	0.576	0.925	0.523	8.595	0.949	0.106
Control	21-0471	228	220	1.868	0.055	1.905	0.472	1.000	0.542	8.331	0.529	0.099
	21-0472	225	220	2.094	0.057	1.725	0.502	0.854	0.565	9.074	1.152	0.120
	21-0481	256	246	1.933	0.069	1.832	0.512	1.037	0.576	10.239	1.057	0.135
	21-0482	274	264	1.726	0.069	1.876	0.677	1.062	0.958	11.019	0.641	0.132
	Mean	**243**	**234**	**1.907**	**0.061**	**1.727**	**0.548**	**0.960**	**0.638**	**9.383**	**0.802**	**0.119**
	SD	**19.1**	**18.0**	**0.1204**	**0.0064**	**0.1968**	**0.0730**	**0.0858**	**0.1640**	**1.0345**	**0.2864**	**0.0141**
	21-0453	247	237	1.990	0.053	1.613	0.562	1.041	0.661	8.662	0.785	0.126
6.25 mg/kg-d	21-0454	217	209	1.875	0.047	1.483	0.456	0.926	0.473	7.421	0.957	0.092
	21-0485	228	223	1.948	0.064	1.746	0.411	0.952	0.623	7.464	0.515	0.094
	21-0486	279	269	2.037	0.066	2.473	0.773	1.215	0.761	11.232	0.580	0.136
	21-0495	236	231	1.809	0.072	1.725	0.537	0.996	0.531	9.038	0.718	0.117
	21-0496	236	233	1.967	0.056	1.883	0.597	1.024	0.556	9.731	0.452	0.150
	Mean	**241**	**234**	**1.938**	**0.060**	**1.821**	**0.556**	**1.026**	**0.601**	**8.925**	**0.668**	**0.119**
	SD	**21.3**	**19.9**	**0.0825**	**0.0093**	**0.3468**	**0.1266**	**0.1023**	**0.1029**	**1.4457**	**0.1884**	**0.0231**
	21-0451	247	237	1.788	0.045	1.616	0.663	0.911	0.784	9.950	0.514	0.134
12.5 mg/kg-d	21-0452	217	209	1.791	0.055	1.578	0.442	0.816	0.551	7.638	0.822	0.094
	21-0465	228	223	1.905	0.053	1.811	0.538	0.906	0.641	7.609	0.512	0.115
	21-0466	279	269	1.906	0.063	1.595	0.564	1.063	0.661	7.511	0.572	0.097
	21-0469	236	231	1.959	0.059	1.799	0.577	0.960	0.483	8.230	0.528	0.116
	21-0470	236	233	2.030	0.061	1.750	0.584	1.006	0.498	9.419	0.626	0.105
	Mean	**241**	**234**	**1.897**	**0.056**	**1.692**	**0.561**	**0.944**	**0.603**	**8.393**	**0.596**	**0.110**
	SD	**21.3**	**19.9**	**0.0947**	**0.0065**	**0.1069**	**0.0720**	**0.0862**	**0.1146**	**1.0456**	**0.1191**	**0.0147**
	21-0455	238	229	1.917	0.063	1.729	0.509	1.051	0.509	9.504	1.131	0.135
25 mg/kg-d	21-0456	263	257	1.956	0.065	1.718	0.797	1.146	0.847	10.274	0.497	0.128
	21-0459	245	236	1.878	0.067	1.853	0.578	1.014	0.549	9.480	0.656	0.116
	21-0460	217	210	1.817	0.058	1.610	0.577	1.003	0.553	8.221	0.531	0.143
	21-0461	226	221	1.844	0.067	1.697	0.567	1.049	0.493	8.987	0.738	0.097
	21-0462	209	200	1.888	0.061	1.537	0.550	0.957	0.567	8.088	1.015	0.106
	Mean	**233**	**226**	**1.883**	**0.064**	**1.691**	**0.596**	**1.037**	**0.586**	**9.092**	**0.761**	**0.121**
	SD	**19.7**	**20.1**	**0.0498**	**0.0036**	**0.1084**	**0.1016**	**0.0637**	**0.1308**	**0.8361**	**0.2591**	**0.0176**
	21-0463	223	214	1.866	0.059	1.627	0.666	0.899	0.662	8.332	0.752	0.129
50 mg/kg-d	21-0464	234	227	1.833	0.049	1.596	0.725	0.970	0.672	8.573	1.211	0.126
	21-0473	244	238	1.959	0.064	1.975	0.535	1.174	0.477	9.641	0.482	0.132
	21-0474	267	258	2.010	0.053	1.924	0.687	1.162	0.585	10.523	0.634	0.107
	21-0487	254	251	2.006	0.064	1.826	0.974	1.041	0.834	10.088	0.713	0.136
	21-0488	231	227	1.821	0.056	1.586	0.547	0.991	0.590	9.343	0.551	0.142
	Mean	**242**	**236**	**1.916**	**0.058**	**1.756**	**0.689**	**1.040**	**0.637**	**9.417**	**0.724**	**0.129**
	SD	**16.2**	**16.5**	**0.0863**	**0.0060**	**0.1745**	**0.1593**	**0.1096**	**0.1193**	**0.8507**	**0.2587**	**0.0120**
	21-0449	197	188	1.825	0.049	1.659	0.569	0.833	0.398	7.423	0.456	0.094
100 mg/kg-d	21-0450	227	215	2.016	0.066	1.833	0.672	1.007	0.548	9.050	0.497	0.068
	21-0483	215	203	1.801	0.048	1.697	0.686	1.008	0.505	8.155	0.590	0.106
	21-0484	235	225	2.128	0.052	2.066	0.813	1.093	0.594	9.702	0.588	0.106
	21-0493	253	239	1.956	0.066	2.250	0.656	1.127	0.637	9.231	1.177	0.098
	21-0494	219	209	2.022	0.062	1.729	0.750	0.929	0.523	7.883	0.369	0.075
	Mean	**224**	**213**	**1.958**	**0.057**	**1.872**	**0.691**	**1.000**	**0.534**	**8.574**	**0.613**	**0.091**
	SD	**19.0**	**17.7**	**0.1255**	**0.0084**	**0.2360**	**0.0835**	**0.1075**	**0.0823**	**0.8841**	**0.2888**	**0.0161**
	21-0475	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
200 mg/kg-d	21-0476	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0479	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0480	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0491	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0492	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	21-0457	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
400 mg/kg-d	21-0458	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0477	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0478	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0489	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0490	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**

[1] = Unfasted day 13 body weight
[2] = Fasted day 14 body weight

Table L-5
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Organ to Body Mass Ratios
Female Rats

Group	Animal ID	Brain	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Uterus	Ovaries
	21-0467	0.0084	0.0002	0.0060	0.0024	0.0038	0.0029	0.0391	0.0021	0.0005
Corn Oil	21-0468	0.0078	0.0002	0.0068	0.0024	0.0038	0.0022	0.0355	0.0039	0.0004
Control	21-0471	0.0082	0.0002	0.0084	0.0021	0.0044	0.0024	0.0365	0.0023	0.0004
	21-0472	0.0093	0.0003	0.0077	0.0022	0.0038	0.0025	0.0403	0.0051	0.0005
	21-0481	0.0076	0.0003	0.0072	0.0020	0.0041	0.0023	0.0400	0.0041	0.0005
	21-0482	0.0063	0.0003	0.0068	0.0025	0.0039	0.0035	0.0402	0.0023	0.0005
	Mean	**0.0079**	**0.0003**	**0.0071**	**0.0023**	**0.0040**	**0.0026**	**0.0386**	**0.0033**	**0.0005**
	SD	**0.00100**	**0.00001**	**0.00082**	**0.00019**	**0.00023**	**0.00050**	**0.00208**	**0.00124**	**0.00004**
	21-0453	0.0081	0.0002	0.0065	0.0023	0.0042	0.0027	0.0351	0.0032	0.0005
6.25 mg/kg-d	21-0454	0.0086	0.0002	0.0068	0.0021	0.0043	0.0022	0.0342	0.0044	0.0004
	21-0485	0.0085	0.0003	0.0077	0.0018	0.0042	0.0027	0.0327	0.0023	0.0004
	21-0486	0.0073	0.0002	0.0089	0.0028	0.0044	0.0027	0.0403	0.0021	0.0005
	21-0495	0.0077	0.0003	0.0073	0.0023	0.0042	0.0023	0.0383	0.0030	0.0005
	21-0496	0.0083	0.0002	0.0080	0.0025	0.0043	0.0024	0.0412	0.0019	0.0006
	Mean	**0.0081**	**0.0002**	**0.0075**	**0.0023**	**0.0043**	**0.0025**	**0.0370**	**0.0028**	**0.0005**
	SD	**0.00052**	**0.00004**	**0.00084**	**0.00034**	**0.00007**	**0.00025**	**0.00346**	**0.00094**	**0.00008**
	21-0451	0.0072	0.0002	0.0065	0.0027	0.0037	0.0032	0.0403	0.0021	0.0005
12.5 mg/kg-d	21-0452	0.0083	0.0003	0.0073	0.0020	0.0038	0.0025	0.0352	0.0038	0.0004
	21-0465	0.0084	0.0002	0.0079	0.0024	0.0040	0.0028	0.0334	0.0022	0.0005
	21-0466	0.0068	0.0002	0.0057	0.0020	0.0038	0.0024	0.0269	0.0021	0.0003
	21-0469	0.0083	0.0003	0.0076	0.0024	0.0041	0.0020	0.0349	0.0022	0.0005
	21-0470	0.0086	0.0003	0.0074	0.0025	0.0043	0.0021	0.0399	0.0027	0.0004
	Mean	**0.0079**	**0.0002**	**0.0071**	**0.0023**	**0.0039**	**0.0025**	**0.0351**	**0.0025**	**0.0005**
	SD	**0.00072**	**0.00003**	**0.00082**	**0.00026**	**0.00022**	**0.00043**	**0.00490**	**0.00066**	**0.00007**
	21-0455	0.0081	0.0003	0.0073	0.0021	0.0044	0.0021	0.0399	0.0048	0.0006
25 mg/kg-d	21-0456	0.0074	0.0002	0.0065	0.0030	0.0044	0.0032	0.0391	0.0019	0.0005
	21-0459	0.0077	0.0003	0.0076	0.0024	0.0041	0.0022	0.0387	0.0027	0.0005
	21-0460	0.0084	0.0003	0.0074	0.0027	0.0046	0.0025	0.0379	0.0024	0.0007
	21-0461	0.0082	0.0003	0.0075	0.0025	0.0046	0.0022	0.0398	0.0033	0.0004
	21-0462	0.0090	0.0003	0.0074	0.0026	0.0046	0.0027	0.0387	0.0049	0.0005
	Mean	**0.0081**	**0.0003**	**0.0073**	**0.0026**	**0.0045**	**0.0025**	**0.0390**	**0.0033**	**0.0005**
	SD	**0.00056**	**0.00002**	**0.00038**	**0.00030**	**0.00019**	**0.00042**	**0.00076**	**0.00124**	**0.00008**
	21-0463	0.0084	0.0003	0.0073	0.0030	0.0040	0.0030	0.0374	0.0034	0.0006
50 mg/kg-d	21-0464	0.0078	0.0002	0.0068	0.0031	0.0041	0.0029	0.0366	0.0052	0.0005
	21-0473	0.0080	0.0003	0.0081	0.0022	0.0048	0.0020	0.0395	0.0020	0.0005
	21-0474	0.0075	0.0002	0.0072	0.0026	0.0044	0.0022	0.0394	0.0024	0.0004
	21-0487	0.0079	0.0003	0.0072	0.0038	0.0041	0.0033	0.0397	0.0028	0.0005
	21-0488	0.0079	0.0002	0.0069	0.0024	0.0043	0.0026	0.0404	0.0024	0.0006
	Mean	**0.0079**	**0.0002**	**0.0072**	**0.0028**	**0.0043**	**0.0026**	**0.0388**	**0.0030**	**0.0005**
	SD	**0.00027**	**0.00003**	**0.00046**	**0.00060**	**0.00028**	**0.00050**	**0.00149**	**0.00116**	**0.00007**
	21-0449	0.0093	0.0002	0.0084	0.0029	0.0042	0.0020	0.0377	0.0023	0.0005
100 mg/kg-d	21-0450	0.0089	0.0003	0.0081	0.0030	0.0044	0.0024	0.0399	0.0022	0.0003
	21-0483	0.0084	0.0002	0.0079	0.0032	0.0047	0.0023	0.0379	0.0027	0.0005
	21-0484	0.0091	0.0002	0.0088	0.0035	0.0047	0.0025	0.0413	0.0025	0.0005
	21-0493	0.0077	0.0003	0.0089	0.0026	0.0045	0.0025	0.0365	0.0047	0.0004
	21-0494	0.0092	0.0003	0.0079	0.0034	0.0042	0.0024	0.0360	0.0017	0.0003
	Mean	**0.0088**	**0.0003**	**0.0083**	**0.0031**	**0.0045**	**0.0024**	**0.0382**	**0.0027**	**0.0004**
	SD	**0.00060**	**0.00003**	**0.00044**	**0.00034**	**0.00019**	**0.00019**	**0.00202**	**0.00103**	**0.00008**
	21-0475	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
200 mg/kg-d	21-0476	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0479	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0480	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0491	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0492	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	21-0457	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
400 mg/kg-d	21-0458	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0477	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0478	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0489	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0490	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**

Table L-6
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Organ to Brain Mass Ratios
Female Rats

Group	Animal ID	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Uterus	Ovaries
	21-0467	0.0288	0.7072	0.2815	0.4520	0.3395	4.6425	0.2491	0.0611
Corn Oil	21-0468	0.0320	0.8785	0.3070	0.4931	0.2788	4.5816	0.5059	0.0565
Control	21-0471	0.0294	1.0198	0.2527	0.5353	0.2901	4.4599	0.2832	0.0530
	21-0472	0.0272	0.8238	0.2397	0.4078	0.2698	4.3333	0.5501	0.0573
	21-0481	0.0357	0.9477	0.2649	0.5365	0.2980	5.2969	0.5468	0.0698
	21-0482	0.0400	1.0869	0.3922	0.6153	0.5550	6.3841	0.3714	0.0765
	Mean	**0.0322**	**0.9107**	**0.2897**	**0.5067**	**0.3385**	**4.9497**	**0.4177**	**0.0624**
	SD	**0.00484**	**0.13734**	**0.05544**	**0.07274**	**0.10877**	**0.77819**	**0.13465**	**0.00899**
	21-0453	0.0266	0.8106	0.2824	0.5231	0.3322	4.3528	0.3945	0.0633
6.25 mg/kg-d	21-0454	0.0251	0.7909	0.2432	0.4939	0.2523	3.9579	0.5104	0.0491
	21-0485	0.0329	0.8963	0.2110	0.4887	0.3198	3.8316	0.2644	0.0483
	21-0486	0.0324	1.2140	0.3795	0.5965	0.3736	5.5140	0.2847	0.0668
	21-0495	0.0398	0.9536	0.2968	0.5506	0.2935	4.9961	0.3969	0.0647
	21-0496	0.0285	0.9573	0.3035	0.5206	0.2827	4.9471	0.2298	0.0763
	Mean	**0.0309**	**0.9371**	**0.2861**	**0.5289**	**0.3090**	**4.5999**	**0.3468**	**0.0614**
	SD	**0.00536**	**0.15259**	**0.05768**	**0.03995**	**0.04237**	**0.65980**	**0.10572**	**0.01085**
	21-0451	0.0252	0.9038	0.3708	0.5095	0.4385	5.5649	0.2875	0.0749
12.5 mg/kg-d	21-0452	0.0307	0.8811	0.2468	0.4556	0.3076	4.2647	0.4590	0.0525
	21-0465	0.0278	0.9507	0.2824	0.4756	0.3365	3.9942	0.2688	0.0604
	21-0466	0.0331	0.8368	0.2959	0.5577	0.3468	3.9407	0.3001	0.0509
	21-0469	0.0301	0.9183	0.2945	0.4900	0.2466	4.2011	0.2695	0.0592
	21-0470	0.0300	0.8621	0.2877	0.4956	0.2453	4.6399	0.3084	0.0517
	Mean	**0.0295**	**0.8921**	**0.2964**	**0.4973**	**0.3202**	**4.4342**	**0.3155**	**0.0583**
	SD	**0.00270**	**0.04082**	**0.04068**	**0.03482**	**0.07232**	**0.60678**	**0.07204**	**0.00910**
	21-0455	0.0329	0.9019	0.2655	0.5483	0.2655	4.9577	0.5900	0.0704
25 mg/kg-d	21-0456	0.0332	0.8783	0.4075	0.5859	0.4330	5.2526	0.2541	0.0654
	21-0459	0.0357	0.9867	0.3078	0.5399	0.2923	5.0479	0.3493	0.0618
	21-0460	0.0319	0.8861	0.3176	0.5520	0.3043	4.5245	0.2922	0.0787
	21-0461	0.0363	0.9203	0.3075	0.5689	0.2674	4.8736	0.4002	0.0526
	21-0462	0.0323	0.8141	0.2913	0.5069	0.3003	4.2839	0.5376	0.0561
	Mean	**0.0337**	**0.8979**	**0.3162**	**0.5503**	**0.3105**	**4.8234**	**0.4039**	**0.0642**
	SD	**0.00184**	**0.05648**	**0.04830**	**0.02687**	**0.06224**	**0.35653**	**0.13447**	**0.00955**
	21-0463	0.0316	0.8719	0.3569	0.4818	0.3548	4.4652	0.4030	0.0691
50 mg/kg-d	21-0464	0.0267	0.8707	0.3955	0.5292	0.3666	4.6770	0.6607	0.0687
	21-0473	0.0327	1.0082	0.2731	0.5993	0.2435	4.9214	0.2460	0.0674
	21-0474	0.0264	0.9572	0.3418	0.5781	0.2910	5.2353	0.3154	0.0532
	21-0487	0.0319	0.9103	0.4855	0.5189	0.4158	5.0289	0.3554	0.0678
	21-0488	0.0308	0.8710	0.3004	0.5442	0.3240	5.1307	0.3026	0.0780
	Mean	**0.0300**	**0.9149**	**0.3589**	**0.5419**	**0.3326**	**4.9098**	**0.3805**	**0.0674**
	SD	**0.00275**	**0.05700**	**0.07545**	**0.04222**	**0.06050**	**0.29016**	**0.14698**	**0.00797**
	21-0449	0.0268	0.9090	0.3118	0.4564	0.2181	4.0674	0.2499	0.0515
100 mg/kg-d	21-0450	0.0327	0.9092	0.3333	0.4995	0.2718	4.4891	0.2465	0.0337
	21-0483	0.0267	0.9423	0.3809	0.5597	0.2804	4.5280	0.3276	0.0589
	21-0484	0.0244	0.9709	0.3820	0.5136	0.2791	4.5592	0.2763	0.0498
	21-0493	0.0337	1.1503	0.3354	0.5762	0.3257	4.7193	0.6017	0.0501
	21-0494	0.0307	0.8551	0.3709	0.4594	0.2587	3.8986	0.1825	0.0371
	Mean	**0.0292**	**0.9561**	**0.3524**	**0.5108**	**0.2723**	**4.3769**	**0.3141**	**0.0468**
	SD	**0.00374**	**0.10270**	**0.02945**	**0.04978**	**0.03489**	**0.31952**	**0.14857**	**0.00951**
	21-0475	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
200 mg/kg-d	21-0476	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0479	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0480	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0491	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0492	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	21-0457	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
400 mg/kg-d	21-0458	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0477	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0478	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0489	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-0490	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	Mean	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**
	SD	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**	**ND**

Table L-7
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Absolute Organ Mass Summary (grams)
Male Rats

Group	Animal ID	Body Weight[1]	Body Weight[2]	Brain	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Testes	Epididymides
Corn Oil Control	**Mean**	321	311	1.998	0.044	2.186	0.623	1.164	0.531	11.398	2.967	0.673
	SD	21.9	20.4	0.0338	0.0050	0.2379	0.0793	0.0992	0.0736	0.8238	0.2156	0.0753
	N	6	6	6	6	6	6	6	6	6	6	6
6.25 mg/kg-d	**Mean**	318	310	2.050	0.040	2.329	0.620	1.248	0.528	11.117	2.873	0.706
	SD	18.1	18.6	0.0771	0.0089	0.1822	0.0917	0.0316	0.0958	0.8752	0.3051	0.0821
	N	6	6	6	6	6	6	6	6	6	6	6
12.5 mg/kg-d	**Mean**	338	329	2.032	0.045	2.333	0.694	1.292	0.608	11.836	2.885	0.696
	SD	32.3	30.8	0.0820	0.0068	0.3338	0.1611	0.1241	0.0866	1.7079	0.4174	0.0596
	N	6	6	6	6	6	6	6	6	5	6	6
25 mg/kg-d	**Mean**	331	322	2.072	0.043	2.366	0.659	1.267	0.513	11.475	3.034	0.739
	SD	34.0	32.3	0.1057	0.0031	0.2289	0.1274	0.1073	0.0606	1.2053	0.1380	0.1228
	N	6	6	6	6	6	6	6	6	6	6	6
50 mg/kg-d	**Mean**	327	317	2.091*	0.044	2.363	0.816*	1.220	0.621	11.591	2.927	0.714
	SD	30.0	28.6	0.0849	0.0071	0.2934	0.0833	0.1387	0.0765	1.6437	0.2911	0.0892
	N	6	6	6	6	6	6	6	6	6	6	6
100 mg/kg-d	**Mean**	289	278	2.044*	0.048*	2.383*	0.958*	1.141	0.581	10.865	2.763	0.636
	SD	16.0	13.9	0.0408	0.0063	0.2307	0.1901	0.0552	0.0589	0.8538	0.1763	0.0659
	N	6	6	6	6	6	6	6	6	6	6	6
200 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0	0	0	0
400 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0	0	0	0

[1] = Unfasted day 13 body weight

[2] = Fasted day 14 body weight

* $p<0.05$ compared to controls

Table L-8
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Organ to Body Mass Ratio Summary
Male Rats

Group	Animal ID	Brain	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Testes	Epididymides
Corn Oil Control	**Mean**	0.0062	0.0001	0.0068	0.0019	0.0036	0.0017	0.0355	0.0093	0.0021
	SD	0.00046	0.00001	0.00043	0.00013	0.00015	0.00022	0.00124	0.00068	0.00030
	N	6	6	6	6	6	6	6	6	6
6.25 mg/kg-d	**Mean**	0.0065	0.0001	0.0073	0.0019	0.0039	0.0017	0.0349	0.0090	0.0022
	SD	0.00021	0.00003	0.00029	0.00021	0.00022	0.00030	0.00175	0.00078	0.00020
	N	6	6	6	6	6	6	6	6	6
12.5 mg/kg-d	**Mean**	0.0060	0.0001	0.0069	0.0020	0.0038	0.0018	0.0347	0.0085	0.0021
	SD	0.00053	0.00002	0.00044	0.00043	0.00028	0.00030	0.00290	0.00085	0.00010
	N	6	6	6	6	6	6	5	6	6
25 mg/kg-d	**Mean**	0.0063	0.0001	0.0072	0.0020	0.0038	0.0016	0.0346	0.0092	0.0022
	SD	0.00046	0.00001	0.00047	0.00029	0.00035	0.00022	0.00128	0.00062	0.00020
	N	6	6	6	6	6	6	6	6	6
50 mg/kg-d	**Mean**	0.0064	0.0001	0.0072	0.0025*	0.0037	0.0019	0.0354	0.0090	0.0022
	SD	0.00043	0.00002	0.00047	0.00013	0.00043	0.00024	0.00289	0.00054	0.00017
	N	6	6	6	6	6	6	6	6	6
100 mg/kg-d	**Mean**	0.0071*	0.0002*	0.0082*	0.0033*	0.0040	0.0020	0.0376	0.0096	0.0022
	SD	0.00049	0.00002	0.00058	0.00062	0.00027	0.00026	0.00249	0.00070	0.00012
	N	6	6	6	6	6	6	6	6	6
200 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0	0
400 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0	0

* $p<0.05$ compared to controls

Table L-9
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Organ to Brain Mass Ratio Summary
Male Rats

Group	Animal ID	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Testes	Epididymides
Corn Oil Control	**Mean**	0.0219	1.0947	0.3118	0.5827	0.2661	5.7093	1.4848	0.3367
	SD	0.00252	0.12502	0.04167	0.05177	0.03847	0.46099	0.09419	0.03723
	N	6	6	6	6	6	6	6	6
6.25 mg/kg-d	**Mean**	0.0196	1.1353	0.3015	0.6093	0.2574	5.4193	1.4024	0.3439
	SD	0.00401	0.06011	0.03669	0.02025	0.04533	0.31604	0.15031	0.03028
	N	6	6	6	6	6	6	6	6
12.5 mg/kg-d	**Mean**	0.0223	1.1480	0.3401	0.6372	0.3008	5.8475	1.4236	0.3430
	SD	0.00315	0.15205	0.06868	0.07168	0.05305	0.71812	0.22936	0.03536
	N	6	6	6	6	6	5	6	6
25 mg/kg-d	**Mean**	0.0207	1.1418	0.3180	0.6124	0.2485	5.5364	1.4648	0.3550
	SD	0.00141	0.09425	0.06280	0.05869	0.03556	0.50285	0.02925	0.04038
	N	6	6	6	6	6	6	6	6
50 mg/kg-d	**Mean**	0.0209	1.1274	0.3900	0.5828	0.2973	5.5423	1.4003	0.3411
	SD	0.00327	0.10447	0.03024	0.05839	0.03753	0.75978	0.13392	0.03620
	N	6	6	6	6	6	6	6	6
100 mg/kg-d	**Mean**	0.0235	1.1658	0.4689*	0.5581	0.2839	5.3152	1.3519	0.3116
	SD	0.00324	0.11440	0.09660	0.02838	0.02590	0.41302	0.08737	0.03599
	N	6	6	6	6	6	6	6	6
200 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0
400 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0

* $p<0.05$ compared to controls

Table L-10
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Absolute Organ Mass Summary (grams)
Female Rats

Group	Animal ID	Body Weight[1]	Body Weight[2]	Brain	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Uterus	Ovaries
Corn Oil Control	**Mean**	243	234	1.907	0.061	1.727	0.548	0.960	0.638	9.383	0.802	0.119
	SD	19.1	18.0	0.1204	0.0064	0.1968	0.0730	0.0858	0.1640	1.0345	0.2864	0.0141
	N	6	6	6	6	6	6	6	6	6	6	6
6.25 mg/kg-d	**Mean**	241	234	1.938	0.060	1.821	0.556	1.026*	0.601	8.925	0.668	0.119
	SD	21.3	19.9	0.0825	0.0093	0.3468	0.1266	0.1023	0.1029	1.4457	0.1884	0.0231
	N	6	6	6	6	6	6	6	6	6	6	6
12.5 mg/kg-d	**Mean**	241	234	1.897	0.056	1.692	0.561	0.944	0.603	8.393*	0.596	0.110
	SD	21.3	19.9	0.0947	0.0065	0.1069	0.0720	0.0862	0.1146	1.0456	0.1191	0.0147
	N	6	6	6	6	6	6	6	6	6	6	6
25 mg/kg-d	**Mean**	233	226	1.883	0.064	1.691	0.596	1.037*	0.586	9.092	0.761	0.121
	SD	19.7	20.1	0.0498	0.0036	0.1084	0.1016	0.0637	0.1308	0.8361	0.2591	0.0176
	N	6	6	6	6	6	6	6	6	6	6	6
50 mg/kg-d	**Mean**	242	236	1.916	0.058	1.756	0.689*	1.040*	0.637	9.417	0.724	0.129
	SD	16.2	16.5	0.0863	0.0060	0.1745	0.1593	0.1096	0.1193	0.8507	0.2587	0.0120
	N	6	6	6	6	6	6	6	6	6	6	6
100 mg/kg-d	**Mean**	224	213	1.958	0.057	1.872	0.691*	1.000*	0.534	8.574	0.613	0.091*
	SD	19.0	17.7	0.1255	0.0084	0.2360	0.0835	0.1075	0.0823	0.8841	0.2888	0.0161
	N	6	6	6	6	6	6	6	6	6	6	6
200 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	N	6	6	6	6	6	6	6	6	6	6	6
400 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	N	6	6	6	6	6	6	6	6	6	6	6

[1] = Unfasted day 13 body weight

[2] = Fasted day 14 body weight

* $p<0.05$ compared to controls

Table L-11
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Organ to Body Mass Ratio Summary
Female Rats

Group	Animal ID	Brain	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Uterus	Ovaries
Corn Oil	**Mean**	0.0079	0.0003	0.0071	0.0023	0.0040	0.0026	0.0386	0.0033	0.0005
Control	**SD**	0.00100	0.00001	0.00082	0.00019	0.00023	0.00050	0.00208	0.00124	0.00004
	N	6	6	6	6	6	6	6	6	6
6.25 mg/kg-d	**Mean**	0.0081	0.0002	0.0075	0.0023	0.0043	0.0025	0.0370	0.0028	0.0005
	SD	0.00052	0.00004	0.00084	0.00034	0.00007	0.00025	0.00346	0.00094	0.00008
	N	6	6	6	6	6	6	6	6	6
12.5 mg/kg-d	**Mean**	0.0079	0.0002	0.0071	0.0023	0.0039	0.0025	0.0351	0.0025	0.0005
	SD	0.00072	0.00003	0.00082	0.00026	0.00022	0.00043	0.00490	0.00066	0.00007
	N	6	6	6	6	6	6	6	6	6
25 mg/kg-d	**Mean**	0.0081	0.0003	0.0073	0.0026	0.0045*	0.0025	0.0390	0.0033	0.0005
	SD	0.00056	0.00002	0.00038	0.00030	0.00019	0.00042	0.00076	0.00124	0.00008
	N	6	6	6	6	6	6	6	6	6
50 mg/kg-d	**Mean**	0.0079	0.0002	0.0072	0.0028	0.0043	0.0026	0.0388	0.0030	0.0005
	SD	0.00027	0.00003	0.00046	0.00060	0.00028	0.00050	0.00149	0.00116	0.00007
	N	6	6	6	6	6	6	6	6	6
100 mg/kg-d	**Mean**	0.0088	0.0003	0.0083*	0.0031*	0.0045*	0.0024	0.0382	0.0027	0.0004
	SD	0.00060	0.00003	0.00044	0.00034	0.00019	0.00019	0.00202	0.00103	0.00008
	N	6	6	6	6	6	6	6	6	6
200 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0	0
400 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND	ND
	N	0	0	0	0	0	0	0	0	0

* $p<0.05$ compared to controls

Table L-12
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Organ to Brain Mass Ratio Summary
Female Rats

Group	Animal ID	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Uterus	Ovaries
Corn Oil Control	**Mean**	0.0322	0.9107	0.2897	0.5067	0.3385	4.9497	0.4177	0.0624
	SD	0.00484	0.13734	0.05544	0.07274	0.10877	0.77819	0.13465	0.00899
		6	6	6	6	6	6	6	6
6.25 mg/kg-d	**Mean**	0.0309	0.9371	0.2861	0.5289	0.3090	4.5999	0.3468	0.0614
	SD	0.00536	0.15259	0.05768	0.03995	0.04237	0.65980	0.10572	0.01085
		6	6	6	6	6	6	6	6
12.5 mg/kg-d	**Mean**	0.0295	0.8921	0.2964	0.4973	0.3202	4.4342	0.3155	0.0583
	SD	0.00270	0.04082	0.04068	0.03482	0.07232	0.60678	0.07204	0.00910
		6	6	6	6	6	6	6	6
25 mg/kg-d	**Mean**	0.0337	0.8979	0.3162	0.5503	0.3105	4.8234	0.4039	0.0642
	SD	0.00184	0.05648	0.04830	0.02687	0.06224	0.35653	0.13447	0.00955
		6	6	6	6	6	6	6	6
50 mg/kg-d	**Mean**	0.0300	0.9149	0.3589	0.5419	0.3326	4.9098	0.3805	0.0674
	SD	0.00275	0.05700	0.07545	0.04222	0.06050	0.29016	0.14698	0.00797
		6	6	6	6	6	6	6	6
100 mg/kg-d	**Mean**	0.0292	0.9561	0.3524	0.5108	0.2723	4.3769	0.3141	0.0468
	SD	0.00374	0.10270	0.02945	0.04978	0.03489	0.31952	0.14857	0.00951
		6	6	6	6	6	6	6	6
200 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND
		0	0	0	0	0	0	0	0
400 mg/kg-d	**Mean**	ND	ND	ND	ND	ND	ND	ND	ND
	SD	ND	ND	ND	ND	ND	ND	ND	ND
		0	0	0	0	0	0	0	0

Appendix M

Micronucleus Assay

Abbreviations:

mg/kg-d: milligrams per kilogram per day
NCE: normochromatic erythrocytes
MN-NCE: micronucleated normochromatic erythrocytes
RET: young (high CD71-positive) reticulocytes
MN-RET: young (high CD71-positive) micronucleated reticulocytes
% RET: frequency (%) of young (high CD71-positive) reticulocytes; calculated as [(Number of RET + Number of MN-RET)/(Number of NCE + Number of MN-NCE + Number of RET + Number of MN-RET)] x 100
% MN-RET: frequency (%) of young (high CD71-positive) micronucleated reticulocytes; calculated as [Number of MN-RET/(Number of RET + Number of MN-RET)] x 100
EMS: ethyl methanesulfonate
SD: standard deviation

Table M-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Micronucleus Assay Results
Male Rats

Group	Sample ID	Date Collected	No. NCE	No. MN-NCE	No. RET	No. MN-RET	%RET	%MN-RET
Corn Oil	21-0435	10-Mar-21	1622481	928	19980	20	1.22	0.10
Control	21-0436	10-Mar-21	1117235	1364	19952	48	1.76	0.24
	21-0391	9-Mar-21	883338	177	19979	21	2.21	0.11
	21-0392	9-Mar-21	1308863	258	19976	24	1.50	0.12
	21-0431	9-Mar-21	1036695	500	19977	23	1.89	0.12
	21-0432	9-Mar-21	769814	393	19968	32	2.53	0.16
		Mean	**1123071**	**603**	**19972**	**28**	**1.85**	**0.14**
		SD	**307794.2**	**456.1**	**10.7**	**10.7**	**0.474**	**0.052**
25 mg/kg-d	21-0409	10-Mar-21	769298	1400	19951	49	2.53	0.25
	21-0410	10-Mar-21	1051805	301	19985	15	1.87	0.08
	21-0395	9-Mar-21	917715	608	19979	21	2.13	0.11
	21-0396	9-Mar-21	1049862	716	19974	26	1.87	0.13
	21-0397	9-Mar-21	830838	319	19983	17	2.35	0.09
	21-0398	9-Mar-21	938234	374	19970	30	2.09	0.15
		Mean	**926292**	**620**	**19974**	**26**	**2.14**	**0.14**
		SD	**114015.6**	**417.3**	**12.4**	**12.4**	**0.263**	**0.062**
50 mg/kg-d	21-0413	10-Mar-21	859400	1177	19954	46	2.27	0.23
	21-0414	10-Mar-21	701591	659	19971	29	2.77	0.15
	21-0429	10-Mar-21	820786	1037	19959	40	2.38	0.20
	21-0430	10-Mar-21	864203	998	19955	45	2.26	0.23
	21-0407	9-Mar-21	1056293	474	19967	33	1.86	0.17
	21-0408	9-Mar-21	1079060	451	19977	23	1.82	0.12
		Mean	**896889**	**799**	**19964**	**36**	**2.23**	**0.18**
		SD	**144915.6**	**311.6**	**9.3**	**9.2**	**0.353**	**0.045**
100 mg/kg-d	21-0433	10-Mar-21	774458	913	19963	37	2.51	0.19
	21-0434	10-Mar-21	985266	993	19978	23	1.99	0.11
	21-0443	10-Mar-21	608463	223	19988	12	3.18	0.06
	21-0444	10-Mar-21	505311	227	19974	26	3.81	0.13
	21-0421	9-Mar-21	1099832	1306	19960	40	1.78	0.20
	21-0422	9-Mar-21	1007140	2151	19936	64	1.94	0.32
		Mean	**830078**	**969**	**19967**	**34**	**2.54**	**0.17**
		SD	**239115.8**	**724.1**	**18.1**	**18.0**	**0.808**	**0.091**
EMS	21-0418	10-Mar-21	1852662	739	19909	91	1.07	0.46
Positive Control	21-0425	10-Mar-21	3593659	2665	19817	182	0.55	0.91
	21-0426	10-Mar-21	3247710	1583	19832	168	0.61	0.84
	21-0389	9-Mar-21	3321840	1137	19824	176	0.60	0.88
	21-0390	9-Mar-21	1874181	179	19885	115	1.06	0.58
	21-0417	9-Mar-21	3672169	727	19796	204	0.54	1.02
		Mean	**2927037**	**1172**	**19844**	**156**	**0.74**	**0.78**
		SD	**839177.5**	**868.4**	**43.5**	**43.4**	**0.255**	**0.215**
Untreated	21-0438	10-Mar-21	809654	650	19960	40	2.41	0.20
Control	21-0439	10-Mar-21	624436	223	19978	21	3.10	0.11
	21-0440	10-Mar-21	691129	220	19976	24	2.81	0.12
	21-0411	9-Mar-21	806792	599	19975	25	2.42	0.13
	21-0412	9-Mar-21	749666	505	19970	30	2.60	0.15
	21-0437	9-Mar-21	709333	711	19953	46	2.74	0.23
		Mean	**731835**	**485**	**19969**	**31**	**2.68**	**0.16**
		SD	**71680.1**	**214.7**	**10.0**	**9.9**	**0.262**	**0.048**

Table M-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Micronucleus Assay Results Summary
Male Rats

Group		No. NCE	No. MN-NCE	No. RET	No. MN-RET	%RET	%MN-RET
Corn Oil	**Mean**	1123071	603	19972	28	1.85	0.14
Control	**SD**	307794.2	456.1	10.7	10.7	0.474	0.052
	N	6	6	6	6	6	6
25 mg/kg-d	**Mean**	926292	620	19974	26	2.14	0.14
	SD	114015.6	417.3	12.4	12.4	0.263	0.062
	N	6	6	6	6	6	6
50 mg/kg-d	**Mean**	896889	799	19964	36	2.23	0.18
	SD	144915.6	311.6	9.3	9.2	0.353	0.045
	N	6	6	6	6	6	6
100 mg/kg-d	**Mean**	830078	969	19967	34	2.54	0.17
	SD	239115.8	724.1	18.1	18.0	0.808	0.091
	N	6	6	6	6	6	6
EMS	**Mean**	2927037*	1172*	19844*	156*	0.74*	0.78*
Positive Control	**SD**	839177.5	868.4	43.5	43.4	0.255	0.215
	N	6	6	6	6	6	6
Untreated	**Mean**	731835	485	19969	31	2.68	0.16
Control	**SD**	71680.1	214.7	10.0	9.9	0.262	0.048
	N	6	6	6	6	6	6

* $p<0.05$ compared to corn oil and untreated controls

Appendix N

Subacute Clinical and Gross Pathological Observations

Abbreviations:

mg/kg-d: milligrams per kilogram per day

Table N-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Clinical Signs

Male Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
Corn Oil Control	21-0391	Normal	0	14
	21-0392	Normal	0	14
	21-0431	Normal	0	14
	21-0432	Normal	0	14
	21-0435	Normal	0	14
	21-0436	Normal	0	14

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.

Table N-1 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Clinical Signs

Male Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
6.25 mg/kg-d	21-0405	Normal	0	14
	21-0406	Normal	0	14
	21-0415	Normal	0	14
	21-0416	Normal	0	14
	21-0445	Normal	0	14
	21-0446	Normal	0	14

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.

Table N-1 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Clinical Signs

Male Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
12.5 mg/kg-d	21-0393	Normal	0	14
	21-0394	Normal	0	14
	21-0441	Normal	0	14
	21-0442	Normal	0	14
	21-0447	Normal	0	14
	21-0448	Normal	0	14

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.

Table N-1 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Clinical Signs

Male Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
25 mg/kg-d	21-0395	Normal	0	14
	21-0396	Normal	0	14
	21-0397	Normal	0	14
	21-0398	Normal	0	14
	21-0409	Normal	0	13
		Irritable	10	12
	21-0410	Normal	0	14

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.

Table N-1 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Clinical Signs

Male Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
50 mg/kg-d	21-0407	Normal	0	14
		Dried red material - nose	2	3
	21-0408	Normal	0	14
	21-0413	Normal	0	14
	21-0414	Normal	0	14
	21-0429	Normal	0	14
		Scab behind right ear	10	12
	21-0430	Normal	0	14
		Irritable	10	11

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.

Table N-1 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Clinical Signs

Male Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
100 mg/kg-d	21-0421	Normal	0	14
		Dried red material - nose	9	9
	21-0422	Normal	0	14
		Dried red material - nose	10	10
	21-0433	Normal	0	14
		Dried red material - nose	3	3
	21-0434	Normal	0	14
	21-0443	Normal	0	14
	21-0444	Normal	0	14
		Irritable	8	8

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.

Table N-1 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Clinical Signs

Male Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
200 mg/kg-d	21-0403	Normal	0	3
		Dried red material - nose	4	6
		Dried red material - mouth	6	6
		Rearing and waving front legs	7	7
		Moribund euthanasia	7	7
	21-0404	Small amount of dose around mouth	0	3
		Normal	1	5
		Dried red material - nose	6	6
		Dried red material - mouth	6	6
		Congested breathing	6	6
		Mortality	7	7
	21-0423	Normal	0	2
		Dried red material - nose	1	3
		Mortality	4	4
	21-0424	Normal	0	4
		Dried red material - nose	5	5
		Lethargic	6	6
		Moribund euthanasia	6	6
	21-0427	Normal	0	4
		Small amount of dose around mouth	3	3
		Dried red material - nose	5	6
		Lethargic	6	6
		Moribund euthanasia	7	7
	21-0428	Normal	0	3
		Diarrheal staining	1	1
		Dried red material - nose	4	4
		Dried red material - face	5	5
		Slightly lethargic	5	6
		Dried red material - face and front paws	6	6
		Moribund euthanasia	7	7

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.

Table N-1 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Clinical Signs

Male Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
400 mg/kg-d	21-0399	Normal	0	4
		Mortality	5	5
	21-0400	Normal	0	3
		Dried red material - nose	4	4
		Mortality	5	5
	21-0401	Normal	0	3
		Dried red material - nose	4	4
		Mortality	5	5
	21-0402	Normal	0	2
		Dried red material - nose	3	4
		Cold to the touch	4	4
		Shaking	4	4
		Lethargic	4	4
		Labored breathing	4	4
		Moribund euthanasia	4	4
	21-0419	Normal	0	3
		Mortality	4	4
	21-0420	Normal	0	3
		Mortality	4	4

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.

Table N-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Clinical Signs

Female Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
Corn Oil Control	21-0467	Normal	0	14
	21-0468	Normal	0	14
	21-0471	Normal	0	14
	21-0472	Normal	0	14
	21-0481	Normal	0	14
	21-0482	Normal	0	14

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.

Table N-2 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Clinical Signs

Female Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
6.25 mg/kg-d	21-0453	Normal	0	14
	21-0454	Normal	0	14
	21-0485	Normal	0	14
	21-0486	Normal	0	14
	21-0495	Normal	0	14
	21-0496	Normal	0	14

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.

Table N-2 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Clinical Signs

Female Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
12.5 mg/kg-d	21-0451	Normal	0	14
	21-0452	Normal	0	14
	21-0465	Normal	0	14
		Irritable	9	9
	21-0466	Normal	0	14
	21-0469	Normal	0	14
	21-0470	Normal	0	14
		Irritable	10	10

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.

Table N-2 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Clinical Signs

Female Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
25 mg/kg-d	21-0455	Normal	0	14
	21-0456	Normal	0	14
	21-0459	Normal	0	14
	21-0460	Normal	0	14
	21-0461	Normal	0	14
	21-0462	Normal	0	14

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.

Table N-2 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Clinical Signs

Female Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
50 mg/kg-d	21-0463	Normal	0	14
	21-0464	Normal	0	14
	21-0473	Normal	0	14
	21-0474	Normal	0	14
		Irritable	9	11
	21-0487	Normal	0	14
	21-0488	Normal	0	14

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.

Table N-2 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Clinical Signs

Female Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
100 mg/kg-d	21-0449	Normal	0	14
	21-0450	Normal	0	14
	21-0483	Normal	0	14
		Dried red material - nose	6	6
		Small amount of dose around mouth	12	12
	21-0484	Normal	0	14
	21-0493	Normal	0	14
	21-0494	Normal	0	14

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.

Table N-2 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Clinical Signs

Female Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
200 mg/kg-d	21-0475	Normal	0	3
		Dried red material - nose	4	4
		Dried red material - nose and mouth	5	5
		Mortality	5	5
	21-0476	Normal	0	3
		Dried red material - nose	4	7
		Dried red material - nose and front paws	6	6
		Seizure activity	7	7
		Moribund euthanasia	7	7
	21-0479	Normal	0	5
		Dried red material - nose	6	6
		Slightly lethargic	6	6
		Moribund euthanasia	6	6
	21-0480	Normal	0	5
		Dried red material - nose	3	6
		Hyperactive	3	3
		Slightly lethargic	6	6
		Dried red material - face and front paws	7	7
		Lethargic	7	7
		Feet are cold	7	7
		Moribund euthanasia	7	7
	21-0491	Normal	0	2
		Dried red material - face	3	3
		Dried red material -nose	4	5
		Dried red material - nose and front paws	6	6
		Lethargic	6	6
		Ataxia	6	6
		Moribund euthanasia	6	6
	21-0492	Normal	0	3
		Dried red material - nose	4	4
		Dried red material - nose and front paws	5	5
		Lethargic	5	5
		Cold to the touch	5	5
		Moribund euthanasia	5	5

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.

Table N-2 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Clinical Signs

Female Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
400 mg/kg-d	21-0457	Normal	0	4
		Dried red material - nose and front paws	5	5
		Moribund euthanasia	5	5
	21-0458	Normal	0	2
		Slightly lethargic	3	3
		Mortality	4	4
	21-0477	Normal	0	2
		Dried red material - nose	1	3
		Dried red material - nose and front paws	4	5
		Diarrheal staining	5	5
		Moribund euthanasia	5	5
	21-0478	Normal	0	2
		Dried red material - nose	3	4
		Hyperactive	3	3
		Dried red material - nose and front paws	5	5
		Urine stains	5	5
		Moribund euthanasia	5	5
	21-0489	Normal	0	3
		Mortality	4	4
	21-0490	Normal	0	2
		Dried red material - nose	1	4
		Mortality	5	5

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.

Table N-3
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Gross Necropsy Observations
Male Rats

Group	Animal ID	Gross Observations
Corn Oil Control	21-0391	No gross lesions recognized
	21-0392	No gross lesions recognized
	21-0431	No gross lesions recognized
	21-0432	No gross lesions recognized
	21-0435	Mottled orange-colored liver; Increased amount of abdominal fat
	21-0436	Middle lobe of liver has 3 millimeter white mass
6.25 mg/kg-d	21-0405	No gross lesions recognized
	21-0406	No gross lesions recognized
	21-0415	No gross lesions recognized
	21-0416	No gross lesions recognized
	21-0445	No gross lesions recognized
	21-0446	No gross lesions recognized
12.5 mg/kg-d	21-0393	No gross lesions recognized
	21-0394	No gross lesions recognized
	21-0441	Scant amount of dark material (blood) adjacent to pyloric mucosa
	21-0442	No gross lesions recognized
	21-0447	No gross lesions recognized
	21-0448	No gross lesions recognized
25 mg/kg-d	21-0395	No gross lesions recognized
	21-0396	No gross lesions recognized
	21-0397	No gross lesions recognized
	21-0398	No gross lesions recognized
	21-0409	No gross lesions recognized
	21-0410	No gross lesions recognized
50 mg/kg-d	21-0407	No gross lesions recognized
	21-0408	No gross lesions recognized
	21-0413	No gross lesions recognized
	21-0414	No gross lesions recognized
	21-0429	No gross lesions recognized
	21-0430	Dried stomach contents; Small amount of dark ingesta (blood) adjacent to pyloric mucosa
100 mg/kg-d	21-0421	No gross lesions recognized
	21-0422	No gross lesions recognized
	21-0433	No gross lesions recognized
	21-0434	No gross lesions recognized
	21-0443	No gross lesions recognized
	21-0444	No gross lesions recognized
200 mg/kg-d	21-0403*	Stomach mildly distended; Mesenteric lymph nodes prominent; Segments of jejunum dark in color; Stomach full of wet and dry ingesta with fluorescent yellow/green material; Wall of pyloric stomach red and irritated
	21-0404*	Nonglandular stomach distended/firm; Swollen/red mesenteric lymph nodes; Stomach full of dry and wet digesta and test material; Glandular stomach contains possible blood; Milliliter of pleural serosanguinous
	21-0423*	Congested subcutaneous vessels; Congestion of mesenteric lymph nodes; Irritated lower stomach; Small amount of blood in ileum
	21-0424*	No gross lesions recognized
	21-0427*	Mesenteric lymph nodes tan in color; Dark material in pyloric stomach; Partially dried ingesta and test material in stomach
	21-0428*	Stomach distended; Dark material in pyloric stomach
400 mg/kg-d	21-0399*	Seminal vesicles appear small; Congestion of subcutaneous vessels; Distended stomach with dried food and test material; Congestion of mesenteric lymph nodes; Blood in lower stomach
	21-0400*	Congestion of subcutaneous vessels; Seminal vesicles appear small; Congestion of mesenteric lymph nodes; Distended stomach with dried food and test material; Blood in lower stomach; Distended cecum; Duodenum appears irritated
	21-0401*	Congestion of subcutaneous vessels and mesenteric lymph nodes; Blood/irritation in glandular stomach, ileum, and jejunum
	21-0402*	Seminal vesicles appear smaller; Congestion of subcutaneous vessels; Slight congestion of mesenteric lymph nodes; Distended stomach with dried food and test material; Blood in lower stomach; Duodenum appears irritated; Blood in ileum
	21-0419*	Congestion of subcutaneous vessels; Seminal vesicles appear small; Congestion of mesenteric lymph nodes; Distended stomach with dried food and test material; Blood throughout entire gastrointestinal tract
	21-0420*	Congestion of subcutaneous vessels; Congestion of mesenteric lymph nodes; Stomach slightly distended with normal ingesta and gas; Small amount of blood in lower stomach; Cecum empty

* Indicates early euthanasia or mortality

Table N-4
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

14-Day Individual Gross Necropsy Observations
Female Rats

Group	Animal ID	Gross Observations
Corn Oil Control	21-0467	No gross lesions recognized
	21-0468	No gross lesions recognized
	21-0471	No gross lesions recognized
	21-0472	No gross lesions recognized
	21-0481	No gross lesions recognized
	21-0482	No gross lesions recognized
6.25 mg/kg-d	21-0453	No gross lesions recognized
	21-0454	No gross lesions recognized
	21-0485	No gross lesions recognized
	21-0486	No gross lesions recognized
	21-0495	No gross lesions recognized
	21-0496	No gross lesions recognized
12.5 mg/kg-d	21-0451	No gross lesions recognized
	21-0452	No gross lesions recognized
	21-0465	No gross lesions recognized
	21-0466	No gross lesions recognized
	21-0469	No gross lesions recognized
	21-0470	No gross lesions recognized
25 mg/kg-d	21-0455	No gross lesions recognized
	21-0456	No gross lesions recognized
	21-0459	No gross lesions recognized
	21-0460	Minimal abdominal fat
	21-0461	No gross lesions recognized
	21-0462	No gross lesions recognized
50 mg/kg-d	21-0463	Minimal abdominal fat
	21-0464	Slightly pale, nutmeg-colored liver; Mildly fluid-filled uterus
	21-0473	No gross lesions recognized
	21-0474	No gross lesions recognized
	21-0487	Pronounced lobular pattern on the thymus, left more than right
	21-0488	No gross lesions recognized
100 mg/kg-d	21-0449	No gross lesions recognized
	21-0450	No gross lesions recognized
	21-0483	No gross lesions recognized
	21-0484	No gross lesions recognized
	21-0493	Fluid-filled uterus
	21-0494	No gross lesions recognized
200 mg/kg-d	21-0475*	Mildly distended stomach; Mesenteric lymph nodes dark in color and mottled; Jejunum segmentally dark and fluid filled (autolysis); Normal ingesta in fundus; Pyloric stomach reddened with dark ingesta; Thymus is mottled purple
	21-0476*	No gross lesions recognized
	21-0479*	Empty stomach and intestinal tract; Scant feces in colon; Pyloric stomach mucosa is reddened and possibly ulcerated
	21-0480*	Stomach mildly distended with dried food and test material
	21-0491*	No gross lesions recognized
	21-0492*	Jejunum and pyloric stomach has dark black contents
400 mg/kg-d	21-0457*	Moderate to markedly distended stomach with dry and wet ingesta and test material; Empty colon
	21-0458*	Congestion of subcutaneous vessels; Stomach distended with dried food and test material; Small amount of irritation and blood in glandular stomach; Congestion of mesenteric lymph nodes; Ovaries appear red and irritated
	21-0477*	Stomach distended with dried ingesta and test material; Dark material in pyloric stomach
	21-0478*	Stomach distended with dried ingesta and test material; Spleen slightly enlarged
	21-0489*	Mildly distended, ingesta filled nonglandular stomach; Stomach full of mix of wet/dry ingesta with test material; Duodenum and proximal jejunum mildly distended, fluid-filled and autolytic
	21-0490*	Red staining around nose; Diarrheal staining; Moderately distended stomach full of ingesta with test material; Pyloric stomach reddened and slightly ulcerated; Ingesta in pylorus is dark in color (blood)

* Indicates early euthanasia or mortality

Appendix O

Subchronic Individual and Summary of Body Mass

Abbreviations:

mg/kg-d: milligrams per kilogram per day
(f): animal died on study
SD: standard deviation

Table O-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Body Mass (grams)
Male Rats

Group	Animal ID	DAY 0	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77	DAY 84	DAY 90	DAY 91[1]
	21-1281	278	340	379	419	447	472	495	512	530	555	572	585	593	613	595
Corn Oil	21-1282	277	316	353	382	405	421	437	455	471	478	492	505	504	520	503
Control	21-1295	303	363	413	448	477	494	520	541	563	584	607	625	638	653	643
	21-1296	278	329	365	404	449	471	498	519	546	565	584	605	614	626	609
	21-1297	269	320	365	402	439	466	493	524	549	565	584	595	612	628	617
	21-1298	292	337	376	414	444	464	484	495	511	522	535	543	548	553	537
	21-1299	254	287	314	336	354	370	382	394	403	413	426	439	448	453	438
	21-1300	315	370	408	450	481	511	530	560	570	587	610	621	638	656	633
	21-1309	304	371	427	478	522	559	595	621	649	663	680	693	706	725	710
	21-1310	285	341	378	408	429	451	472	497	515	527	541	556	564	575	558
	Mean	**285.5**	**337.4**	**377.8**	**414.1**	**444.7**	**467.9**	**490.6**	**511.8**	**530.7**	**545.9**	**563.1**	**576.7**	**586.5**	**600.2**	**584.3**
	SD	**18.29**	**26.33**	**32.64**	**39.39**	**45.27**	**50.50**	**56.23**	**60.47**	**64.69**	**67.39**	**69.82**	**70.47**	**73.79**	**77.49**	**77.71**
	21-1293	258	317	365	399	423	438	452	471	486	503	512	523	531	540	529
1.09 mg/kg-d	21-1294	282	337	380	408	436	456	478	494	514	529	541	552	567	572	558
	21-1315	288	334	369	408	432	457	474	486	505	518	528	543	555	572	559
	21-1316	282	332	372	411	437	457	478	500	521	531	550	561	575	603	584
	21-1317	251	293	331	359	383	396	418	438	452	466	473	488	493	497	485
	21-1318	249	299	332	361	387	395	415	434	454	460	470	486	491	496	483
	21-1321	304	366	409	453	494	523	541	560	575	587	586	594	620	643	627
	21-1322	280	339	389	437	473	509	533	558	580	602	611	624	634	655	630
	21-1323	305	359	405	441	478	503	531	557	583	603	623	641	662	680	664
	21-1324	305	357	388	418	444	467	489	521	548	567	581	608	627	645	630
	Mean	**280.4**	**333.3**	**374.0**	**409.5**	**438.7**	**460.1**	**480.9**	**501.9**	**521.8**	**536.6**	**547.5**	**562.0**	**575.5**	**590.3**	**574.9**
	SD	**21.56**	**24.51**	**26.60**	**31.15**	**36.34**	**43.60**	**44.85**	**47.01**	**49.15**	**52.25**	**53.32**	**54.22**	**59.59**	**65.79**	**63.23**
	21-1275	257	315	348	381	415	445	459	480	495	513	533	549	548	562	549
4.38 mg/kg-d	21-1276	260	310	342	380	408	425	441	467	479	490	499	515	525	534	520
	21-1277	236	278	305	329	357	382	398	419	429	442	456	475	481	475	466
	21-1278	247	284	315	336	353	370	385	401	420	430	444	460	466	460	448
	21-1279	292	353	394	433	461	487	506	521	543	555	567	581	583	599	577
	21-1280	281	336	370	408	437	459	482	508	527	544	553	561	570	590	569
	21-1291	273	324	364	403	431	458	474	492	510	512	530	540	546	561	539
	21-1292	268	316	356	394	427	454	480	508	533	555	576	599	610	631	615
	21-1313	289	354	399	445	484	520	548	571	595	617	629	651	665	684	668
	21-1314	303	360	402	431	464	489	512	527	544	552	562	576	595	606	586
	Mean	**270.6**	**323.0**	**359.5**	**394.0**	**423.7**	**448.9**	**468.5**	**489.4**	**507.5**	**521.0**	**534.9**	**550.7**	**558.9**	**570.2**	**553.7**
	SD	**21.13**	**28.34**	**33.48**	**39.05**	**43.03**	**46.68**	**50.28**	**50.70**	**53.82**	**56.42**	**56.21**	**57.16**	**59.64**	**68.17**	**65.73**
	21-1283	301	354	412	446	476	505	525	547	550	565	579	588	606	617	598
17.5 mg/kg-d	21-1284	285	353	400	446	482	507	544	572	572	599	620	633	642	660	642
	21-1289	255	298	329	361	386	412	433	450	459	468	480	492	494	507	493
	21-1290	297	362	421	465	501	534	562	601	632	660	685	705	715	728	714
	21-1301	274	316	347	372	393	416	429	431	446	452	469	472	477	488	473
	21-1302	253	288	321	349	375	398	404	417	433	441	450	455	464	476	464
	21-1305	277	332	373	414	452	478	506	521	542	558	575	578	586	595	579
	21-1306	287	345	386	431	470	498	519	541	563	579	600	610	631	651	625
	21-1311	249	280	302	326	348	367	383	394	403	414	423	434	434	447	431
	21-1312	275	314	346	382	413	444	460	475	496	507	525	534	535	537	521
	Mean	**275.3**	**324.2**	**363.7**	**399.2**	**429.6**	**455.9**	**476.5**	**494.9**	**509.6**	**524.3**	**540.6**	**550.1**	**558.4**	**570.6**	**554.0**
	SD	**18.16**	**29.37**	**40.75**	**47.51**	**53.01**	**56.07**	**62.64**	**71.08**	**73.36**	**79.99**	**84.61**	**87.51**	**91.60**	**93.22**	**91.62**
	21-1285	252	293	325	331	341	361	379	382	383	404	408	416	423	415	391
70 mg/kg-d	21-1286	273	310	350	358	376	401	402	413	414	416	423	428	435	428	409
	21-1287	262	299	317	339	346	367	380	391	400	410	417	420	433	442	426
	21-1288	273	328	376	380	412	443	455	466	470	477	490	504	519	531	506
	21-1303	305	347	364	386	412	431	440	455	457	451	457	462	450	470	437
	21-1304	288	339	375	397	432	436	440	472	490	473	487	502	523	526	498
	21-1307	252	282	307	314	337	356	371	369	371	379	415	404	407	402	386
	21-1308	274	311	320	315	338	358	366	365	371	372	367	388	399	407	387
	21-1319	273	307	310	325	334	341	348	352	371	367	365	(f)	(f)	(f)	(f)
	21-1320	283	311	322	346	364	389	402	415	432	432	459	458	461	482	458
	Mean	**273.5**	**312.7**	**336.6**	**349.1**	**369.2**	**388.3**	**398.3**	**408.0**	**415.9**	**418.1**	**428.8**	**442.4**	**450**	**455.9**	**433.1**
	SD	**16.16**	**20.18**	**26.97**	**30.01**	**36.91**	**37.49**	**36.13**	**43.73**	**44.41**	**39.85**	**44.13**	**41.55**	**44.59**	**49.21**	**45.97**

[1] Fasted Day 91 body weights

Table O-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Body Mass (grams)
Female Rats

Group	Animal ID	DAY 0	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77	DAY 84	DAY 90	DAY 91[1]
	21-1325	197	211	221	240	248	257	256	267	272	280	278	290	296	284	279
Corn Oil	21-1326	194	216	224	233	234	249	245	253	262	267	260	272	283	285	264
Control	21-1331	221	240	254	265	268	286	287	294	299	300	301	299	307	310	296
	21-1332	213	226	245	257	258	275	277	286	284	292	298	293	296	308	294
	21-1345	223	245	263	275	285	294	304	313	312	324	329	333	330	344	323
	21-1346	205	216	240	254	260	257	274	282	288	291	294	302	306	306	287
	21-1347	198	224	234	248	251	276	263	271	275	280	278	285	279	286	270
	21-1348	231	246	263	271	276	288	292	300	300	315	314	319	322	325	310
	21-1363	242	257	274	282	298	308	314	311	325	334	334	344	343	348	334
	21-1364	234	244	263	280	286	291	300	308	311	310	319	324	324	330	312
	Mean	**215.8**	**232.5**	**248.1**	**260.5**	**266.4**	**278.1**	**281.2**	**288.5**	**292.8**	**299.3**	**300.5**	**306.1**	**308.6**	**312.6**	**296.9**
	SD	**16.99**	**15.81**	**18.14**	**16.90**	**19.89**	**18.93**	**22.23**	**20.35**	**20.07**	**21.31**	**23.95**	**22.98**	**20.86**	**23.70**	**22.83**
	21-1333	208	216	238	246	250	252	267	275	277	279	288	296	293	300	285
1.09 mg/kg-d	21-1334	193	210	221	226	236	246	250	259	265	265	265	273	272	264	256
	21-1335	211	221	233	246	252	255	258	265	274	276	277	283	285	287	279
	21-1336	200	217	232	241	251	258	260	261	264	273	274	276	278	280	274
	21-1341	206	227	241	253	254	264	267	276	272	282	288	291	286	293	277
	21-1342	224	261	264	282	300	315	314	313	324	327	335	335	339	342	324
	21-1371	200	220	233	243	251	254	267	271	280	281	282	286	283	291	274
	21-1372	211	220	240	251	259	260	274	283	280	289	296	289	291	303	288
	21-1373	198	203	222	239	245	242	249	260	267	264	272	283	280	287	269
	21-1374	211	229	245	249	266	274	278	276	289	293	294	306	305	306	299
	Mean	**206.2**	**222.4**	**236.9**	**247.6**	**256.4**	**262.0**	**268.4**	**273.9**	**279.2**	**282.9**	**287.1**	**291.8**	**291.2**	**295.3**	**282.5**
	SD	**8.87**	**15.52**	**12.28**	**14.28**	**17.23**	**20.67**	**18.57**	**15.95**	**17.54**	**18.03**	**19.55**	**17.91**	**19.09**	**20.42**	**18.57**
	21-1339	197	219	229	244	256	263	269	277	279	282	286	292	294	291	281
4.38 mg/kg-d	21-1340	206	231	248	262	272	290	296	301	301	310	318	320	313	321	309
	21-1351	214	220	245	256	254	274	273	276	281	284	290	287	286	286	271
	21-1352	207	228	244	260	264	278	285	291	292	298	304	306	296	303	293
	21-1355	246	263	275	293	309	316	318	330	338	341	351	350	337	351	337
	21-1356	181	192	207	213	226	232	238	235	247	254	258	257	260	259	248
	21-1357	209	232	247	264	279	286	293	300	305	311	312	316	320	319	311
	21-1358	213	230	244	258	270	276	291	302	305	306	312	317	312	318	304
	21-1359	216	216	237	243	262	274	275	278	288	299	300	300	304	306	295
	21-1360	223	229	250	262	265	265	278	288	290	290	291	297	301	298	280
	Mean	**211.2**	**226.0**	**242.6**	**255.5**	**265.7**	**275.4**	**281.6**	**287.8**	**292.6**	**297.5**	**302.2**	**304.2**	**302.3**	**305.2**	**292.9**
	SD	**16.82**	**17.64**	**17.15**	**20.23**	**20.91**	**21.42**	**20.96**	**24.62**	**23.25**	**22.79**	**24.32**	**24.48**	**20.80**	**24.64**	**24.64**
	21-1327	222	235	257	270	278	277	293	297	302	300	310	316	314	315	301
17.5 mg/kg-d	21-1328	193	218	231	237	252	266	268	270	281	286	290	291	287	286	275
	21-1329	187	211	229	237	254	264	271	271	279	281	286	281	284	284	275
	21-1330	180	206	228	239	255	269	275	276	291	294	300	300	300	301	292
	21-1343	220	242	270	283	293	300	306	311	314	315	319	312	(f)	(f)	(f)
	21-1344	196	217	231	244	247	263	270	277	277	290	299	300	292	301	288
	21-1353	211	222	243	257	265	272	281	288	289	287	295	302	301	307	287
	21-1354	217	242	246	269	282	288	303	307	314	312	324	340	333	335	320
	21-1367	203	229	247	256	263	275	282	284	284	290	302	300	296	295	280
	21-1368	232	251	259	276	288	295	294	305	315	316	318	320	322	322	305
	Mean	**206.1**	**227.3**	**244.1**	**256.8**	**267.7**	**276.9**	**284.3**	**288.6**	**294.6**	**297.1**	**304.3**	**306.2**	**303.2**	**305.1**	**291.4**
	SD	**16.96**	**14.89**	**14.54**	**17.14**	**16.38**	**13.14**	**13.90**	**15.46**	**15.34**	**12.92**	**12.92**	**16.54**	**16.51**	**16.68**	**14.98**
	21-1337	216	241	238	248	250	257	253	256	258	261	263	266	258	256	244
70 mg/kg-d	21-1338	196	206	214	228	233	235	233	246	248	256	251	261	260	259	249
	21-1349	191	197	198	208	216	222	228	227	232	233	230	232	229	229	218
	21-1350	184	209	213	213	220	222	226	225	232	235	233	230	236	241	233
	21-1361	232	232	247	256	256	250	247	265	256	259	256	259	268	255	242
	21-1362	272	286	289	293	291	290	290	298	305	322	307	322	317	303	285
	21-1365	223	238	254	253	256	271	280	280	279	295	301	302	303	298	286
	21-1366	202	207	216	214	218	223	229	229	232	235	238	236	235	236	223
	21-1369	210	215	227	231	231	240	239	238	244	(f)	(f)	(f)	(f)	(f)	(f)
	21-1370	248	248	263	271	271	281	279	279	286	281	272	278	273	273	259
	Mean	**217.4**	**227.9**	**235.9**	**241.5**	**244.2**	**249.1**	**250.4**	**254.3**	**257.2**	**264.1**	**261.2**	**265.1**	**264.3**	**261.1**	**248.8**
	SD	**27.34**	**26.80**	**27.74**	**27.67**	**24.92**	**25.09**	**24.19**	**25.55**	**25.29**	**30.32**	**27.93**	**31.61**	**30.27**	**25.96**	**24.32**

[1] Fasted Day 91 body weights

Table O-3
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Body Mass Summary (grams)
Male Rats

Group	Animal ID	DAY 0	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77	DAY 84	DAY 90	DAY 91[1]
Corn Oil Control	**Mean**	285.5	337.4	377.8	414.1	444.7	467.9	490.6	511.8	530.7	545.9	563.1	576.7	586.5	600.2	584.3
	SD	18.29	26.33	32.64	39.39	45.27	50.50	56.23	60.47	64.69	67.39	69.82	70.47	73.79	77.49	77.71
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1.09 mg/kg-d	**Mean**	280.4	333.3	374.0	409.5	438.7	460.1	480.9	501.9	521.8	536.6	547.5	562.0	575.5	590.3	574.9
	SD	21.56	24.51	26.60	31.15	36.34	43.60	44.85	47.01	49.15	52.25	53.32	54.22	59.59	65.79	63.23
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
4.38 mg/kg-d	**Mean**	270.6	323.0	359.5	394.0	423.7	448.9	468.5	489.4	507.5	521.0	534.9	550.7	558.9	570.2	553.7
	SD	21.13	28.34	33.48	39.05	43.03	46.68	50.28	50.70	53.82	56.42	56.21	57.16	59.64	68.17	65.73
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
17.5 mg/kg-d	**Mean**	275.3	324.2	363.7	399.2	429.6	455.9	476.5	494.9	509.6	524.3	540.6	550.1	558.4	570.6	554.0
	SD	18.16	29.37	40.75	47.51	53.01	56.07	62.64	71.08	73.36	79.99	84.61	87.51	91.60	93.22	91.62
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
70 mg/kg-d	**Mean**	273.5	312.7	336.6	349.1*	369.2*	388.3*	398.3*	408.0*	415.9*	418.1*	428.8*	442.4*	450.0*	455.9*	433.1*
	SD	16.16	20.18	26.97	30.01	36.91	37.49	36.13	43.73	44.41	39.85	44.13	41.55	44.59	49.21	45.97
	N	10	10	10	10	10	10	10	10	10	10	10	9	9	9	9

[1] Fasted day 91 body weights
* p<0.05 compared to controls

Table O-4
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Body Mass Summary (grams)
Female Rats

Group	Animal ID	DAY 0	DAY 7	DAY 14	DAY 21	DAY 28	DAY 35	DAY 42	DAY 49	DAY 56	DAY 63	DAY 70	DAY 77	DAY 84	DAY 90	DAY 91[1]
Corn Oil Control	**Mean**	215.8	232.5	248.1	260.5	266.4	278.1	281.2	288.5	292.8	299.3	300.5	306.1	308.6	312.6	296.9
	SD	16.99	15.81	18.14	16.90	19.89	18.93	22.23	20.35	20.07	21.31	23.95	22.98	20.86	23.70	22.83
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1.09 mg/kg-d	**Mean**	206.2	222.4	236.9	247.6	256.4	262.0	268.4	273.9	279.2	282.9	287.1	291.8	291.2	295.3	282.5
	SD	8.87	15.52	12.28	14.28	17.23	20.67	18.57	15.95	17.54	18.03	19.55	17.91	19.09	20.42	18.57
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
4.38 mg/kg-d	**Mean**	211.2	226.0	242.6	255.5	265.7	275.4	281.6	287.8	292.6	297.5	302.2	304.2	302.3	305.2	292.9
	SD	16.82	17.64	17.15	20.23	20.91	21.42	20.96	24.62	23.25	22.79	24.32	24.48	20.80	24.64	24.64
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
17.5 mg/kg-d	**Mean**	206.1	227.3	244.1	256.8	267.7	276.9	284.3	288.6	294.6	297.1	304.3	306.2	303.2	305.1	291.4
	SD	16.96	14.89	14.54	17.14	16.38	13.14	13.90	15.46	15.34	12.92	12.92	16.54	16.51	16.68	14.98
	N	10	10	10	10	10	10	10	10	10	10	10	10	9	9	9
70 mg/kg-d	**Mean**	217.4	227.9	235.9	241.5	244.2	249.1*	250.4*	254.3*	257.2*	264.1*	261.2*	265.1*	264.3*	261.1*	248.8*
	SD	27.34	26.80	27.74	27.67	24.92	25.09	24.19	25.55	25.29	30.32	27.93	31.61	30.27	25.96	24.32
	N	10	10	10	10	10	10	10	10	10	9	9	9	9	9	9

[1] Fasted Day 91 body weights
* $p<0.05$ compared to controls

Appendix P

Subchronic Individual and Summary of Body Mass Change

Abbreviations:

mg/kg-d: milligrams per kilogram per day
(f): animal died on study
SD: standard deviation

Table P-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Body Mass Change (grams)
Male Rats

Group	Animal ID	DAYS 0-7	DAYS 7-14	DAYS 14-21	DAYS 21-28	DAYS 28-35	DAYS 35-42	DAYS 42-49	DAYS 49-56	DAYS 56-63	DAYS 63-70	DAYS 70-77	DAYS 77-84	DAYS 84-90	FINAL
	21-1281	62	39	40	28	25	23	17	18	25	17	13	8	20	335
Corn Oil	21-1282	39	37	29	23	16	16	18	16	7	14	13	-1	16	243
Control	21-1295	60	50	35	29	17	26	21	22	21	23	18	13	15	350
	21-1296	51	36	39	45	22	27	21	27	19	19	21	9	12	348
	21-1297	51	45	37	37	27	27	31	25	16	19	11	17	16	359
	21-1298	45	39	38	30	20	20	11	16	11	13	58	5	5	311
	21-1299	33	27	22	18	16	12	12	9	10	13	13	9	5	199
	21-1300	55	38	42	31	30	19	30	10	17	23	11	17	18	341
	21-1309	67	56	51	44	37	36	26	28	14	17	13	13	19	421
	21-1310	56	37	30	21	22	21	25	18	12	14	15	8	11	290
	Mean	**51.9**	**40.4**	**36.3**	**30.6**	**23.2**	**22.7**	**21.2**	**18.9**	**15.2**	**17.2**	**18.6**	**9.8**	**13.7**	**319.7**
	SD	**10.51**	**8.09**	**7.97**	**9.11**	**6.75**	**6.73**	**6.89**	**6.59**	**5.49**	**3.79**	**14.19**	**5.49**	**5.38**	**62.91**
	21-1293	59	48	34	24	15	14	19	15	17	9	11	8	9	282
1.09 mg/kg-d	21-1294	55	43	28	28	20	22	16	20	15	12	11	15	5	290
	21-1315	46	35	39	24	25	17	12	19	13	10	15	12	17	284
	21-1316	50	40	39	26	20	21	22	21	10	19	11	14	28	321
	21-1317	42	38	28	24	13	22	20	14	14	7	15	5	4	246
	21-1318	50	33	29	26	8	20	19	20	6	10	16	5	5	247
	21-1321	62	43	44	41	29	18	19	15	12	-1	8	26	23	339
	21-1322	59	50	48	36	36	24	25	22	22	9	13	10	21	375
	21-1323	54	46	36	37	25	28	26	26	20	20	18	21	18	375
	21-1324	52	31	30	26	23	22	32	27	19	14	27	19	18	340
	Mean	**52.9**	**40.7**	**35.5**	**29.2**	**21.4**	**20.8**	**21.0**	**19.9**	**14.8**	**10.9**	**14.5**	**13.5**	**14.8**	**309.9**
	SD	**6.21**	**6.43**	**7.00**	**6.32**	**8.13**	**3.88**	**5.60**	**4.43**	**4.87**	**6.01**	**5.30**	**6.95**	**8.48**	**47.42**
	21-1275	58	33	33	34	30	14	21	15	18	20	16	-1	14	305
4.38 mg/kg-d	21-1276	50	32	38	28	17	16	26	12	11	9	16	10	9	274
	21-1277	42	27	24	28	25	16	21	10	13	14	19	6	-6	239
	21-1278	37	31	21	17	17	15	16	19	10	14	16	6	-6	213
	21-1279	61	41	39	28	26	19	15	22	12	12	14	2	16	307
	21-1280	55	34	38	29	22	23	26	19	17	9	8	9	20	309
	21-1291	51	40	39	28	27	16	18	18	2	18	10	6	15	288
	21-1292	48	40	38	33	27	26	28	25	22	21	23	11	21	363
	21-1313	65	45	46	39	36	28	23	24	22	12	22	14	19	395
	21-1314	57	42	29	33	25	23	15	17	8	10	14	19	11	303
	Mean	**52.4**	**36.5**	**34.5**	**29.7**	**25.2**	**19.6**	**20.9**	**18.1**	**13.5**	**13.9**	**15.8**	**8.2**	**11.3**	**299.6**
	SD	**8.59**	**5.84**	**7.71**	**5.77**	**5.69**	**5.02**	**4.82**	**4.86**	**6.33**	**4.41**	**4.73**	**5.77**	**9.87**	**52.98**
	21-1283	53	58	34	30	29	20	22	3	15	14	9	18	11	316
17.5 mg/kg-d	21-1284	68	47	46	36	25	37	28	0	27	21	13	9	18	375
	21-1289	43	31	32	25	26	21	17	9	9	12	12	2	13	252
	21-1290	65	59	44	36	33	28	39	31	28	25	20	10	13	431
	21-1301	42	31	25	21	23	13	2	15	6	17	3	5	11	214
	21-1302	35	33	28	26	23	6	13	16	8	9	5	9	12	223
	21-1305	55	41	41	38	26	28	15	21	16	17	3	8	9	318
	21-1306	58	41	45	39	28	21	22	22	16	21	10	21	20	364
	21-1311	31	22	24	22	19	16	11	9	11	9	11	0	13	198
	21-1312	39	32	36	31	31	16	15	21	11	18	9	1	2	262
	Mean	**48.9**	**39.5**	**35.5**	**30.4**	**26.3**	**20.6**	**18.4**	**14.7**	**14.7**	**16.3**	**9.5**	**8.3**	**12.2**	**295.3**
	SD	**12.71**	**12.17**	**8.28**	**6.69**	**4.14**	**8.77**	**10.11**	**9.53**	**7.54**	**5.31**	**5.13**	**6.93**	**4.87**	**77.97**
	21-1285	41	32	6	10	20	18	3	1	21	4	8	7	-8	163
70 mg/kg-d	21-1286	37	40	8	18	25	1	11	1	2	7	5	7	-7	155
	21-1287	37	18	22	7	21	13	11	9	10	7	3	13	9	180
	21-1288	55	48	4	32	31	12	11	4	7	13	14	15	12	258
	21-1303	42	17	22	26	19	9	15	2	-6	6	5	-12	20	165
	21-1304	51	36	22	35	4	4	32	18	-17	14	15	21	3	238
	21-1307	30	25	7	23	19	15	-2	2	8	36	-11	3	-5	150
	21-1308	37	9	-5	23	20	8	-1	6	1	-5	21	11	8	133
	21-1319	34	3	15	9	7	7	4	19	-4	-2	(f)	(f)	(f)	(f)
	21-1320	28	11	24	18	25	13	13	17	0	27	-1	3	21	199
	Mean	**39.2**	**23.9**	**12.5**	**20.1**	**19.1**	**10.0**	**9.7**	**7.9**	**2.2**	**10.7**	**6.6**	**7.6**	**5.9**	**182.3**
	SD	**8.51**	**14.76**	**9.89**	**9.55**	**8.10**	**5.19**	**9.83**	**7.40**	**10.28**	**12.58**	**9.49**	**9.37**	**10.98**	**41.84**

Table P-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Body Mass Change (grams)
Female Rats

Group	Animal ID	DAYS 0-7	DAYS 7-14	DAYS 14-21	DAYS 21-28	DAYS 28-35	DAYS 35-42	DAYS 42-49	DAYS 49-56	DAYS 56-63	DAYS 63-70	DAYS 70-77	DAYS 77-84	DAYS 84-90	FINAL
	21-1325	14	10	19	8	9	-1	11	5	8	-2	12	6	-12	87
Corn Oil	21-1326	22	8	9	1	15	-4	8	9	5	-7	12	11	2	91
Control	21-1331	19	14	11	3	18	1	7	5	1	1	-2	8	3	89
	21-1332	13	19	12	1	17	2	9	-2	8	6	-5	3	12	95
	21-1345	22	18	12	10	9	10	9	-1	12	5	4	-3	14	121
	21-1346	11	24	14	6	-3	17	8	6	3	3	8	4	0	101
	21-1347	26	10	14	3	25	-13	8	4	5	-2	7	-6	7	88
	21-1348	15	17	8	5	12	4	8	0	15	-1	5	3	3	94
	21-1363	15	17	8	16	10	6	-3	14	9	0	10	-1	5	106
	21-1364	10	19	17	6	5	9	8	3	-1	9	5	0	6	96
	Mean	**16.7**	**15.6**	**12.4**	**5.9**	**11.7**	**3.1**	**7.3**	**4.3**	**6.5**	**1.2**	**5.6**	**2.5**	**4.0**	**96.8**
	SD	**5.29**	**5.02**	**3.69**	**4.58**	**7.70**	**8.28**	**3.77**	**4.81**	**4.90**	**4.66**	**5.60**	**5.15**	**7.12**	**10.37**
	21-1333	8	22	8	4	2	15	8	2	2	9	8	-3	7	92
1.09 mg/kg-d	21-1334	17	11	5	10	10	4	9	6	0	0	8	-1	-8	71
	21-1335	10	12	13	6	3	3	7	9	2	1	6	2	2	76
	21-1336	17	15	9	10	7	2	1	3	9	1	2	2	2	80
	21-1341	21	14	12	1	10	3	9	-4	10	6	3	-5	7	87
	21-1342	37	3	18	18	15	-1	-1	11	3	8	0	4	3	118
	21-1371	20	13	10	8	3	13	4	9	1	1	4	-3	8	91
	21-1372	9	20	11	8	1	14	9	-3	9	7	-7	2	12	92
	21-1373	5	19	17	6	-3	7	11	7	-3	8	11	-3	7	89
	21-1374	18	16	4	17	8	4	-2	13	4	1	12	-1	1	95
	Mean	**16.2**	**14.5**	**10.7**	**8.8**	**5.6**	**6.4**	**5.5**	**5.3**	**3.7**	**4.2**	**4.7**	**-0.6**	**4.1**	**89.1**
	SD	**9.17**	**5.40**	**4.57**	**5.33**	**5.34**	**5.62**	**4.67**	**5.72**	**4.32**	**3.68**	**5.64**	**2.95**	**5.47**	**12.81**
	21-1339	22	10	15	12	7	6	8	2	3	4	6	2	-3	94
4.38 mg/kg-d	21-1340	25	17	14	10	18	6	5	0	9	8	2	-7	8	115
	21-1351	6	25	11	-2	20	-1	3	5	3	6	-3	-1	0	72
	21-1352	21	16	16	4	14	7	6	1	6	6	2	-10	7	96
	21-1355	17	12	18	16	7	2	12	8	3	10	-1	-13	14	105
	21-1356	11	15	6	13	6	6	-3	12	7	4	-1	3	-1	78
	21-1357	23	15	17	15	7	7	7	5	6	1	4	4	-1	110
	21-1358	17	14	14	12	6	15	11	3	1	6	5	-5	6	105
	21-1359	0	21	6	19	12	1	3	10	11	1	0	4	2	90
	21-1360	6	21	12	3	0	13	10	2	0	1	6	4	-3	75
	Mean	**14.8**	**16.6**	**12.9**	**10.2**	**9.7**	**6.2**	**6.2**	**4.8**	**4.9**	**4.7**	**2.0**	**-1.9**	**2.9**	**94**
	SD	**8.56**	**4.55**	**4.20**	**6.56**	**6.17**	**4.96**	**4.49**	**4.02**	**3.51**	**3.09**	**3.20**	**6.40**	**5.63**	**15.13**
	21-1327	13	22	13	8	-1	16	4	5	-2	10	6	-2	1	93
17.5 mg/kg-d	21-1328	25	13	6	15	14	2	2	11	5	4	1	-4	-1	93
	21-1329	24	18	8	17	10	7	0	8	2	5	-5	3	0	97
	21-1330	26	22	11	16	14	6	1	15	3	6	0	0	1	121
	21-1343	22	28	13	10	7	6	5	3	1	4	-7	(f)	(f)	(f)
	21-1344	21	14	13	3	16	7	7	0	13	9	1	-8	9	105
	21-1353	11	21	14	8	7	9	7	1	-2	8	7	-1	6	96
	21-1354	25	4	23	13	6	15	4	7	-2	12	16	-7	2	118
	21-1367	26	18	9	7	12	7	2	0	6	12	-2	-4	-1	92
	21-1368	19	8	17	12	7	-1	11	10	1	2	2	2	0	90
	Mean	**21.2**	**16.8**	**12.7**	**10.9**	**9.2**	**7.4**	**4.3**	**6.0**	**2.5**	**7.2**	**1.9**	**-2.3**	**1.9**	**100.6**
	SD	**5.37**	**7.18**	**4.83**	**4.48**	**5.05**	**5.15**	**3.33**	**5.10**	**4.65**	**3.52**	**6.57**	**3.77**	**3.41**	**11.59**
	21-1337	25	-3	10	2	7	-4	3	2	3	2	3	-8	-2	40
70 mg/kg-d	21-1338	10	8	14	5	2	-2	13	2	8	-5	10	-1	-1	63
	21-1349	6	1	10	8	6	6	-1	5	1	-3	2	-3	0	38
	21-1350	25	4	0	7	2	4	-1	7	3	-2	-3	6	5	57
	21-1361	0	15	9	0	-6	-3	18	-9	3	-3	3	9	-13	23
	21-1362	14	3	4	-2	-1	0	8	7	17	-15	15	-5	-14	31
	21-1365	15	16	-1	3	15	9	0	-1	16	6	1	1	-5	75
	21-1366	5	9	-2	4	5	6	0	3	3	3	-2	-1	1	34
	21-1369	5	12	4	0	9	-1	-1	6	(f)	(f)	(f)	(f)	(f)	(f)
	21-1370	0	15	8	0	10	-2	0	7	-5	-9	6	-5	0	25
	Mean	**10.5**	**8.0**	**5.6**	**2.7**	**4.9**	**1.3**	**3.9**	**2.9**	**5.4**	**-2.9**	**3.9**	**-0.8**	**-3.2**	**42.9**
	SD	**9.16**	**6.58**	**5.42**	**3.30**	**5.97**	**4.55**	**6.81**	**4.98**	**7.11**	**6.39**	**5.71**	**5.45**	**6.40**	**18.04**

Table P-3
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Body Mass Change Summary (grams)
Male Rats

Group	Animal ID	DAYS 0-7	DAYS 7-14	DAYS 14-21	DAYS 21-28	DAYS 28-35	DAYS 35-42	DAYS 42-49	DAYS 49-56	DAYS 56-63	DAYS 63-70	DAYS 70-77	DAYS 77-84	DAYS 84-90	FINAL
Corn Oil Control	**Mean**	51.9	40.4	36.3	30.6	23.2	22.7	21.2	18.9	15.2	17.2	18.6	9.8	13.7	319.7
	SD	10.51	8.09	7.97	9.11	6.75	6.73	6.89	6.59	5.49	3.79	14.19	5.49	5.38	62.91
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1.09 mg/kg-d	**Mean**	52.9	40.7	35.5	29.2	21.4	20.8	21.0	19.9	14.8	10.9	14.5	13.5	14.8	309.9
	SD	6.21	6.43	7.00	6.32	8.13	3.88	5.60	4.43	4.87	6.01	5.30	6.95	8.48	47.42
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10
4.38 mg/kg-d	**Mean**	52.4	36.5	34.5	29.7	25.2	19.6	20.9	18.1	13.5	13.9	15.8	8.2	11.3	299.6
	SD	8.59	5.84	7.71	5.77	5.69	5.02	4.82	4.86	6.33	4.41	4.73	5.77	9.87	52.98
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10
17.5 mg/kg-d	**Mean**	48.9	39.5	35.5	30.4	26.3	20.6	18.4	14.7	14.7	16.3	9.5	8.3	12.2	295.3
	SD	12.71	12.17	8.28	6.69	4.14	8.77	10.11	9.53	7.54	5.31	5.13	6.93	4.87	77.97
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10
70 mg/kg-d	**Mean**	39.2*	23.9	12.5*	20.1*	19.1	10.0*	9.7*	7.9*	2.2*	10.7	6.6	7.6	5.9	182.3*
	SD	8.51	14.76	9.89	9.55	8.10	5.19	9.83	7.40	10.28	12.58	9.49	9.37	10.98	41.84
	N	10	10	10	10	10	10	10	10	10	10	9	9	9	9

* $p<0.05$ compard to controls

Table P-4
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Body Mass Change Summary (grams)
Female Rats

Group	Animal ID	DAYS 0-7	DAYS 7-14	DAYS 14-21	DAYS 21-28	DAYS 28-35	DAYS 35-42	DAYS 42-49	DAYS 49-56	DAYS 56-63	DAYS 63-70	DAYS 70-77	DAYS 77-84	DAYS 84-90	FINAL
Corn Oil Control	**Mean**	16.7	15.6	12.4	5.9	11.7	3.1	7.3	4.3	6.5	1.2	5.6	2.5	4.0	96.8
	SD	5.29	5.02	3.69	4.58	7.70	8.28	3.77	4.81	4.90	4.66	5.60	5.15	7.12	10.37
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1.09 mg/kg-d	**Mean**	16.2	14.5	10.7	8.8	5.6	6.4	5.5	5.3	3.7	4.2	4.7	-0.6	4.1	89.1
	SD	9.17	5.40	4.57	5.33	5.34	5.62	4.67	5.72	4.32	3.68	5.64	2.95	5.47	12.81
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10
4.38 mg/kg-d	**Mean**	14.8	16.6	12.9	10.2	9.7	6.2	6.2	4.8	4.9	4.7	2.0	-1.9	2.9	94.0
	SD	8.56	4.55	4.20	6.56	6.17	4.96	4.49	4.02	3.51	3.09	3.20	6.40	5.63	15.13
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10
17.5 mg/kg-d	**Mean**	21.2	16.8	12.7	10.9	9.2	7.4	4.3	6.0	2.5	7.2*	1.9	-2.3	1.9*	100.6
	SD	5.37	7.18	4.83	4.48	5.05	5.15	3.33	5.10	4.65	3.52	6.57	3.77	3.41	11.59
	N	10	10	10	10	10	10	10	10	10	10	10	9	9	9
70 mg/kg-d	**Mean**	10.5	8.0*	5.6*	2.7	4.9	1.3	3.9	2.9	5.4	-2.9	3.9	-0.8	-3.2*	42.9*
	SD	9.16	6.58	5.42	3.30	5.97	4.55	6.81	4.98	7.11	6.39	5.71	5.45	6.40	18.04
	N	10	10	10	10	10	10	10	10	9	9	9	9	9	9

* $p<0.05$ compared to controls

Appendix Q

Subchronic Individual and Summary of Food Consumption and Food Efficiency

Abbreviations:

mg/kg-d: milligrams per kilogram per day
ND: no data
SD: standard deviation

Table Q-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Food Consumption (grams consumption per gram rat)
Male Rats

Group	Animal ID	DAYS 0-7	DAYS 7-14	DAYS 14-21	DAYS 21-28	DAYS 28-35	DAYS 35-42	DAYS 42-49	DAYS 49-56	DAYS 56-63	DAYS 63-70	DAYS 70-77	DAYS 77-84	DAYS 84-90	FINAL
Corn Oil Control	21-1281/21-1282	0.547	0.463	0.413	0.358	0.349	0.338	0.299	0.293	0.282	0.276	0.268	0.243	0.209	4.339
	21-1295/21-1296	0.549	0.464	0.394	0.379	0.342	0.320	0.308	0.293	0.279	0.264	0.265	0.232	0.204	4.294
	21-1297/21-1298	0.543	0.464	0.412	0.381	0.360	0.332	0.299	0.287	0.270	0.267	0.246	0.234	0.200	4.295
	21-1299/21-1300	0.537	0.447	0.407	0.383	0.354	0.325	0.304	0.289	0.277	0.287	0.271	0.242	0.206	4.329
	21-1309/21-1310	0.573	0.477	0.422	0.387	0.352	0.330	0.313	0.293	0.272	0.256	0.253	0.231	0.207	4.368
	Mean	**0.550**	**0.463**	**0.410**	**0.378**	**0.352**	**0.329**	**0.305**	**0.291**	**0.276**	**0.270**	**0.261**	**0.237**	**0.205**	**4.325**
	SD	**0.0136**	**0.0105**	**0.0102**	**0.0113**	**0.0067**	**0.0068**	**0.0061**	**0.0029**	**0.0046**	**0.0118**	**0.0106**	**0.0057**	**0.0035**	**0.0311**
1.09 mg/kg-d	21-1293/21-1294	0.575	0.498	0.429	0.374	0.334	0.328	0.310	0.295	0.279	0.264	0.254	0.235	0.202	4.377
	21-1315/21-1316	0.545	0.457	0.404	0.359	0.329	0.297	0.284	0.287	0.263	0.257	0.250	0.249	0.203	4.185
	21-1317/21-1318	0.574	0.481	0.429	0.406	0.364	0.357	0.334	0.317	0.308	0.296	0.295	0.266	0.222	4.648
	21-1321/21-1322	0.572	0.489	0.430	0.397	0.359	0.339	0.314	0.298	0.272	0.247	0.246	0.242	0.212	4.417
	21-1323/21-1324	0.538	0.454	0.427	0.372	0.361	0.342	0.323	0.315	0.303	0.282	0.275	0.253	0.222	4.466
	Mean	**0.561**	**0.476**	**0.424**	**0.382**	**0.349**	**0.333**	**0.313**	**0.302**	**0.285**	**0.269**	**0.264**	**0.249**	**0.212**	**4.419**
	SD	**0.0179**	**0.0194**	**0.0111**	**0.0195**	**0.0163**	**0.0222**	**0.0186**	**0.0131**	**0.0194**	**0.0195**	**0.0205**	**0.0119**	**0.0094**	**0.1668**
4.38 mg/kg-d	21-1275/21-1276	0.574	0.467	0.420	0.395	0.357	0.324	0.325	0.301	0.288	0.290	0.278	0.242	0.209	4.472
	21-1277/21-1278	0.536	0.468	0.398	0.386	0.359	0.346	0.321	0.314	0.297	0.294	0.283	0.263	0.209	4.474
	21-1279/21-1280	0.550	0.466	0.401	0.359	0.334	0.312	0.288	0.286	0.275	0.258	0.241	0.220	0.197	4.185
	21-1291/21-1292	0.556	0.468	0.417	0.392	0.359	0.347	0.318	0.304	0.288	0.273	0.260	0.247	0.212	4.439
	21-1313/21-1314	0.560	0.469	0.410	0.369	0.358	0.335	0.301	0.282	0.277	0.249	0.252	0.224	0.197	4.283
	Mean	**0.555**	**0.468**	**0.409**	**0.380**	**0.353**	**0.333**	**0.310**	**0.297**	**0.285**	**0.273**	**0.263**	**0.239**	**0.205**	**4.371**
	SD	**0.0142**	**0.0013**	**0.0096**	**0.0156**	**0.0108**	**0.0150**	**0.0158**	**0.0134**	**0.0090**	**0.0195**	**0.0179**	**0.0175**	**0.0073**	**0.1301**
17.5 mg/kg-d	21-1283/21-1284	0.615	0.539	0.466	0.421	0.375	0.350	0.335	0.273	0.299	0.277	0.279	0.248	0.206	4.683
	21-1289/21-1290	0.518	0.459	0.393	0.356	0.322	0.293	0.289	0.273	0.251	0.245	0.236	0.226	0.187	4.049
	21-1301/21-1302	0.523	0.457	0.408	0.380	0.349	0.316	0.292	0.281	0.272	0.267	0.250	0.239	0.209	4.242
	21-1305/21-1306	0.548	0.487	0.408	0.379	0.351	0.317	0.301	0.285	0.273	0.270	0.247	0.237	0.200	4.304
	21-1311/21-1312	0.557	0.461	0.427	0.407	0.382	0.352	0.328	0.308	0.302	0.287	0.273	0.259	0.224	4.567
	Mean	**0.552**	**0.481**	**0.420**	**0.389**	**0.356**	**0.326**	**0.309**	**0.284**	**0.279**	**0.269**	**0.257**	**0.242**	**0.205**	**4.369**
	SD	**0.0388**	**0.0351**	**0.0282**	**0.0255**	**0.0236**	**0.0250**	**0.0210**	**0.0145**	**0.0212**	**0.0157**	**0.0183**	**0.0125**	**0.0133**	**0.2554**
70 mg/kg-d	21-1285/21-1286	0.507	0.453	0.366	0.370	0.350	0.320	0.312	0.286	0.295	0.270	0.267	0.263	0.184	4.243
	21-1287/21-1288	0.536	0.481	0.414	0.376	0.384	0.347	0.312	0.309	0.295	0.287	0.274	0.286	0.230	4.531
	21-1303/21-1304	0.536	0.475	0.427	0.425	0.359	0.347	0.341	0.340	0.300	0.301	0.285	0.292	0.248	4.675
	21-1307/21-1308	0.477	0.416	0.337	0.387	0.357	0.326	0.271	0.294	0.277	0.311	0.283	0.268	0.205	4.209
	21-1319/21-1320	0.489	0.400	0.568	ND	ND	ND	0.342	0.305	0.298	0.312	ND	0.310	0.270	ND
	Mean	**0.509**	**0.445**	**0.422**	**0.389**	**0.363**	**0.335**	**0.315**	**0.307**	**0.293**	**0.296**	**0.277**	**0.284**	**0.227**	**4.414**
	SD	**0.0269**	**0.0355**	**0.0890**	**0.0250**	**0.0147**	**0.0141**	**0.0288**	**0.0207**	**0.0092**	**0.0179**	**0.0086**	**0.0189**	**0.0339**	**0.2260**

Table Q-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Paired Food Consumption (grams consumption per gram rat)
Female Rats

Group	Animal ID	DAYS 0-7	DAYS 7-14	DAYS 14-21	DAYS 21-28	DAYS 28-35	DAYS 35-42	DAYS 42-49	DAYS 49-56	DAYS 56-63	DAYS 63-70	DAYS 70-77	DAYS 77-84	DAYS 84-90	FINAL
	21-1325/21-1326	0.506	0.467	0.465	0.417	0.403	0.391	ND	0.382	0.369	0.379	0.381	0.320	0.281	ND
Corn Oil	21-1331/21-1332	0.509	0.447	0.437	0.426	0.424	0.372	0.379	0.376	0.363	0.329	0.326	0.318	0.299	5.005
Control	21-1345/21-1346	0.544	0.519	0.484	0.468	0.430	0.422	0.417	0.388	0.410	0.369	0.353	0.327	0.297	5.428
	21-1347/21-1348	0.540	0.471	0.478	0.452	0.424	0.362	0.394	0.369	0.380	0.367	0.359	0.324	0.306	5.226
	21-1363/21-1364	0.477	0.447	0.425	0.392	0.379	0.366	0.351	0.335	0.329	0.323	0.316	0.279	0.271	4.691
	Mean	**0.515**	**0.470**	**0.458**	**0.431**	**0.412**	**0.383**	**0.385**	**0.370**	**0.370**	**0.353**	**0.347**	**0.314**	**0.291**	**5.087**
	SD	**0.0277**	**0.0294**	**0.0257**	**0.0297**	**0.0211**	**0.0246**	**0.0278**	**0.0209**	**0.0291**	**0.0255**	**0.0261**	**0.0198**	**0.0143**	**0.3159**
	21-1333/21-1334	0.528	0.495	0.468	0.418	0.422	0.435	0.408	0.391	0.379	0.385	0.369	0.329	0.309	5.336
1.09 mg/kg-d	21-1335/21-1336	0.484	0.473	0.427	0.392	0.363	0.355	0.352	0.344	0.332	0.316	0.326	0.293	0.273	4.729
	21-1341/21-1342	0.559	0.503	0.479	0.453	0.439	0.380	0.392	0.384	0.374	0.372	0.353	0.331	0.304	5.324
	21-1371/21-1372	0.516	0.493	0.464	0.445	0.420	0.416	0.401	0.371	0.361	0.356	0.318	0.321	0.295	5.177
	21-1373/21-1374	0.502	0.488	0.461	0.429	0.401	0.383	0.369	0.358	0.361	0.343	0.338	0.308	0.292	5.033
	Mean	**0.518**	**0.490**	**0.460**	**0.427**	**0.409**	**0.394**	**0.384**	**0.370**	**0.361**	**0.355**	**0.341**	**0.316**	**0.294**	**5.120**
	SD	**0.0284**	**0.0110**	**0.0194**	**0.0242**	**0.0291**	**0.0316**	**0.0234**	**0.0192**	**0.0184**	**0.0269**	**0.0206**	**0.0160**	**0.0136**	**0.2511**
	21-1339/21-1340	0.560	0.522	0.488	0.462	0.439	0.414	0.401	0.371	0.375	0.354	0.351	0.320	0.286	5.344
4.38 mg/kg-d	21-1351/21-1352	0.520	0.470	0.450	0.411	0.408	0.375	0.370	0.354	0.347	0.345	0.332	0.301	0.273	4.956
	21-1355/21-1356	0.486	0.473	0.466	0.430	0.392	0.371	0.373	0.361	0.339	0.325	0.313	0.271	0.262	4.863
	21-1357/21-1358	0.548	0.497	0.467	0.437	0.416	0.416	0.389	0.348	0.350	0.338	0.330	0.278	0.270	5.085
	21-1359/21-1360	0.470	0.476	0.459	0.442	0.419	0.420	0.401	0.374	0.377	0.367	0.342	0.317	0.295	5.159
	Mean	**0.517**	**0.488**	**0.466**	**0.437**	**0.415**	**0.399**	**0.387**	**0.361**	**0.358**	**0.346**	**0.334**	**0.297**	**0.277**	**5.082**
	SD	**0.0388**	**0.0218**	**0.0142**	**0.0185**	**0.0172**	**0.0243**	**0.0147**	**0.0110**	**0.0171**	**0.0159**	**0.0143**	**0.0220**	**0.0130**	**0.1859**
	21-1327/21-1328	0.543	0.502	0.467	0.447	0.407	0.396	0.370	0.357	0.353	0.333	0.338	0.300	0.253	5.066
17.5 mg/kg-d	21-1329/21-1330	0.568	0.545	0.540	0.536	0.462	0.434	0.430	0.418	0.379	0.391	0.380	0.351	0.289	5.722
	21-1343/21-1344	0.545	0.499	0.480	0.441	0.428	0.403	0.395	0.347	0.383	0.371	0.343	ND	0.319	ND
	21-1353/21-1354	0.476	0.454	0.439	0.411	0.420	0.389	0.338	0.320	0.311	0.320	0.302	0.263	0.246	4.689
	21-1367/21-1368	0.544	0.506	0.483	0.465	0.446	0.405	0.397	0.379	0.389	0.379	0.342	0.316	0.288	5.338
	Mean	**0.535**	**0.501**	**0.482**	**0.460**	**0.432**	**0.405**	**0.386**	**0.364**	**0.363**	**0.359**	**0.341**	**0.307**	**0.279**	**5.204**
	SD	**0.0346**	**0.0323**	**0.0368**	**0.0468**	**0.0215**	**0.0173**	**0.0342**	**0.0366**	**0.0325**	**0.0306**	**0.0277**	**0.0364**	**0.0298**	**0.4362**
	21-1337/21-1338	0.483	0.482	0.489	ND	ND	ND	ND	ND	ND	ND	ND	0.357	ND	ND
70 mg/kg-d	21-1349/21-1350	0.473	0.477	0.451	0.472	0.480	0.436	0.405	0.401	0.389	0.367	0.320	0.342	0.291	5.305
	21-1361/21-1362	0.502	0.444	0.443	0.393	0.393	0.384	0.490	0.378	0.491	0.371	0.788	0.244	0.244	5.564
	21-1365/21-1366	0.490	0.489	0.428	0.445	0.474	0.454	0.424	0.386	0.411	0.384	0.375	0.368	0.309	5.438
	21-1369/21-1370	0.451	0.486	0.442	0.424	0.441	0.371	0.366	0.353	ND	0.294	0.374	0.282	0.271	ND
	Mean	**0.480**	**0.476**	**0.451**	**0.434**	**0.447**	**0.411**	**0.421**	**0.379**	**0.430**	**0.354**	**0.465**	**0.319**	**0.279**	**5.436**
	SD	**0.0191**	**0.0183**	**0.0232**	**0.0335**	**0.0399**	**0.0402**	**0.0521**	**0.0201**	**0.0534**	**0.0407**	**0.2174**	**0.0532**	**0.0281**	**0.1296**

Table Q-3
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Summary of 90-Day Paired Food Consumption (grams consumption per gram rat)
Male Rats

Group	Animal ID	DAYS 0-7	DAYS 7-14	DAYS 14-21	DAYS 21-28	DAYS 28-35	DAYS 35-42	DAYS 42-49	DAYS 49-56	DAYS 56-63	DAYS 63-70	DAYS 70-77	DAYS 77-84	DAYS 84-90	FINAL
Corn Oil Control	**Mean**	0.550	0.463	0.410	0.378	0.352	0.329	0.305	0.291	0.276	0.270	0.261	0.237	0.205	4.325
	SD	0.0136	0.0105	0.0102	0.0113	0.0067	0.0068	0.0061	0.0029	0.0046	0.0118	0.0106	0.0057	0.0035	0.0311
	N (Pairs)	5	5	5	5	5	5	5	5	5	5	5	5	5	5
1.09 mg/kg-d	**Mean**	0.561	0.476	0.424	0.382	0.349	0.333	0.313	0.302	0.285	0.269	0.264	0.249	0.212	4.419
	SD	0.0179	0.0194	0.0111	0.0195	0.0163	0.0222	0.0186	0.0131	0.0194	0.0195	0.0205	0.0119	0.0094	0.1668
	N (Pairs)	5	5	5	5	5	5	5	5	5	5	5	5	5	5
4.38 mg/kg-d	**Mean**	0.555	0.468	0.409	0.380	0.353	0.333	0.310	0.297	0.285	0.273	0.263	0.239	0.205	4.371
	SD	0.0142	0.0013	0.0096	0.0156	0.0108	0.0150	0.0158	0.0134	0.0090	0.0195	0.0179	0.0175	0.0073	0.1301
	N (Pairs)	5	5	5	5	5	5	5	5	5	5	5	5	5	5
17.5 mg/kg-d	**Mean**	0.552	0.481	0.420	0.389	0.356	0.326	0.309	0.284	0.279	0.269	0.257	0.242	0.205	4.369
	SD	0.0388	0.0351	0.0282	0.0255	0.0236	0.0250	0.0210	0.0145	0.0212	0.0157	0.0183	0.0125	0.0133	0.2554
	N (Pairs)	5	5	5	5	5	5	5	5	5	5	5	5	5	5
70 mg/kg-d	**Mean**	0.509	0.445	0.422	0.389	0.363	0.335	0.315	0.307	0.293	0.296	0.277	0.284*	0.227	4.414
	SD	0.0269	0.0355	0.0890	0.0250	0.0147	0.0141	0.0288	0.0207	0.0092	0.0179	0.0086	0.0189	0.0339	0.2260
	N (Pairs)	5	5	5	4	4	4	5	5	5	5	4	5	5	4

* $p<0.05$ compared to controls

Table Q-4
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Summary of 90-Day Paired Food Consumption (grams consumption per gram rat)
Female Rats

Group	Animal ID	DAYS 0-7	DAYS 7-14	DAYS 14-21	DAYS 21-28	DAYS 28-35	DAYS 35-42	DAYS 42-49	DAYS 49-56	DAYS 56-63	DAYS 63-70	DAYS 70-77	DAYS 77-84	DAYS 84-90	FINAL
Corn Oil Control	Mean	0.515	0.470	0.458	0.431	0.412	0.383	0.385	0.370	0.370	0.353	0.347	0.314	0.291	5.087
	SD	0.0277	0.0294	0.0257	0.0297	0.0211	0.0246	0.0278	0.0209	0.0291	0.0255	0.0261	0.0198	0.0143	0.3159
	N (Pairs)	5	5	5	5	5	5	4	5	5	5	5	5	5	4
1.09 mg/kg-d	Mean	0.518	0.490	0.460	0.427	0.409	0.394	0.384	0.370	0.361	0.355	0.341	0.316	0.294	5.120
	SD	0.0284	0.0110	0.0194	0.0242	0.0291	0.0316	0.0234	0.0192	0.0184	0.0269	0.0206	0.0160	0.0136	0.2511
	N (Pairs)	5	5	5	5	5	5	5	5	5	5	5	5	5	5
4.38 mg/kg-d	Mean	0.517	0.488	0.466	0.437	0.415	0.399	0.387	0.361	0.358	0.346	0.334	0.297	0.277	5.082
	SD	0.0388	0.0218	0.0142	0.0185	0.0172	0.0243	0.0147	0.0110	0.0171	0.0159	0.0143	0.0220	0.0130	0.1859
	N (Pairs)	5	5	5	5	5	5	5	5	5	5	5	5	5	5
17.5 mg/kg-d	Mean	0.535	0.501	0.482	0.460	0.432	0.405	0.386	0.364	0.363	0.359	0.341	0.307	0.279	5.223
	SD	0.0346	0.0323	0.0368	0.0468	0.0215	0.0173	0.0342	0.0366	0.0325	0.0306	0.0277	0.0364	0.0298	0.3802
	N (Pairs)	5	5	5	5	5	5	5	5	5	5	5	4	5	4
70 mg/kg-d	Mean	0.480	0.476	0.451	0.434	0.447	0.411	0.421	0.379	0.430	0.354	0.465	0.319	0.279	5.352
	SD	0.0191	0.0183	0.0232	0.0335	0.0399	0.0402	0.0521	0.0201	0.0534	0.0407	0.2174	0.0532	0.0281	0.1984
	N (Pairs)	5	5	5	4	4	4	4	4	3	4	4	5	4	3

Table Q-5
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Paired Food Consumption (total grams consumption per pair)
Male Rats

Group	Animal ID	DAYS 0-7	DAYS 7-14	DAYS 14-21	DAYS 21-28	DAYS 28-35	DAYS 35-42	DAYS 42-49	DAYS 49-56	DAYS 56-63	DAYS 63-70	DAYS 70-77	DAYS 77-84	DAYS 84-90	FINAL
	21-1281/21-1282	359	339	331	305	312	315	289	293	291	294	292	267	237	3924.0
Corn Oil	21-1295/21-1296	380	361	336	351	330	326	327	325	320	314	326	291	261	4248.0
Control	21-1297/21-1298	357	344	336	336	335	324	305	304	294	299	280	271	236	4021.0
	21-1299/21-1300	353	323	320	320	312	296	290	281	277	297	287	263	228	3847.0
	21-1309/21-1310	408	384	374	368	356	352	350	341	324	313	316	294	269	4449.0
	Mean	**371.4**	**350.2**	**339.4**	**336.0**	**329.0**	**322.6**	**312.2**	**308.8**	**301.2**	**303.4**	**300.2**	**277.2**	**246.2**	**4097.8**
	SD	**22.98**	**23.25**	**20.42**	**24.83**	**18.33**	**20.27**	**26.13**	**24.21**	**20.09**	**9.40**	**19.78**	**14.29**	**17.74**	**247.44**
	21-1293/21-1294	376	371	346	321	299	305	299	295	288	278	273	258	225	3934.0
1.09 mg/kg-d	21-1315/21-1316	363	339	331	312	301	283	280	294	276	277	276	281	239	3852.0
	21-1317/21-1318	340	319	309	313	288	297	291	287	285	279	287	262	220	3777.0
	21-1321/21-1322	403	390	383	384	370	364	351	344	324	296	300	303	275	4487.0
	21-1323/21-1324	385	360	367	343	350	349	348	356	354	339	344	326	294	4515.0
	Mean	**373.4**	**355.8**	**347.2**	**334.6**	**321.6**	**319.6**	**313.8**	**315.2**	**305.4**	**293.8**	**296.0**	**286.0**	**250.6**	**4113.0**
	SD	**23.67**	**27.64**	**29.14**	**30.30**	**36.10**	**35.00**	**33.30**	**32.20**	**32.75**	**26.45**	**28.85**	**28.61**	**32.42**	**358.66**
	21-1275/21-1276	359	322	320	325	311	292	308	293	289	299	296	260	229	3903.0
4.38 mg/kg-d	21-1277/21-1278	301	290	265	274	270	271	263	267	259	265	265	249	195	3434.0
	21-1279/21-1280	379	356	337	322	316	308	296	306	302	289	275	254	234	3974.0
	21-1291/21-1292	356	337	332	336	327	331	318	317	307	302	296	285	253	4097.0
	21-1313/21-1314	400	376	359	350	361	355	330	321	324	297	309	282	254	4318.0
	Mean	**359.0**	**336.2**	**322.6**	**321.4**	**317.0**	**311.4**	**303.0**	**300.8**	**296.2**	**290.4**	**288.2**	**266.0**	**233.0**	**3945.2**
	SD	**36.93**	**32.84**	**35.16**	**28.68**	**32.72**	**32.81**	**25.63**	**21.80**	**24.28**	**14.99**	**17.80**	**16.48**	**23.99**	**326.33**
	21-1283/21-1284	435	438	416	403	379	374	375	306	348	332	341	310	263	4720.0
17.5 mg/kg-d	21-1289/21-1290	342	344	325	316	305	292	304	298	283	285	282	273	231	3880.0
	21-1301/21-1302	316	305	294	292	284	263	248	247	243	245	232	225	201	3395.0
	21-1305/21-1306	371	370	345	349	343	325	320	315	310	317	294	289	249	4197.0
	21-1311/21-1312	331	299	302	310	310	297	285	277	278	272	264	251	220	3696.0
	Mean	**359.0**	**351.2**	**336.4**	**334.0**	**324.2**	**310.2**	**306.4**	**288.6**	**292.4**	**290.2**	**282.6**	**269.6**	**232.8**	**3977.6**
	SD	**47.02**	**56.57**	**48.79**	**43.73**	**37.22**	**41.90**	**46.81**	**27.17**	**39.17**	**34.88**	**40.15**	**33.00**	**24.25**	**506.84**
	21-1285/21-1286	306	306	252	265	267	250	248	228	242	224	225	226	155	3194.0
70 mg/kg-d	21-1287/21-1288	336	333	298	285	311	290	267	269	262	260	253	272	224	3660.0
	21-1303/21-1304	368	351	334	359	311	305	316	322	277	284	275	284	247	4033.0
	21-1307/21-1308	283	261	212	261	255	240	199	218	208	243	224	216	166	2986.0
	21-1319/21-1320	302	253	381	ND	ND	ND	262	245	238	257	ND	143	130	ND
	Mean	**319.0**	**300.8**	**295.4**	**292.5**	**286.0**	**271.3**	**258.4**	**256.4**	**245.4**	**253.6**	**244.3**	**228.2**	**184.4**	**3468.3**
	SD	**33.33**	**43.16**	**66.45**	**45.56**	**29.28**	**31.19**	**41.96**	**41.45**	**26.17**	**22.17**	**24.51**	**55.78**	**49.12**	**470.28**

Table Q-6
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Paired Food Consumption (total grams consumption per pair)
Female Rats

Group	Animal ID	DAYS 0-7	DAYS 7-14	DAYS 14-21	DAYS 21-28	DAYS 28-35	DAYS 35-42	DAYS 42-49	DAYS 49-56	DAYS 56-63	DAYS 63-70	DAYS 70-77	DAYS 77-84	DAYS 84-90	FINAL
	21-1325/21-1326	216	208	220	201	204	196	ND	204	202	204	214	185	160	ND
Corn Oil	21-1331/21-1332	237	223	228	224	238	210	220	219	215	197	193	192	185	2781.0
Control	21-1345/21-1346	251	261	256	255	237	244	248	233	252	230	224	208	193	3092.0
	21-1347/21-1348	254	234	248	238	239	201	225	212	226	217	217	195	187	2893.0
	21-1363/21-1364	239	240	239	229	227	225	217	213	212	211	211	186	184	2833.0
	Mean	**239.4**	**233.2**	**238.2**	**229.4**	**229.0**	**215.2**	**227.5**	**216.2**	**221.4**	**211.8**	**211.8**	**193.2**	**181.8**	**2899.8**
	SD	**15.01**	**19.74**	**14.57**	**19.78**	**14.78**	**19.51**	**14.06**	**10.80**	**19.13**	**12.64**	**11.56**	**9.26**	**12.68**	**136.09**
	21-1333/21-1334	225	227	221	203	210	225	218	212	206	213	210	186	174	2730.0
1.09 mg/kg-d	21-1335/21-1336	212	220	208	197	186	184	185	185	182	174	182	165	155	2435.0
	21-1341/21-1342	273	254	256	251	254	221	231	229	228	232	221	207	193	3050.0
	21-1371/21-1372	227	233	229	227	216	225	222	208	206	206	183	184	175	2741.0
	21-1373/21-1374	217	228	225	219	207	202	198	199	201	194	199	180	173	2642.0
	Mean	**230.8**	**232.4**	**227.8**	**219.4**	**214.6**	**211.4**	**210.8**	**206.6**	**204.6**	**203.8**	**199.0**	**184.4**	**174.0**	**2719.6**
	SD	**24.36**	**12.93**	**17.63**	**21.37**	**24.75**	**18.04**	**18.81**	**16.26**	**16.40**	**21.61**	**16.96**	**15.08**	**13.45**	**221.78**
	21-1339/21-1340	252	249	247	244	243	234	232	215	222	214	215	194	175	2936.0
4.38 mg/kg-d	21-1351/21-1352	233	230	232	213	225	209	210	203	202	205	197	175	161	2695.0
	21-1355/21-1356	221	228	236	230	215	206	211	211	202	198	190	162	160	2670.0
	21-1357/21-1358	253	244	244	240	234	243	234	212	216	211	209	176	172	2888.0
	21-1359/21-1360	209	232	232	233	226	232	227	216	222	217	204	192	178	2820.0
	Mean	**233.6**	**236.6**	**238.2**	**232.0**	**228.6**	**224.8**	**222.8**	**211.4**	**212.8**	**209.0**	**203.0**	**179.8**	**169.2**	**2801.8**
	SD	**19.23**	**9.32**	**6.94**	**11.98**	**10.50**	**16.36**	**11.52**	**5.13**	**10.16**	**7.58**	**9.82**	**13.27**	**8.23**	**116.78**
	21-1327/21-1328	246	245	237	237	221	222	210	208	207	200	205	180	152	2770.0
17.5 mg/kg-d	21-1329/21-1330	237	249	257	273	246	237	235	238	218	229	221	205	169	3014.0
	21-1343/21-1344	250	250	253	238	241	232	232	205	232	229	210	ND	96	ND
	21-1353/21-1354	221	222	231	225	235	227	201	193	186	198	194	167	158	2658.0
	21-1367/21-1368	261	256	257	256	254	233	234	227	236	235	212	195	178	3034.0
	Mean	**243.0**	**244.4**	**247.0**	**245.8**	**239.4**	**230.2**	**222.4**	**214.2**	**215.8**	**218.2**	**208.4**	**186.8**	**150.6**	**2869.0**
	SD	**15.02**	**13.13**	**12.17**	**18.81**	**12.42**	**5.81**	**15.79**	**18.05**	**20.25**	**17.71**	**9.91**	**16.70**	**32.12**	**184.91**
	21-1337/21-1338	216	218	233	ND	ND	ND	ND	ND	ND	ND	ND	185	ND	ND
70 mg/kg-d	21-1349/21-1350	192	196	190	206	213	198	183	186	182	170	148	159	137	2360.0
	21-1361/21-1362	260	238	243	215	212	206	276	212	285	209	458	143	136	3093.0
	21-1365/21-1366	218	230	200	211	234	231	216	197	218	207	202	198	165	2727.0
	21-1369/21-1370	209	238	222	213	230	192	189	187	ND	80	104	77	74	ND
	Mean	**219.0**	**224.0**	**217.6**	**211.3**	**222.3**	**206.8**	**216.0**	**195.5**	**228.3**	**166.5**	**228.0**	**152.4**	**128.0**	**2726.7**
	SD	**25.10**	**17.66**	**22.21**	**3.86**	**11.38**	**17.15**	**42.50**	**12.07**	**52.27**	**60.39**	**158.48**	**47.33**	**38.43**	**366.50**

Table Q-7
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Summary of 90-Day Paired Food Consumption (total grams consumption per pair)
Male Rats

Group		DAYS 0-7	DAYS 7-14	DAYS 14-21	DAYS 21-28	DAYS 28-35	DAYS 35-42	DAYS 42-49	DAYS 49-56	DAYS 56-63	DAYS 63-70	DAYS 70-77	DAYS 77-84	DAYS 84-90	FINAL
Corn Oil Control	**Mean**	371.4	350.2	339.4	336.0	329.0	322.6	312.2	308.8	301.2	303.4	300.2	277.2	246.2	4097.8
	SD	22.98	23.25	20.42	24.83	18.33	20.27	26.13	24.21	20.09	9.40	19.78	14.29	17.74	247.44
	N	5	5	5	5	5	5	5	5	5	5	5	5	5	5
1.09 mg/kg-d	**Mean**	373.4	355.8	347.2	334.6	321.6	319.6	313.8	315.2	305.4	293.8	296.0	286.0	250.6	4113.0
	SD	23.67	27.64	29.14	30.30	36.10	35.00	33.30	32.20	32.75	26.45	28.85	28.61	32.42	358.66
	N	5	5	5	5	5	5	5	5	5	5	5	5	5	5
4.38 mg/kg-d	**Mean**	359.0	336.2	322.6	321.4	317.0	311.4	303.0	300.8	296.2	290.4	288.2	266.0	233.0	3945.2
	SD	36.93	32.84	35.16	28.68	32.72	32.81	25.63	21.80	24.28	14.99	17.80	16.48	23.99	326.33
	N	5	5	5	5	5	5	5	5	5	5	5	5	5	5
17.5 mg/kg-d	**Mean**	359.0	351.2	336.4	334.0	324.2	310.2	306.4	288.6	292.4	290.2	282.6	269.6	232.8	3977.6
	SD	47.02	56.57	48.79	43.73	37.22	41.90	46.81	27.17	39.17	34.88	40.15	33.00	24.25	506.84
	N	5	5	5	5	5	5	5	5	5	5	5	5	5	5
70 mg/kg-d	**Mean**	319.0	300.8	295.4	292.5	286.0	271.3	258.4	256.4	245.4	253.6	244.3	228.2	184.4	3468.3
	SD	33.33	43.16	66.45	45.56	29.28	31.19	41.96	41.45	26.17	22.17	24.51	55.78	49.12	470.28
	N	5	5	5	4	4	4	5	5	5	5	4	5	5	4

Food consumption data were analyzed as grams consumption per gram rat and were not analyzed separately as total grams consumption per pair. See Table Q-3.

Table Q-8
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Summary of 90-Day Paired Food Consumption (total grams consumption per pair)
Female Rats

Group		DAYS 0-7	DAYS 7-14	DAYS 14-21	DAYS 21-28	DAYS 28-35	DAYS 35-42	DAYS 42-49	DAYS 49-56	DAYS 56-63	DAYS 63-70	DAYS 70-77	DAYS 77-84	DAYS 84-90	FINAL
Corn Oil Control	**Mean**	239.4	233.2	238.2	229.4	229.0	215.2	227.5	216.2	221.4	211.8	211.8	193.2	181.8	2899.8
	SD	15.01	19.74	14.57	19.78	14.78	19.51	14.06	10.80	19.13	12.64	11.56	9.26	12.68	136.09
	N	5	5	5	5	5	5	4	5	5	5	5	5	5	4
1.09 mg/kg-d	**Mean**	230.8	232.4	227.8	219.4	214.6	211.4	210.8	206.6	204.6	203.8	199.0	184.4	174.0	2719.6
	SD	24.36	12.93	17.63	21.37	24.75	18.04	18.81	16.26	16.40	21.61	16.96	15.08	13.45	221.78
	N	5	5	5	5	5	5	5	5	5	5	5	5	5	5
4.38 mg/kg-d	**Mean**	233.6	236.6	238.2	232.0	228.6	224.8	222.8	211.4	212.8	209.0	203.0	179.8	169.2	2801.8
	SD	19.23	9.32	6.94	11.98	10.50	16.36	11.52	5.13	10.16	7.58	9.82	13.27	8.23	116.78
	N	5	5	5	5	5	5	5	5	5	5	5	5	5	5
17.5 mg/kg-d	**Mean**	243.0	244.4	247.0	245.8	239.4	230.2	222.4	214.2	215.8	218.2	208.4	186.8	150.6	2869.0
	SD	15.02	13.13	12.17	18.81	12.42	5.81	15.79	18.05	20.25	17.71	9.91	16.70	32.12	184.91
	N	5	5	5	5	5	5	5	5	5	5	5	4	5	4
70 mg/kg-d	**Mean**	219.0	224.0	217.6	211.3	222.3	206.8	216.0	195.5	228.3	166.5	228.0	152.4	128.0	2726.7
	SD	25.10	17.66	22.21	3.86	11.38	17.15	42.50	12.07	52.27	60.39	158.48	47.33	38.43	366.50
	N	5	5	5	4	4	4	4	4	3	4	4	5	4	3

Food consumption data were analyzed as grams consumption per gram rat and were not analyzed separately as total grams consumption per pair. See Table Q-4.

Table Q-9
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Paired Food Efficiency
Male Rats

Group	Animal ID	DAYS 0-7	DAYS 7-14	DAYS 14-21	DAYS 21-28	DAYS 28-35	DAYS 35-42	DAYS 42-49	DAYS 49-56	DAYS 56-63	DAYS 63-70	DAYS 70-77	DAYS 77-84	DAYS 84-90	FINAL
	21-1281/21-1282	0.28	0.22	0.21	0.17	0.13	0.12	0.12	0.12	0.11	0.11	0.09	0.03	0.15	0.15
Corn Oil	21-1295/21-1296	0.29	0.24	0.22	0.21	0.12	0.16	0.13	0.15	0.13	0.13	0.12	0.08	0.10	0.16
Control	21-1297/21-1298	0.27	0.24	0.22	0.20	0.14	0.15	0.14	0.13	0.09	0.11	0.25	0.08	0.09	0.17
	21-1299/21-1300	0.25	0.20	0.20	0.15	0.15	0.10	0.14	0.07	0.10	0.12	0.08	0.10	0.10	0.14
	21-1309/21-1310	0.30	0.24	0.22	0.18	0.17	0.16	0.15	0.13	0.08	0.10	0.09	0.07	0.11	0.16
	Mean	**0.279**	**0.230**	**0.214**	**0.181**	**0.141**	**0.140**	**0.136**	**0.121**	**0.101**	**0.113**	**0.125**	**0.071**	**0.111**	**0.156**
	SD	**0.0204**	**0.0179**	**0.0094**	**0.0235**	**0.0178**	**0.0251**	**0.0106**	**0.0322**	**0.0172**	**0.0140**	**0.0691**	**0.0270**	**0.0241**	**0.0114**
	21-1293/21-1294	0.30	0.25	0.18	0.16	0.12	0.12	0.12	0.12	0.11	0.08	0.08	0.09	0.06	0.15
1.09 mg/kg-d	21-1315/21-1316	0.26	0.22	0.24	0.16	0.15	0.13	0.12	0.14	0.08	0.10	0.09	0.09	0.19	0.16
	21-1317/21-1318	0.27	0.22	0.18	0.16	0.07	0.14	0.13	0.12	0.07	0.06	0.11	0.04	0.04	0.13
	21-1321/21-1322	0.30	0.24	0.24	0.20	0.18	0.12	0.13	0.11	0.10	0.03	0.07	0.12	0.16	0.16
	21-1323/21-1324	0.28	0.21	0.18	0.18	0.14	0.14	0.17	0.15	0.11	0.10	0.13	0.12	0.12	0.16
	Mean	**0.283**	**0.228**	**0.204**	**0.173**	**0.130**	**0.130**	**0.133**	**0.126**	**0.096**	**0.074**	**0.097**	**0.092**	**0.115**	**0.150**
	SD	**0.0178**	**0.0131**	**0.0312**	**0.0182**	**0.0385**	**0.0130**	**0.0199**	**0.0164**	**0.0183**	**0.0317**	**0.0238**	**0.0338**	**0.0627**	**0.0123**
	21-1275/21-1276	0.30	0.20	0.22	0.19	0.15	0.10	0.15	0.09	0.10	0.10	0.11	0.03	0.10	0.15
4.38 mg/kg-d	21-1277/21-1278	0.26	0.20	0.17	0.16	0.16	0.11	0.14	0.11	0.09	0.11	0.13	0.05	-0.06	0.13
	21-1279/21-1280	0.31	0.21	0.23	0.18	0.15	0.14	0.14	0.13	0.10	0.07	0.08	0.04	0.15	0.16
	21-1291/21-1292	0.28	0.24	0.23	0.18	0.17	0.13	0.14	0.14	0.08	0.13	0.11	0.06	0.14	0.16
	21-1313/21-1314	0.31	0.23	0.21	0.21	0.17	0.14	0.12	0.13	0.09	0.07	0.12	0.12	0.12	0.16
	Mean	**0.290**	**0.216**	**0.212**	**0.184**	**0.159**	**0.125**	**0.138**	**0.120**	**0.091**	**0.096**	**0.110**	**0.061**	**0.091**	**0.151**
	SD	**0.0194**	**0.0172**	**0.0253**	**0.0155**	**0.0081**	**0.0165**	**0.0140**	**0.0187**	**0.0084**	**0.0235**	**0.0189**	**0.0328**	**0.0876**	**0.0120**
	21-1283/21-1284	0.28	0.24	0.19	0.16	0.14	0.15	0.13	0.01	0.12	0.11	0.06	0.09	0.11	0.15
17.5 mg/kg-d	21-1289/21-1290	0.32	0.26	0.23	0.19	0.19	0.17	0.18	0.13	0.13	0.13	0.11	0.04	0.11	0.18
	21-1301/21-1302	0.24	0.21	0.18	0.16	0.16	0.07	0.06	0.13	0.06	0.11	0.03	0.06	0.11	0.13
	21-1305/21-1306	0.30	0.22	0.25	0.22	0.16	0.15	0.12	0.14	0.10	0.12	0.04	0.10	0.12	0.16
	21-1311/21-1312	0.21	0.18	0.20	0.17	0.16	0.11	0.09	0.11	0.08	0.10	0.08	0.00	0.07	0.12
	Mean	**0.271**	**0.223**	**0.211**	**0.182**	**0.163**	**0.130**	**0.117**	**0.103**	**0.098**	**0.112**	**0.066**	**0.060**	**0.104**	**0.148**
	SD	**0.0432**	**0.0306**	**0.0293**	**0.0251**	**0.0186**	**0.0394**	**0.0465**	**0.0532**	**0.0300**	**0.0124**	**0.0309**	**0.0380**	**0.0204**	**0.0219**
	21-1285/21-1286	0.25	0.24	0.06	0.11	0.17	0.08	0.06	0.01	0.10	0.05	0.06	0.06	-0.10	0.10
70 mg/kg-d	21-1287/21-1288	0.27	0.20	0.09	0.14	0.17	0.09	0.08	0.05	0.06	0.08	0.07	0.10	0.09	0.12
	21-1303/21-1304	0.25	0.15	0.13	0.17	0.07	0.04	0.15	0.06	-0.08	0.07	0.07	0.03	0.09	0.10
	21-1307/21-1308	0.24	0.13	0.01	0.18	0.15	0.10	-0.02	0.04	0.04	0.13	0.04	0.06	0.02	0.09
	21-1319/21-1320	0.21	0.06	0.10	ND	ND	ND	0.06	0.15	-0.02	0.10	ND	0.02	0.16	ND
	Mean	**0.245**	**0.154**	**0.077**	**0.147**	**0.141**	**0.075**	**0.067**	**0.061**	**0.021**	**0.084**	**0.061**	**0.056**	**0.054**	**0.103**
	SD	**0.0256**	**0.0687**	**0.0468**	**0.0326**	**0.0450**	**0.0232**	**0.0587**	**0.0521**	**0.0710**	**0.0297**	**0.0123**	**0.0321**	**0.0984**	**0.0110**

Table Q-10
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Paired Food Efficiency
Female Rats

Group	Animal ID	DAYS 0-7	DAYS 7-14	DAYS 14-21	DAYS 21-28	DAYS 28-35	DAYS 35-42	DAYS 42-49	DAYS 49-56	DAYS 56-63	DAYS 63-70	DAYS 70-77	DAYS 77-84	DAYS 84-90	FINAL
	21-1325/21-1326	0.17	0.09	0.13	0.04	0.12	-0.03	ND	0.07	0.06	-0.04	0.11	0.09	-0.06	ND
Corn Oil	21-1331/21-1332	0.14	0.15	0.10	0.02	0.15	0.01	0.07	0.01	0.04	0.04	-0.04	0.06	0.08	0.07
Control	21-1345/21-1346	0.13	0.16	0.10	0.06	0.03	0.11	0.07	0.02	0.06	0.03	0.05	0.00	0.07	0.07
	21-1347/21-1348	0.16	0.12	0.09	0.03	0.15	-0.04	0.07	0.02	0.09	-0.01	0.06	-0.02	0.05	0.06
	21-1363/21-1364	0.10	0.15	0.10	0.10	0.07	0.07	0.02	0.08	0.04	0.04	0.07	-0.01	0.06	0.07
	Mean	**0.140**	**0.132**	**0.105**	**0.051**	**0.102**	**0.024**	**0.059**	**0.040**	**0.058**	**0.011**	**0.051**	**0.027**	**0.041**	**0.068**
	SD	**0.0251**	**0.0307**	**0.0141**	**0.0300**	**0.0553**	**0.0644**	**0.0239**	**0.0312**	**0.0203**	**0.0382**	**0.0543**	**0.0460**	**0.0588**	**0.0043**
	21-1333/21-1334	0.11	0.15	0.06	0.07	0.06	0.08	0.08	0.04	0.01	0.04	0.08	-0.02	-0.01	0.06
1.09 mg/kg-d	21-1335/21-1336	0.13	0.12	0.11	0.08	0.05	0.03	0.04	0.06	0.06	0.01	0.04	0.02	0.03	0.06
	21-1341/21-1342	0.21	0.07	0.12	0.08	0.10	0.01	0.03	0.03	0.06	0.06	0.01	0.00	0.05	0.07
	21-1371/21-1372	0.13	0.14	0.09	0.07	0.02	0.12	0.06	0.03	0.05	0.04	-0.02	-0.01	0.11	0.07
	21-1373/21-1374	0.11	0.15	0.09	0.11	0.02	0.05	0.05	0.10	0.00	0.05	0.12	-0.02	0.05	0.07
	Mean	**0.137**	**0.126**	**0.093**	**0.080**	**0.050**	**0.059**	**0.052**	**0.053**	**0.036**	**0.040**	**0.047**	**-0.006**	**0.046**	**0.065**
	SD	**0.0433**	**0.0349**	**0.0219**	**0.0146**	**0.0319**	**0.0444**	**0.0169**	**0.0305**	**0.0267**	**0.0178**	**0.0517**	**0.0188**	**0.0441**	**0.0038**
	21-1339/21-1340	0.19	0.11	0.12	0.09	0.10	0.05	0.06	0.01	0.05	0.06	0.04	-0.03	0.03	0.07
4.38 mg/kg-d	21-1351/21-1352	0.12	0.18	0.12	0.01	0.15	0.03	0.04	0.03	0.04	0.06	-0.01	-0.06	0.04	0.06
	21-1355/21-1356	0.13	0.12	0.10	0.13	0.06	0.04	0.04	0.09	0.05	0.07	-0.01	-0.06	0.08	0.07
	21-1357/21-1358	0.16	0.12	0.13	0.11	0.06	0.09	0.08	0.04	0.03	0.03	0.04	-0.01	0.03	0.07
	21-1359/21-1360	0.03	0.18	0.08	0.09	0.05	0.06	0.06	0.06	0.05	0.01	0.03	0.04	-0.01	0.06
	Mean	**0.123**	**0.141**	**0.108**	**0.087**	**0.085**	**0.054**	**0.055**	**0.045**	**0.046**	**0.046**	**0.019**	**-0.023**	**0.035**	**0.067**
	SD	**0.0596**	**0.0355**	**0.0193**	**0.0455**	**0.0424**	**0.0237**	**0.0140**	**0.0322**	**0.0083**	**0.0244**	**0.0249**	**0.0435**	**0.0314**	**0.0065**
	21-1327/21-1328	0.15	0.14	0.08	0.10	0.06	0.08	0.03	0.08	0.01	0.07	0.03	-0.03	0.00	0.07
17.5 mg/kg-d	21-1329/21-1330	0.21	0.16	0.07	0.12	0.10	0.05	0.00	0.10	0.02	0.05	-0.02	0.01	0.01	0.07
	21-1343/21-1344	0.17	0.17	0.10	0.05	0.10	0.06	0.05	0.01	0.06	0.06	-0.03	ND	0.09	ND
	21-1353/21-1354	0.16	0.11	0.16	0.09	0.06	0.11	0.05	0.04	-0.02	0.10	0.12	-0.05	0.05	0.08
	21-1367/21-1368	0.17	0.10	0.10	0.07	0.07	0.03	0.06	0.04	0.03	0.06	0.00	-0.01	-0.01	0.06
	Mean	**0.175**	**0.137**	**0.104**	**0.088**	**0.076**	**0.065**	**0.039**	**0.055**	**0.021**	**0.067**	**0.020**	**-0.019**	**0.029**	**0.070**
	SD	**0.0217**	**0.0292**	**0.0340**	**0.0250**	**0.0198**	**0.0302**	**0.0224**	**0.0322**	**0.0295**	**0.0205**	**0.0602**	**0.0274**	**0.0425**	**0.0086**
	21-1337/21-1338	0.16	0.02	0.10	ND	ND	ND	ND	ND	ND	ND	ND	-0.05	ND	ND
70 mg/kg-d	21-1349/21-1350	0.16	0.03	0.05	0.07	0.04	0.05	-0.01	0.06	0.02	-0.03	-0.01	0.02	0.04	0.04
	21-1361/21-1362	0.05	0.08	0.05	-0.01	-0.03	-0.01	0.09	-0.01	0.07	-0.09	0.04	0.03	-0.20	0.02
	21-1365/21-1366	0.09	0.11	-0.02	0.03	0.09	0.06	0.00	0.01	0.09	0.04	0.00	0.00	-0.02	0.04
	21-1369/21-1370	0.02	0.11	0.05	0.00	0.08	-0.02	-0.01	0.07	ND	-0.11	0.06	-0.06	0.00	ND
	Mean	**0.099**	**0.069**	**0.050**	**0.024**	**0.043**	**0.021**	**0.019**	**0.034**	**0.060**	**-0.046**	**0.021**	**-0.013**	**-0.047**	**0.033**
	SD	**0.0625**	**0.0436**	**0.0420**	**0.0372**	**0.0553**	**0.0425**	**0.0500**	**0.0394**	**0.0338**	**0.0691**	**0.0323**	**0.0413**	**0.1043**	**0.0131**

Table Q-11
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Summary of 90-Day Paired Food Efficiency
Male Rats

Group		DAYS 0-7	DAYS 7-14	DAYS 14-21	DAYS 21-28	DAYS 28-35	DAYS 35-42	DAYS 42-49	DAYS 49-56	DAYS 56-63	DAYS 63-70	DAYS 70-77	DAYS 77-84	DAYS 84-90	FINAL
Corn Oil Control	**Mean**	0.279	0.230	0.214	0.181	0.141	0.140	0.136	0.121	0.101	0.113	0.125	0.071	0.111	0.156
	SD	0.0204	0.0179	0.0094	0.0235	0.0178	0.0251	0.0106	0.0322	0.0172	0.0140	0.0691	0.0270	0.0241	0.0114
	N	5	5	5	5	5	5	5	5	5	5	5	5	5	5
1.09 mg/kg-d	**Mean**	0.283	0.228	0.204	0.173	0.130	0.130	0.133	0.126	0.096	0.074	0.097	0.092	0.115	0.150
	SD	0.0178	0.0131	0.0312	0.0182	0.0385	0.0130	0.0199	0.0164	0.0183	0.0317	0.0238	0.0338	0.0627	0.0123
	N	5	5	5	5	5	5	5	5	5	5	5	5	5	5
4.38 mg/kg-d	**Mean**	0.290	0.216	0.212	0.184	0.159	0.125	0.138	0.120	0.091	0.096	0.110	0.061	0.091	0.151
	SD	0.0194	0.0172	0.0253	0.0155	0.0081	0.0165	0.0140	0.0187	0.0084	0.0235	0.0189	0.0328	0.0876	0.0120
	N	5	5	5	5	5	5	5	5	5	5	5	5	5	5
17.5 mg/kg-d	**Mean**	0.271	0.223	0.211	0.182	0.163	0.130	0.117	0.103	0.098	0.112	0.066	0.060	0.104	0.148
	SD	0.0432	0.0306	0.0293	0.0251	0.0186	0.0394	0.0465	0.0532	0.0300	0.0124	0.0309	0.0380	0.0204	0.0219
	N	5	5	5	5	5	5	5	5	5	5	5	5	5	5
70 mg/kg-d	**Mean**	0.245	0.154	0.077*	0.147	0.141	0.075	0.067	0.061	0.021	0.084	0.061	0.056	0.054	0.103*
	SD	0.0256	0.0687	0.0468	0.0326	0.0450	0.0232	0.0587	0.0521	0.0710	0.0297	0.0123	0.0321	0.0984	0.0110
	N	5	5	5	4	4	4	5	5	5	5	4	5	5	4

* p<0.05 compared to controls

Table Q-12
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

Summary of 90-Day Paired Food Efficiency
Female Rats

Group		DAYS 0-7	DAYS 7-14	DAYS 14-21	DAYS 21-28	DAYS 28-35	DAYS 35-42	DAYS 42-49	DAYS 49-56	DAYS 56-63	DAYS 63-70	DAYS 70-77	DAYS 77-84	DAYS 84-90	FINAL
Corn Oil Control	**Mean**	0.140	0.132	0.105	0.051	0.102	0.024	0.059	0.040	0.058	0.011	0.051	0.027	0.041	0.068
	SD	0.0251	0.0307	0.0141	0.0300	0.0553	0.0644	0.0239	0.0312	0.0203	0.0382	0.0543	0.0460	0.0588	0.0043
	N	5	5	5	5	5	5	4	5	5	5	5	5	5	4
1.09 mg/kg-d	**Mean**	0.137	0.126	0.093	0.080	0.050	0.059	0.052	0.053	0.036	0.040	0.047	-0.006	0.046	0.065
	SD	0.0433	0.0349	0.0219	0.0146	0.0319	0.0444	0.0169	0.0305	0.0267	0.0178	0.0517	0.0188	0.0441	0.0038
	N	5	5	5	5	5	5	5	5	5	5	5	5	5	5
4.38 mg/kg-d	**Mean**	0.123	0.141	0.108	0.087	0.085	0.054	0.055	0.045	0.046	0.046	0.019	-0.023	0.035	0.067
	SD	0.0596	0.0355	0.0193	0.0455	0.0424	0.0237	0.0140	0.0322	0.0083	0.0244	0.0249	0.0435	0.0314	0.0065
	N	5	5	5	5	5	5	5	5	5	5	5	5	5	5
17.5 mg/kg-d	**Mean**	0.175	0.137	0.104	0.088	0.076	0.065	0.039	0.055	0.021	0.067*	0.020	-0.019	0.029	0.070
	SD	0.0217	0.0292	0.0340	0.0250	0.0198	0.0302	0.0224	0.0322	0.0295	0.0205	0.0602	0.0274	0.0425	0.0086
	N	5	5	5	5	5	5	5	5	5	5	5	4	5	4
70 mg/kg-d	**Mean**	0.099	0.069	0.050*	0.024	0.043	0.021	0.019	0.034	0.060	-0.046	0.021	-0.013	-0.047	0.033*
	SD	0.0625	0.0436	0.0420	0.0372	0.0553	0.0425	0.0500	0.0394	0.0338	0.0691	0.0323	0.0413	0.1043	0.0131
	N	5	5	5	4	4	4	4	4	3	4	4	5	4	3

*p<0.05 compared to controls

Appendix R

Subchronic Individual and Summary of Clinical Chemistry

Abbreviations:

mg/kg-d: milligrams per kilogram per day
(f): animal died on study
ND: no data
g/dL: grams per deciliter
U/L: units per liter
mg/dl: milligrams per deciliter
ALB: albumin
ALB/GLOB ratio: albumin/globulin ratio
ALP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
BUN: blood urea nitrogen
BUN/CREA ratio: blood urea nitrogen/creatinine ratio
CA: calcium
CHOL: cholesterol
CK: creatinine kinase
CREA: creatinine
GLOB calc: globulin calculated
GLU: glucose
PHOS: phosphate
TP: total protein
TRIG: triglycerides
AMY: amylase
LPS: lipase
SD: standard deviation

Table R-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Clinical Chemistry
Male Rats

Group	Animal ID	ALB (g/dL)	ALB / GLOB ratio (g/dL)	ALP (U/L)	ALT (U/L)	AMY (U/L)	AST (U/L)	BUN (mg/dL)	BUN / CREA ratio	CA (mg/dL)	CHOL (mg/dL)	CK (U/L)	CREA (mg/dL)	GLOB calc. (g/dL)	GLU (mg/dL)	LPS (U/L)	PHOS (mg/dL)	TP (g/dL)	TRIG (g/dL)
	21-1281	4.3	1.30	70	34	2535	81	12	60.00	12.4	57	163	0.2	3.3	226	8.6	13.5	7.6	66
Corn Oil	21-1282	4.2	1.20	51	37	2606	95	16	53.33	11.9	72	149	0.3	3.5	216	8.4	12.5	7.7	45
Control	21-1295	4.5	1.50	60	47	3442	91	13	43.33	12.2	78	93	0.3	3.0	274	6.5	11.9	7.5	155
	21-1296	4.4	1.33	122	40	3239	92	15	37.50	12.2	118	102	0.4	3.3	258	6.7	13.7	7.7	69
	21-1297	4.2	1.31	84	44	2140	85	16	40.00	12.0	61	153	0.4	3.2	283	10.1	14.3	7.4	90
	21-1298	4.2	1.24	73	40	2198	130	16	40.00	12.0	68	441	0.4	3.4	228	5.2	15.6	7.6	36
	21-1299	3.9	1.26	102	47	1872	99	14	35.00	11.3	39	123	0.4	3.1	105	6.9	13.2	7.0	29
	21-1300	4.3	1.02	112	31	2793	87	14	28.00	12.5	89	117	0.5	4.2	227	9.4	13.9	8.5	50
	21-1309	3.9	1.15	90	45	2343	98	17	34.00	12.4	91	164	0.5	3.4	249	7.4	13.7	7.3	49
	21-1310	4.4	1.42	76	41	2538	84	16	53.33	12.3	79	95	0.3	3.1	258	10.8	11.4	7.5	61
	Mean	**4.2**	**1.27**	**84**	**41**	**2571**	**94**	**15**	**42.45**	**12.1**	**75**	**160**	**0.4**	**3.4**	**232**	**8.0**	**13.4**	**7.6**	**65**
	SD	**0.20**	**0.135**	**22.7**	**5.4**	**485.7**	**13.9**	**1.6**	**10.10**	**0.35**	**21.6**	**102.4**	**0.09**	**0.34**	**50.0**	**1.77**	**1.21**	**0.39**	**36.2**
	21-1293	4.6	1.24	62	35	2328	77	12	40.00	12.7	106	90	0.3	3.7	299	10.6	14.0	8.3	75
1.09 mg/kg-d	21-1294	4.1	1.28	80	33	2126	85	16	53.33	12.6	66	101	0.3	3.2	243	7.0	14.2	7.3	63
	21-1315	4.3	1.39	96	34	2660	88	13	32.50	12.3	64	176	0.4	3.1	157	6.2	15.0	7.4	97
	21-1316	4.2	1.20	75	37	2315	73	16	40.00	11.9	61	94	0.4	3.5	244	9.0	13.8	7.7	66
	21-1317	4.3	1.26	75	37	1892	98	13	26.00	13.4	81	240	0.5	3.4	351	7.0	14.1	7.7	59
	21-1318	4.1	1.32	69	36	2345	82	15	37.50	12.2	79	161	0.4	3.1	159	6.2	11.8	7.2	40
	21-1321	4.1	1.17	75	34	2437	89	15	37.50	12.1	69	127	0.4	3.5	201	9.3	13.8	7.6	69
	21-1322	4.4	1.22	85	41	2456	87	15	37.50	12.5	96	128	0.4	3.6	202	6.5	13.4	8.0	78
	21-1323	4.2	1.11	67	33	3299	90	15	50.00	12.1	126	147	0.3	3.8	262	12.4	13.1	8.0	70
	21-1324	4.3	1.23	125	38	2661	84	18	60.00	12.6	57	144	0.3	3.5	266	9.8	13.1	7.8	117
	Mean	**4.3**	**1.24**	**81**	**36**	**2452**	**85**	**15**	**41.43**	**12.4**	**81**	**141**	**0.4**	**3.4**	**238**	**8.4**	**13.6**	**7.7**	**73**
	SD	**0.16**	**0.078**	**18.2**	**2.5**	**375.7**	**7.0**	**1.8**	**10.16**	**0.43**	**22.4**	**45.0**	**0.07**	**0.24**	**60.9**	**2.14**	**0.86**	**0.34**	**21.1**
	21-1275	4.2	1.24	74	38	2277	92	12	30.00	12.7	93	115	0.4	3.4	200	6.6	14.7	7.6	28
4.38 mg/kg-d	21-1276	4.5	1.29	81	45	2295	94	14	28.00	12.6	66	124	0.5	3.5	204	8.1	13.0	8.0	72
	21-1277	4.1	1.28	72	35	2152	75	16	40.00	12.5	91	123	0.4	3.2	322	6.8	14.5	7.3	37
	21-1278	4.3	1.19	95	38	2325	104	14	46.67	12.1	54	184	0.3	3.6	215	8.1	13.8	7.9	50
	21-1279	4.1	1.24	63	36	2842	96	15	30.00	12.0	86	111	0.5	3.3	246	7.1	14.2	7.4	53
	21-1280	4.0	1.14	75	34	2619	93	14	35.00	12.8	87	153	0.4	3.5	229	9.3	15.9	7.5	43
	21-1291	3.8	1.27	52	33	1855	82	15	37.50	11.6	61	169	0.4	3.0	141	6.3	11.4	6.8	62
	21-1292	4.1	1.14	89	40	2653	82	16	40.00	12.5	80	122	0.4	3.6	242	7.7	13.8	7.7	73
	21-1313	4.2	1.20	68	35	2661	70	13	32.50	12.9	99	107	0.4	3.5	190	5.7	12.9	7.7	70
	21-1314	4.3	1.30	68	38	3264	81	15	37.50	12.6	89	79	0.4	3.3	301	10.8	12.4	7.6	60
	Mean	**4.2**	**1.23**	**74**	**37**	**2494**	**87**	**14**	**35.72**	**12.4**	**81**	**129**	**0.4**	**3.4**	**229**	**7.7**	**13.7**	**7.6**	**55**
	SD	**0.19**	**0.059**	**12.5**	**3.5**	**397.7**	**10.5**	**1.3**	**5.76**	**0.41**	**15.1**	**31.3**	**0.06**	**0.19**	**52.9**	**1.52**	**1.28**	**0.34**	**15.4**
	21-1283	4.2	1.31	60	31	2531	79	11	27.50	12.5	90	101	0.4	3.2	226	4.8	13.1	7.4	75
17.5 mg/kg-d	21-1284	4.5	1.25	57	33	2390	87	14	35.00	12.2	111	113	0.4	3.6	210	8.1	11.9	8.1	73
	21-1289	4.5	1.18	63	23	2454	69	19	38.00	12.2	108	52	0.5	3.8	258	7.8	14.6	8.3	60
	21-1290	4.3	1.23	88	33	2351	66	15	37.50	13.3	98	77	0.4	3.5	275	6.4	13.4	7.8	65
	21-1301	4.1	1.05	62	31	2194	75	12	30.00	12.2	78	92	0.4	3.9	122	5.1	12.0	8.0	56
	21-1302	4.3	1.19	61	35	2003	73	16	32.00	11.9	79	110	0.5	3.6	187	7.8	11.5	7.9	35
	21-1305	4.3	1.34	87	34	2509	80	14	28.00	12.9	110	66	0.5	3.2	206	5.2	12.8	7.5	91
	21-1306	4.2	1.14	76	31	3365	81	14	35.00	12.3	77	68	0.4	3.7	227	9.8	13.9	7.9	88
	21-1311	4.0	1.18	76	38	1862	81	15	37.50	12.3	75	78	0.4	3.4	297	7.0	16.4	7.4	27
	21-1312	4.0	1.11	74	32	1969	87	17	34.00	12.5	93	76	0.5	3.6	341	10.1	15.4	7.6	37
	Mean	**4.2**	**1.20**	**70**	**32**	**2363**	**78**	**15**	**33.45**	**12.4**	**92**	**83**	**0.4**	**3.6**	**235**	**7.2**	**13.5**	**7.8**	**61**
	SD	**0.18**	**0.088**	**11.4**	**3.9**	**425.2**	**7.0**	**2.3**	**3.91**	**0.40**	**14.4**	**20.1**	**0.05**	**0.23**	**61.4**	**1.87**	**1.59**	**0.31**	**22.2**
	21-1285	4.3	1.26	50	26	1512	72	17	42.50	12.3	151	57	0.4	3.4	193	6.7	11.9	7.7	36
70 mg/kg-d	21-1286	4.1	1.58	44	28	1599	73	11	36.67	11.4	19	68	0.3	2.6	161	4.8	12.5	6.7	47
	21-1287	4.2	1.14	94	40	2222	71	18	45.00	11.6	21	52	0.4	3.7	192	5.1	12.6	7.9	69
	21-1288	4.6	1.44	119	39	2597	66	16	53.33	12.3	108	70	0.3	3.2	195	6.0	13.2	7.8	66
	21-1303	4.4	1.22	102	33	1366	113	20	40.00	11.6	151	86	0.5	3.6	141	6.3	11.6	8.0	25
	21-1304	4.3	1.10	55	21	2672	61	13	32.50	11.9	131	51	0.4	3.9	210	9.8	13.6	8.2	59
	21-1307	3.9	1.08	113	47	1180	96	22	44.00	11.1	40	93	0.5	3.6	103	6.5	11.3	7.5	22
	21-1308	4.2	1.14	96	37	2892	82	18	36.00	11.7	96	66	0.5	3.7	155	9.3	15.3	7.9	35
	21-1319	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1320	4.1	1.21	99	37	1463	77	18	45.00	11.8	86	69	0.4	3.4	175	5.7	13.8	7.5	27
	Mean	**4.2**	**1.24**	**86**	**34**	**1945**	**79**	**17**	**41.67**	**11.7**	**89**	**68**	**0.4**	**3.5**	**169**	**6.7**	**12.9**	**7.7**	**43**
	SD	**0.20**	**0.167**	**28.3**	**8.0**	**650.7**	**16.2**	**3.4**	**6.21**	**0.39**	**52.2**	**14.2**	**0.08**	**0.38**	**33.3**	**1.74**	**1.26**	**0.43**	**18.1**

Table R-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Clinical Chemistry
Female Rats

Group	Animal ID	ALB (g/dL)	ALB / GLOB ratio (g/dL)	ALP (U/L)	ALT (U/L)	AMY (U/L)	AST (U/L)	BUN (mg/dL)	BUN / CREA ratio	CA (mg/dL)	CHOL (mg/dL)	CK (U/L)	CREA (mg/dL)	GLOB calc. (g/dL)	GLU (mg/dL)	LPS (U/L)	PHOS (mg/dL)	TP (g/dL)	TRIG (g/dL)
	21-1325	4.9	1.36	31	50	2339	171	16	32.00	13.6	71	187	0.5	3.6	215	13.9	17.4	8.5	40
Corn Oil	21-1326	4.9	1.48	45	61	1695	165	23	46.00	13.3	66	207	0.5	3.3	311	6.9	15.1	8.2	46
Control	21-1331	5.0	1.43	42	47	1615	133	25	50.00	12.9	80	182	0.5	3.5	157	7.0	17.3	8.5	26
	21-1332	5.7	1.50	25	28	2468	125	20	50.00	13.8	96	146	0.4	3.8	376	7.8	14.2	9.5	60
	21-1345	4.6	1.53	32	37	1596	168	26	52.00	12.6	91	225	0.5	3.0	212	8.1	13.7	7.6	45
	21-1346	4.8	1.23	75	33	1518	136	23	38.33	11.8	74	130	0.6	3.9	163	8.8	11.1	8.7	55
	21-1347	4.3	1.30	32	35	1554	125	17	34.00	12.6	97	172	0.5	3.3	178	8.3	15.2	7.6	40
	21-1348	4.5	1.45	21	29	1752	112	21	52.50	12.5	84	247	0.4	3.1	284	13.1	14.4	7.6	57
	21-1363	5.1	1.50	42	55	1676	208	23	38.33	13.7	88	135	0.6	3.4	300	9.1	14.0	8.5	53
	21-1364	4.6	1.53	46	39	1955	107	24	60.00	12.8	81	93	0.4	3.0	269	12.8	14.2	7.6	73
	Mean	**4.8**	**1.43**	**39**	**41**	**1817**	**145**	**22**	**45.32**	**13.0**	**83**	**172**	**0.5**	**3.4**	**247**	**9.6**	**14.7**	**8.2**	**50**
	SD	**0.39**	**0.102**	**15.2**	**11.3**	**333.8**	**31.9**	**3.3**	**9.18**	**0.63**	**10.4**	**47.2**	**0.07**	**0.31**	**72.7**	**2.65**	**1.81**	**0.64**	**13.0**
	21-1333	4.7	1.34	37	36	1324	108	19	47.50	12.3	85	115	0.4	3.5	227	9.4	12.4	8.2	39
1.09 mg/kg-d	21-1334	4.5	1.32	51	45	1676	97	14	28.00	12.6	71	122	0.5	3.4	167	6.2	12.2	7.9	41
	21-1335	5.3	1.39	25	47	1434	179	17	34.00	13.6	82	177	0.5	3.8	326	12.0	14.9	9.1	37
	21-1336	4.8	1.66	69	37	1371	106	22	36.67	12.4	73	149	0.6	2.9	123	6.8	12.7	7.7	45
	21-1341	4.8	1.50	47	30	1335	103	21	52.50	12.6	73	112	0.4	3.2	255	13.5	14.0	8.0	26
	21-1342	4.2	1.35	35	34	1495	107	15	30.00	11.8	75	170	0.5	3.1	200	6.3	11.2	7.3	48
	21-1371	4.9	1.32	33	32	1657	83	18	36.00	12.6	80	74	0.5	3.7	118	13.3	13.0	8.6	30
	21-1372	5.0	1.47	31	40	1517	163	19	47.50	12.9	75	470	0.4	3.4	208	6.9	13.5	8.4	49
	21-1373	5.1	1.34	27	31	2962	81	15	30.00	13.9	109	132	0.5	3.8	353	11.4	12.7	8.9	105
	21-1374	5.4	1.46	34	33	1928	172	22	36.67	13.9	114	137	0.6	3.7	302	6.4	12.4	9.1	56
	Mean	**4.9**	**1.42**	**39**	**37**	**1670**	**120**	**18**	**37.88**	**12.9**	**84**	**166**	**0.5**	**3.5**	**228**	**9.2**	**12.9**	**8.3**	**48**
	SD	**0.36**	**0.109**	**13.3**	**5.8**	**490.7**	**36.9**	**2.9**	**8.45**	**0.71**	**15.3**	**110.9**	**0.07**	**0.31**	**81.3**	**3.06**	**1.03**	**0.61**	**22.1**
	21-1339	4.9	1.32	48	35	1662	121	17	34.00	12.4	102	147	0.5	3.7	196	8.8	11.6	8.6	41
4.38 mg/kg-d	21-1340	4.7	1.47	31	36	1289	154	18	25.71	13.0	105	191	0.7	3.2	253	7.6	14.8	7.9	54
	21-1351	4.3	1.23	42	35	1326	95	20	40.00	12.1	69	104	0.5	3.5	173	5.5	13.8	7.8	37
	21-1352	4.5	1.45	41	34	1222	86	28	46.67	12.0	72	73	0.6	3.1	222	5.4	12.3	7.6	54
	21-1355	5.6	1.51	18	27	2194	72	15	25.00	13.6	123	109	0.6	3.7	266	8.3	12.4	9.3	71
	21-1356	5.0	1.72	32	25	1398	78	26	52.00	12.7	101	97	0.5	2.9	251	14.1	12.4	7.9	89
	21-1357	5.1	1.38	27	40	1949	119	15	37.50	13.6	107	69	0.4	3.7	334	7.4	14.6	8.8	133
	21-1358	4.8	1.30	37	34	1658	102	16	26.67	12.7	104	212	0.6	3.7	244	12.0	11.2	8.5	101
	21-1359	4.7	1.57	26	33	1487	115	21	70.00	12.8	60	192	0.3	3.0	218	5.8	14.4	7.7	36
	21-1360	4.0	1.08	45	30	1890	100	22	36.67	12.1	87	72	0.6	3.7	202	11.0	13.6	7.7	53
	Mean	**4.8**	**1.40**	**35**	**33**	**1608**	**104**	**20**	**39.42**	**12.7**	**93**	**127**	**0.5**	**3.4**	**236**	**8.6**	**13.1**	**8.2**	**67**
	SD	**0.44**	**0.182**	**9.5**	**4.4**	**322.1**	**24.2**	**4.5**	**13.93**	**0.58**	**20.1**	**54.8**	**0.12**	**0.33**	**45.1**	**2.94**	**1.29**	**0.58**	**31.8**
	21-1327	5.5	1.34	30	66	2123	263	17	34.00	13.5	131	114	0.5	4.1	314	10.9	14.3	9.6	39
17.5 mg/kg-d	21-1328	4.4	1.33	32	32	1674	78	24	40.00	12.9	114	95	0.6	3.3	229	6.6	14.9	7.7	43
	21-1329	4.7	1.21	31	39	1670	93	17	42.50	12.0	101	153	0.4	3.9	126	12.4	12.6	8.6	27
	21-1330	4.5	1.13	28	40	1602	85	17	34.00	12.8	99	88	0.5	4.0	194	6.4	12.1	8.5	44
	21-1343	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1344	5.4	1.42	42	30	1622	138	15	30.00	13.3	107	184	0.5	3.8	184	9.1	13.6	9.2	36
	21-1353	5.1	1.38	33	38	1687	114	22	55.00	12.7	109	210	0.4	3.7	180	7.5	12.6	8.8	59
	21-1354	4.7	1.09	28	39	1679	116	19	38.00	12.5	117	256	0.5	4.3	162	10.5	12.4	9.0	52
	21-1367	5.0	1.43	45	34	1659	84	15	37.50	12.5	87	147	0.4	3.5	212	6.1	12.6	8.5	54
	21-1368	4.7	1.27	31	122	2026	464	15	30.00	12.6	113	194	0.5	3.7	175	12.2	13.4	8.4	48
	Mean	**4.9**	**1.29**	**33**	**49**	**1749**	**159**	**18**	**37.89**	**12.8**	**109**	**160**	**0.5**	**3.8**	**197**	**9.1**	**13.2**	**8.7**	**45**
	SD	**0.39**	**0.123**	**6.0**	**29.4**	**188.1**	**127.6**	**3.2**	**7.69**	**0.45**	**12.4**	**56.1**	**0.07**	**0.31**	**52.6**	**2.52**	**0.95**	**0.54**	**9.9**
	21-1337	4.9	1.29	28	33	2160	78	16	32.00	11.8	119	123	0.5	3.8	148	10.4	11.5	8.7	30
70 mg/kg-d	21-1338	4.5	1.15	51	26	1852	91	16	32.00	12.2	118	115	0.5	3.9	169	6.6	11.3	8.4	24
	21-1349	5.0	1.43	42	36	2120	137	22	44.00	12.6	137	514	0.5	3.5	328	7.3	15.9	8.5	36
	21-1350	4.7	1.27	56	66	2217	137	23	46.00	12.0	114	515	0.5	3.7	132	6.6	13.0	8.4	30
	21-1361	4.4	0.90	49	24	2548	76	19	31.67	12.1	132	71	0.6	4.9	183	9.1	13.8	9.3	24
	21-1362	4.8	1.20	53	21	1574	56	21	42.00	11.6	172	54	0.5	4.0	173	7.6	9.7	8.8	39
	21-1365	4.5	1.13	35	25	1510	73	18	30.00	13.4	153	62	0.6	4.0	214	4.5	14.3	8.5	30
	21-1366	5.1	1.55	33	35	1929	76	23	57.50	13.1	132	83	0.4	3.3	241	14.6	13.0	8.4	30
	21-1369	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1370	5.5	1.96	53	35	1882	69	19	31.67	12.1	159	95	0.6	2.8	134	8.6	10.9	8.3	25
	Mean	**4.8**	**1.32**	**44**	**33**	**1977**	**88**	**20**	**38.54**	**12.3**	**137**	**181**	**0.5**	**3.8**	**191**	**8.4**	**12.6**	**8.6**	**30**
	SD	**0.35**	**0.303**	**10.2**	**13.4**	**325.0**	**29.2**	**2.7**	**9.42**	**0.60**	**20.1**	**190.2**	**0.07**	**0.57**	**62.5**	**2.88**	**1.93**	**0.31**	**5.2**

Table R-3
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Clinical Chemistry Summary
Male Rats

Group	Animal ID	ALB (g/dL)	ALB / GLOB ratio (g/dL)	ALP (U/L)	ALT (U/L)	AMY (U/L)	AST (U/L)	BUN (mg/dL)	BUN / CREA ratio	CA (mg/dL)	CHOL (mg/dL)	CK (U/L)	CREA (mg/dL)	GLOB calc. (g/dL)	GLU (mg/dL)	LPS (U/L)	PHOS (mg/dL)	TP (g/dL)	TRIG (g/dL)
Corn Oil Control	**Mean**	4.2	1.27	84	41	2571	94	15	42.45	12.1	75	160	0.4	3.4	232	8.0	13.4	7.6	65
	SD	0.20	0.135	22.7	5.4	485.7	13.9	1.6	10.10	0.35	21.6	102.4	0.09	0.34	50.0	1.77	1.21	0.39	36.2
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1.09 mg/kg-d	**Mean**	4.3	1.24	81	36	2452	85	15	41.43	12.4	81	141	0.4	3.4	238	8.4	13.6	7.7	73
	SD	0.16	0.078	18.2	2.5	375.7	7.0	1.8	10.16	0.43	22.4	45.0	0.07	0.24	60.9	2.14	0.86	0.34	21.1
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
4.38 mg/kg-d	**Mean**	4.2	1.23	74	37	2494	87	14	35.72	12.4	81	129	0.4	3.4	229	7.7	13.7	7.6	55
	SD	0.19	0.059	12.5	3.5	397.7	10.5	1.3	5.76	0.41	15.1	31.3	0.06	0.19	52.9	1.52	1.28	0.34	15.4
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
17.5 mg/kg-d	**Mean**	4.2	1.20	70	32*	2363	78*	15	33.45*	12.4	92	83*	0.4	3.6	235	7.2	13.5	7.8	61
	SD	0.18	0.088	11.4	3.9	425.2	7.0	2.3	3.91	0.40	14.4	20.1	0.05	0.23	61.4	1.87	1.59	0.31	22.2
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
70 mg/kg-d	**Mean**	4.2	1.24	86	34*	1945	79*	17	41.67	11.7	89	68*	0.4	3.5	169*	6.7	12.9	7.7	43
	SD	0.20	0.167	28.3	8.0	650.7	16.2	3.4	6.21	0.39	52.2	14.2	0.08	0.38	33.3	1.74	1.26	0.43	18.1
	N	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9

* $p<0.05$ compared to controls

Table R-4
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Clinical Chemistry Summary
Female Rats

Group	Animal ID	ALB (g/dL)	ALB / GLOB ratio (g/dL)	ALP (U/L)	ALT (U/L)	AMY (U/L)	AST (U/L)	BUN (mg/dL)	BUN / CREA ratio	CA (mg/dL)	CHOL (mg/dL)	CK (U/L)	CREA (mg/dL)	GLOB calc. (g/dL)	GLU (mg/dL)	LPS (U/L)	PHOS (mg/dL)	TP (g/dL)	TRIG (g/dL)
Corn Oil Control	**Mean**	4.8	1.43	39	41	1817	145	22	45.32	13.0	83	172	0.5	3.4	247	9.6	14.7	8.2	50
	SD	0.39	0.102	15.2	11.3	333.8	31.9	3.3	9.18	0.63	10.4	47.2	0.07	0.31	72.7	2.65	1.81	0.64	13.0
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1.09 mg/kg-d	**Mean**	4.9	1.42	39	37	1670	120	18	37.88	12.9	84	166	0.5	3.5	228	9.2	12.9*	8.3	48
	SD	0.36	0.109	13.3	5.8	490.7	36.9	2.9	8.45	0.71	15.3	110.9	0.07	0.31	81.3	3.06	1.03	0.61	22.1
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
4.38 mg/kg-d	**Mean**	4.8	1.40	35	33	1608	104	20	39.42	12.7	93	127	0.5	3.4	236	8.6	13.1	8.2	67
	SD	0.44	0.182	9.5	4.4	322.1	24.2	4.5	13.93	0.58	20.1	54.8	0.12	0.33	45.1	2.94	1.29	0.58	31.8
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
17.5 mg/kg-d	**Mean**	4.9	1.29	33	49	1749	159	18	37.89	12.8	109*	160	0.5	3.8*	197	9.1	13.2	8.7	45
	SD	0.39	0.123	6.0	29.4	188.1	127.6	3.2	7.69	0.45	12.4	56.1	0.07	0.31	52.6	2.52	0.95	0.54	9.9
	N	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
70 mg/kg-d	**Mean**	4.8	1.32	44	33	1977	88*	20	38.54	12.3	137*	181	0.5	3.8	191	8.4	12.6*	8.6	30*
	SD	0.35	0.303	10.2	13.4	325.0	29.2	2.7	9.42	0.60	20.1	190.2	0.07	0.57	62.5	2.88	1.93	0.31	5.2
	N	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9

*p<0.05 compared to controls

Appendix S

Subchronic Individual and Summary of Hematology

Abbreviations:

mg/kg-d: milligrams per kilogram per day
(f): animal died on study
ND: no data
K/uL: thousands per microliter
M/uL: million per microliter
g/dL: grams per deciliter
%: percent
fL: femtoliter
pg: picogram
WBC: white blood cell
RBC: red blood cell
HGB: hemoglobin
HCT: hematocrit
MCV: mean corpuscular volume
MCH: mean corpuscular hemoglobin
MCHC: mean corpuscular hemoglobin concentration
PLT: platelet
RDW-SD: red blood cell distribution width-standard deviation
RDW-CV: red blood cell distribution width-coefficient of variation
MPV: mean platelet volume
NRBC: nucleated red blood cells
NEUT: neutrophils
LYMPH: lymphocytes
MONO: monophils
EO: eosinophils
BASO: basophils
RET: reticulocytes
IRF: immature red blood cell fraction
RET-He: reticulocyte hemoglobin concentration
PLT-F: platelet count fluorescent
SD: standard deviation

Table S-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Hematology
Male Rats

Group	Animal ID	WBC (K/uL)	RBC (M/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT (K/uL)	RDW-SD (fL)	RDW-CV (%)	MPV (fL)	NRBC (K/uL)	NRBC (%)	NEUT (K/uL)	NEUT (%)	LYMPH (K/uL)	LYMPH (%)	MONO (K/uL)	MONO (%)	EO (K/uL)	EO (%)	BASO (K/uL)	BASO (%)	RET (K/uL)	RET (%)	IRF (%)	RET-He (pg)	PLT-F (K/uL)	NEU/LYM Ratio
	21-1281	16.25	8.45	16.0	47.2	55.9	18.9	33.9	1020	26.1	15.6	8.6	0.02	0.1	2.27	13.9	12.70	78.2	1.18	7.3	0.08	0.5	0.02	0.1	0.2628	3.11	53.5	22.0	1020	0.18
Corn Oil	21-1282	16.10	8.94	16.2	48.5	54.3	18.1	33.4	1007	24.6	15.8	8.4	0.04	0.2	2.25	14.1	12.69	78.8	0.92	5.7	0.20	1.2	0.04	0.2	0.2146	2.40	50.3	21.5	1007	0.18
Control	21-1295	16.59	9.13	16.8	49.8	54.5	18.4	33.7	968	26.8	17.1	8.6	0.00	0.0	1.82	11.0	12.98	78.2	1.62	9.8	0.12	0.7	0.05	0.3	0.2538	2.78	57.1	22.0	698	0.14
	21-1296	16.17	9.23	16.0	49.6	53.7	17.3	32.3	1194	26.1	17.1	8.3	0.00	0.0	2.68	16.6	11.84	73.2	1.44	8.9	0.17	1.1	0.04	0.2	0.2575	2.79	55.7	20.6	1194	0.23
	21-1297	11.74	9.10	16.5	49.9	54.8	18.1	33.1	947	24.8	16.0	8.3	0.00	0.0	2.14	18.2	8.55	72.8	0.94	8.0	0.08	0.7	0.03	0.3	0.1847	2.03	44.1	21.6	947	0.25
	21-1298	13.97	9.09	16.8	51.5	56.7	18.5	32.6	1084	26.7	16.2	8.2	0.04	0.3	2.90	20.8	9.59	68.6	1.33	9.5	0.12	0.9	0.03	0.2	0.2809	3.09	43.2	21.7	1084	0.30
	21-1299	2.18	9.58	16.3	50.1	52.3	17.0	32.5	1076	22.0	15.5	7.5	0.00	0.0	0.54	24.7	1.46	67.0	0.17	7.8	0.01	0.5	0.00	0.0	0.1590	1.66	39.4	20.5	1076	0.37
	21-1300	12.47	8.30	15.6	48.3	58.2	18.8	32.3	1232	28.1	15.9	7.9	0.00	0.0	2.02	16.1	9.21	73.9	1.12	9.0	0.10	0.8	0.02	0.2	0.3561	4.29	60.5	22.2	1232	0.22
	21-1309	12.53	8.39	15.8	48.3	57.6	18.8	32.7	1250	26.5	14.8	8.0	0.00	0.0	1.30	10.4	9.97	79.6	1.18	9.4	0.05	0.4	0.03	0.2	0.2885	3.44	48.0	22.1	1250	0.13
	21-1310	13.25	8.85	16.6	50.3	56.8	18.8	33.0	1033	27.0	16.2	7.9	0.00	0.0	1.97	14.9	9.85	74.3	1.26	9.5	0.14	1.1	0.03	0.2	0.2292	2.59	51.7	22.8	1033	0.20
	Mean	**13.13**	**8.91**	**16.3**	**49.4**	**55.5**	**18.3**	**33.0**	**1081**	**25.9**	**16.0**	**8.2**	**0.01**	**0.1**	**1.99**	**16.1**	**9.88**	**74.5**	**1.12**	**8.5**	**0.11**	**0.8**	**0.03**	**0.2**	**0.25**	**2.8180**	**50.4**	**21.7**	**1054**	**0.22**
	SD	**4.257**	**0.412**	**0.41**	**1.26**	**1.87**	**0.66**	**0.57**	**108.7**	**1.70**	**0.70**	**0.35**	**0.017**	**0.11**	**0.673**	**4.34**	**3.375**	**4.32**	**0.394**	**1.29**	**0.056**	**0.281**	**0.014**	**0.088**	**0.056**	**0.73815**	**6.70**	**0.71**	**160.9**	**0.073**
	21-1293	15.06	8.86	16.7	50.3	56.8	18.8	33.2	1231	26.9	16.1	8.1	0.00	0.0	2.38	15.8	11.04	73.3	1.40	1.1	0.17	1.1	0.07	0.5	0.2268	2.56	54.9	21.9	1231	0.22
1.09 mg/kg-d	21-1294	14.74	8.95	16.6	50.5	56.4	18.5	32.9	1195	26.2	16.0	8.5	0.02	0.1	2.22	15.0	10.77	73.1	1.61	10.9	0.10	0.7	0.04	0.3	0.2613	2.92	48.0	21.8	1195	0.21
	21-1315	10.20	9.38	16.8	51.3	54.7	17.9	32.7	1013	26.7	16.9	8.4	0.02	0.2	1.48	14.5	7.98	78.2	0.68	6.7	0.05	0.5	0.01	0.1	0.3161	3.37	51.4	21.6	1013	0.19
	21-1316	17.34	8.58	16.3	49.4	57.6	19.0	33.0	1254	26.4	14.9	8.0	0.03	0.2	2.07	12.0	13.84	79.8	1.30	7.5	0.09	0.5	0.04	0.2	0.2445	2.85	46.1	22.7	1254	0.15
	21-1317	22.15	9.68	18.3	54.9	56.7	18.9	33.3	1285	26.1	16.7	7.9	0.00	0.0	2.41	10.9	17.76	80.2	1.76	7.9	0.14	0.6	0.08	0.4	0.2488	2.57	46.8	22.2	1285	0.14
	21-1318	6.35	8.88	15.6	47.2	53.2	17.6	33.1	997	24.4	16.0	8.2	0.00	0.0	0.72	11.2	5.23	82.4	0.36	5.7	0.03	0.5	0.01	0.2	0.2193	2.47	49.6	21.1	997	0.14
	21-1321	14.88	8.68	16.5	49.5	57.0	19.0	33.3	1064	28.1	16.4	7.9	0.00	0.0	1.22	8.2	12.36	83.1	1.12	7.5	0.14	0.9	0.04	0.3	0.2691	3.10	49.0	22.9	1064	0.10
	21-1322	18.39	8.44	15.2	46.1	54.6	18.0	33.0	1123	25.5	15.9	8.6	0.00	0.0	2.99	16.3	14.04	76.3	1.22	6.6	0.07	0.4	0.07	0.4	0.2768	3.28	59.1	21.9	1123	0.21
	21-1323	21.99	8.59	15.8	47.4	55.2	18.4	33.3	1059	25.4	15.6	8.7	0.02	0.1	2.90	13.1	16.99	77.3	1.96	8.9	0.08	0.4	0.06	0.3	0.3204	3.73	58.5	21.8	1059	0.17
	21-1324	14.48	8.94	17.8	53.2	59.5	19.9	33.5	1017	28.6	16.1	8.3	0.03	0.2	1.77	12.2	10.86	75.0	1.72	11.9	0.09	0.6	0.04	0.3	0.2691	3.01	47.5	23.7	1017	0.16
	Mean	**15.56**	**8.90**	**16.6**	**50.0**	**56.2**	**18.6**	**33.1**	**1124**	**26.4**	**16.1**	**8.3**	**0.01**	**0.1**	**2.02**	**12.9**	**12.09**	**77.9**	**1.31**	**7.5**	**0.10**	**0.6**	**0.05**	**0.3**	**0.27**	**2.9860**	**51.1**	**22.2**	**1124**	**0.17**
	SD	**4.854**	**0.381**	**0.95**	**2.72**	**1.79**	**0.67**	**0.24**	**109.1**	**1.25**	**0.56**	**0.29**	**0.013**	**0.09**	**0.724**	**2.52**	**3.821**	**3.52**	**0.498**	**2.96**	**0.043**	**0.225**	**0.024**	**0.115**	**0.033**	**0.40064**	**4.78**	**0.75**	**109.1**	**0.038**
	21-1275	11.19	9.52	16.2	49.9	52.4	17.0	32.5	973	24.7	17.1	8.1	0.00	0.0	1.70	15.1	8.45	75.5	0.98	8.8	0.03	0.3	0.03	0.3	0.1904	2.00	46.3	20.5	973	0.20
4.38 mg/kg-d	21-1276	12.10	9.08	16.0	48.2	53.1	17.6	33.2	1139	24.6	16.3	7.7	0.00	0.0	2.33	19.3	8.52	70.4	1.15	9.5	0.07	0.6	0.03	0.2	0.2007	2.21	48.2	20.9	1139	0.27
	21-1277	9.79	9.09	16.6	49.8	54.8	18.3	33.3	1090	25.8	16.5	8.1	0.00	0.0	1.47	15.0	7.33	74.9	0.91	9.3	0.06	0.6	0.02	0.2	0.2118	2.33	47.9	21.7	1090	0.20
	21-1278	9.61	9.15	16.5	49.3	53.9	18.0	33.5	1019	24.9	16.4	7.7	0.00	0.0	1.55	16.2	7.16	74.5	0.82	8.5	0.07	0.7	0.01	0.1	0.1839	2.01	49.6	21.6	1019	0.22
	21-1279	18.33	8.39	15.1	45.7	54.5	18.0	33.0	1106	26.5	16.2	8.2	0.00	0.0	3.22	17.5	13.54	73.9	1.43	7.8	0.11	0.6	0.03	0.2	0.2735	3.26	56.2	21.2	ND	0.24
	21-1280	13.57	8.05	15.7	46.6	57.9	19.5	33.7	1183	28.4	16.2	8.5	0.00	0.0	2.74	20.3	9.68	71.3	1.06	7.8	0.07	0.50	0.02	0.1	0.3148	3.91	57.10	22.10	ND	0.28
	21-1291	7.93	8.26	15.5	46.9	56.8	18.8	33.0	1030	26.9	15.0	7.9	0.03	0.4	1.24	15.7	6.09	76.8	0.55	6.9	0.04	0.5	0.01	0.1	0.2321	2.81	45.9	22.6	1030	0.20
	21-1292	14.60	8.38	16.8	49.5	59.1	20.0	33.9	1030	27.7	14.8	8.1	0.02	0.1	2.09	14.3	10.90	74.7	1.49	10.2	0.09	0.6	0.03	0.2	0.2497	2.98	47.5	23.4	1030	0.19
	21-1313	15.99	8.59	16.7	50.1	58.3	19.4	33.3	1125	28.9	16.5	8.5	0.02	0.1	3.57	22.3	11.03	69.0	1.23	7.7	0.11	0.7	0.05	0.3	0.2646	3.08	50.6	22.8	1125	0.32
	21-1314	18.17	8.08	15.8	47.8	59.2	19.6	33.1	1313	29.3	15.9	7.8	0.00	0.0	1.79	9.8	14.98	82.4	1.25	6.9	0.12	0.7	0.03	0.2	0.2973	3.68	60.1	23.1	1313	0.12
	Mean	**13.13**	**8.66**	**16.1**	**48.4**	**56.0**	**18.6**	**33.3**	**1101**	**26.8**	**16.1**	**8.1**	**0.01**	**0.1**	**2.17**	**16.6**	**9.77**	**74.3**	**1.09**	**8.3**	**0.08**	**0.6**	**0.03**	**0.2**	**0.24**	**2.8270**	**50.9**	**22.0**	**1090**	**0.23**
	SD	**3.627**	**0.513**	**0.57**	**1.57**	**2.56**	**0.99**	**0.40**	**98.3**	**1.76**	**0.70**	**0.29**	**0.012**	**0.13**	**0.783**	**3.52**	**2.864**	**3.75**	**0.286**	**1.11**	**0.030**	**0.123**	**0.012**	**0.074**	**0.046**	**0.67945**	**5.02**	**0.97**	**106.4**	**0.057**
	21-1283	18.98	8.05	14.8	44.6	55.4	18.4	33.2	1210	29.8	16.9	8.4	0.03	0.2	2.61	13.8	15.02	79.1	1.23	6.5	0.08	0.4	0.04	0.2	0.3373	4.19	62.3	21.6	1210	0.17
17.5 mg/kg-d	21-1284	14.99	8.29	15.2	46.6	56.2	18.3	32.6	999	26.2	15.0	8.7	0.00	0.0	1.48	9.9	12.14	81.0	1.24	8.3	0.08	0.5	0.05	0.3	0.2537	3.06	55.5	21.4	999	0.12
	21-1289	15.41	9.23	16.2	48.5	52.5	17.6	33.4	933	25.0	17.1	8.2	0.02	0.1	2.26	14.7	11.99	77.8	1.04	6.7	0.06	0.4	0.06	0.4	0.2372	2.57	53.1	20.0	933	0.19
	21-1290	14.16	8.42	15.1	45.7	54.3	17.9	33.0	1257	24.7	15.0	8.1	0.00	0.0	0.95	6.8	11.67	82.4	1.38	9.7	0.10	0.7	0.06	0.4	0.2602	3.09	57.4	21.0	1257	0.08
	21-1301	11.44	8.69	15.2	46.4	53.4	17.5	32.8	918	25.0	15.8	8.3	0.00	0.0	1.73	15.1	8.69	76.0	0.93	8.1	0.07	0.6	0.02	0.2	0.2016	2.32	48.9	20.9	918	0.20
	21-1302	10.50	8.75	15.4	45.5	52.0	17.6	33.8	906	24.4	16.4	8.4	0.04	0.4	1.20	11.4	8.63	82.2	0.60	5.7	0.05	0.5	0.02	0.2	0.2433	2.78	54.9	20.8	906	0.14
	21-1305	16.96	8.90	15.3	47.1	52.9	17.2	32.5	1077	25.0	16.7	7.9	0.00	0.0	1.43	8.5	14.03	82.7	1.34	7.9	0.11	0.6	0.05	0.3	0.2172	2.44	54.4	20.2	1077	0.10
	21-1306	25.63	9.32	15.9	48.4	51.9	17.1	32.9	1076	27.2	18.1	8.4	0.03	0.1	2.78	10.8	20.54	80.1	2.09	8.2	0.15	0.6	0.07	0.3	0.3206	3.44	52.8	20.1	1076	0.14
	21-1311	12.48	9.54	16.1	49.5	51.9	16.9	32.5	936	24.5	17.0	8.5	0.00	0.0	1.96	15.7	8.63	69.2	1.75	14.0	0.11	0.9	0.03	0.2	0.2395	2.51	47.8	20.5	936	0.23
	21-1312	10.67	8.73	15.7	47.7	54.6	18.0	32.9	1005	26.1	16.0	8.0	0.00	0.0	1.78	16.6	7.51	70.4	1.29	12.1	0.07	0.7	0.02	0.2	0.2497	2.86	46.5	29.9	1005	0.24
	Mean	**15.12**	**8.79**	**15.5**	**47.0**	**53.5**	**17.7**	**33.0**	**1032**	**25.8**	**16.4**	**8.3**	**0.01**	**0.1**	**1.82**	**12.3**	**11.89**	**78.1**	**1.29**	**8.7**	**0.09**	**0.6**	**0.04**	**0.3**	**0.26**	**2.9260**	**53.4**	**21.6**	**1032**	**0.16**
	SD	**4.612**	**0.471**	**0.46**	**1.53**	**1.55**	**0.50**	**0.41**	**122.9**	**1.67**	**0.97**	**0.24**	**0.016**	**0.13**	**0.594**	**3.32**	**3.944**	**4.86**	**0.413**	**2.58**	**0.030**	**0.152**	**0.019**	**0.082**	**0.042**	**0.56131**	**4.74**	**2.95**	**122.9**	**0.053**
	21-1285	29.40	7.98	14.0	42.3	53.0	17.5	33.1	514	27.3	16.6	9.8	0.00	0.0	1.99	6.8	24.96	84.9	2.35	8.0	0.01	0.0	0.09	0.3	0.2234	2.80	47.2	19.8	514	0.08
70 mg/kg-d	21-1286	18.27	8.42	13.9	41.8	49.6	16.5	33.3	541	26.5	17.6	9.7	0.03	0.2	2.75	15.1	13.09	71.6	2.38	13.0	0.00	0.0	0.05	0.3	0.2029	2.41	51.9	20.8	541	0.21
	21-1287	27.04	7.54	13.6	40.4	53.6	18.0	33.7	629	24.8	14.3	9.6	0.02	0.1	5.48	20.2	18.51	68.5	2.93	10.8	0.02	0.1	0.10	0.4	0.3137	4.16	58.6	21.6	629	0.30
	21-1288	17.65	8.38	15.9	47.1	56.2	19.0	33.8	717	29.1	17.0	10.7	0.02	0.1	2.23	12.6	13.76	78.0	1.60	9.1	0.02	0.1	0.04	0.2	0.2849	3.40	46.7	22.1	717	0.16
	21-1303	32.03	7.07	13.1	39.4	55.7	18.5	33.2	589	29.2	15.9	10.6	0.04	0.1	6.23	19.5	22.74	71.0	2.96	9.2	0.02	0.1	0.08	0.2	0.3026	4.28	57.4	21.3	589	0.27
	21-1304	30.80	8.65	14.6	44.2	51.1	16.9	33.0	693	32.1	19.7	9.7	0.05	0.2	4.06	13.2	22.76	73.9	3.86	12.5	0.03	0.1	0.09	0.3	0.2993	3.46	58.4	19.0	693	0.18
	21-1307	10.99	7.46	13.1	38.5	51.6	17.6	34.0	536	24.0	14.4	9.6	0.00	0.0	2.71	24.6	7.15	65.1	1.11	10.1	0.00	0.0	0.02	0.2	0.2544	3.41	51.2	20.7	536	0.38
	21-1308	34.32	8.69	15.4	45.8	52.7	17.7	33.6	681	29.2	17.9	9.1	0.03	0.1	5.29	15.5	25.99	75.7	2.82	8.2	0.11	0.3	0.11	0.3	0.3007	3.46	59.8	20.8	681	0.20
	21-1319	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1320	21.13	7.97	14.2	43.0	54.0	17.8	33.0	740	28.6	17.0	9.3	0.02	0.1	2.42	11.5	16.50	78.1	2.13	10.1	0.03	0.1	0.05	0.2	0.3547	4.45	56.8	20.4	740	0.15
	Mean	**24.63**	**8.02**	**14.2**	**42.5**	**53.1**	**17.7**	**33.4**	**627**	**27.9**	**16.7**	**9.8**	**0.02**	**0.1**	**3.68**	**15.4**	**18.38**	**74.1**	**2.46**	**10.1**	**0.03**	**0.1**	**0.07**	**0.3**	**0.28**	**3.5367**	**54.2**	**20.7**	**627**	**0.21**
	SD	**7.927**	**0.569**	**0.96**	**2.87**	**2.12**	**0.75**	**0.37**	**85.2**	**2.50**	**1.70**	**0.53**	**0.017**	**0.07**	**1.614**	**5.32**	**6.309**	**5.90**	**0.810**	**1.75**	**0.033**	**0.093**	**0.031**	**0.071**	**0.047**	**0.67396**	**5.06**	**0.93**	**85.2**	**0.090**

Table S-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Hematology
Female Rats

Group	Animal ID	WBC (K/uL)	RBC (M/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT (K/uL)	RDW-SD (fL)	RDW-CV (%)	MPV (fL)	NRBC (K/uL)	NRBC (%)	NEUT (K/uL)	NEUT (%)	LYMPH (K/uL)	LYMPH (%)	MONO (K/uL)	MONO (%)	EO (K/uL)	EO (%)	BASO (K/uL)	BASO (%)	RET (K/uL)	RET (%)	IRF (%)	RET-He (pg)	PLT-F (K/uL)	NEU/LYM Ratio
	21-1325	6.96	8.48	15.9	47.3	55.8	18.8	33.6	1425	22.3	12.7	8.2	0.00	0.0	0.87	12.6	5.30	76.1	0.69	9.9	0.07	1.0	0.03	0.4	0.1721	2.03	33.7	22.1	1425	0.16
Corn Oil	21-1326	10.51	8.86	16.5	49.8	56.2	18.6	33.1	758	22.0	12.5	8.1	0.00	0.0	1.36	12.9	8.07	76.8	0.99	9.4	0.07	0.7	0.02	0.2	0.2330	2.63	45.4	23.0	758	0.17
Control	21-1331	10.69	8.88	16.8	50.4	56.8	18.9	33.3	1292	22.9	13.4	7.9	0.00	0.0	1.73	16.2	7.85	73.4	1.03	9.6	0.06	0.6	0.02	0.2	0.2433	2.74	47.1	23.3	1292	0.22
	21-1332	7.04	7.55	14.6	43.7	57.9	19.3	33.4	1208	25.0	12.5	8.0	0.00	0.0	0.57	8.1	5.78	82.1	0.61	8.7	0.07	1.0	0.01	0.1	0.2197	2.91	47.6	23.7	1208	0.10
	21-1345	10.87	8.49	16.4	47.2	55.6	19.3	34.7	1231	24.8	14.6	8.4	0.00	0.0	1.64	15.1	8.13	74.8	0.96	8.8	0.11	1.0	0.03	0.3	0.1970	2.32	55.8	23.2	1231	0.20
	21-1346	7.79	8.53	15.7	47.0	55.1	18.4	33.4	955	23.2	13.4	8.2	0.00	0.0	0.99	12.7	6.26	80.4	0.48	6.2	0.05	0.6	0.01	0.1	0.2090	2.45	45.3	22.0	955	0.16
	21-1347	9.19	8.47	15.7	47.6	56.2	18.5	33.0	1164	22.8	12.8	7.5	0.00	0.0	1.00	10.9	7.37	80.2	0.75	8.2	0.05	0.5	0.02	0.2	0.2185	2.58	51.1	23.0	1164	0.14
	21-1348	11.92	7.41	14.7	43.9	59.2	19.8	33.5	948	27.5	13.0	8.8	0.00	0.0	0.66	5.5	10.48	87.9	0.71	6.0	0.05	0.4	0.02	0.2	0.2734	3.69	38.2	23.4	948	0.06
	21-1363	11.41	8.07	15.7	46.8	58.0	19.5	33.5	1316	22.7	11.9	8.2	0.00	0.0	1.90	16.5	8.35	73.2	1.01	8.9	0.12	1.1	0.03	0.3	0.2332	2.89	49.4	23.4	1316	0.23
	21-1364	12.86	8.31	15.7	46.9	56.4	18.9	33.5	1396	24.9	13.5	7.3	0.00	0.0	1.90	14.7	9.60	74.7	1.21	9.4	0.13	1.0	0.02	0.2	0.2302	2.77	50.7	22.1	1396	0.20
	Mean	**9.92**	**8.31**	**15.8**	**47.1**	**56.7**	**19.0**	**33.5**	**1169**	**23.8**	**13.0**	**8.1**	**0.00**	**0.0**	**1.26**	**12.5**	**7.72**	**78.0**	**0.84**	**8.5**	**0.08**	**0.8**	**0.02**	**0.2**	**0.22**	**2.7010**	**46.4**	**22.9**	**1169**	**0.16**
	SD	**2.077**	**0.495**	**0.71**	**2.12**	**1.27**	**0.46**	**0.46**	**216.7**	**1.71**	**0.74**	**0.43**	**0.000**	**0.00**	**0.508**	**3.53**	**1.624**	**4.66**	**0.228**	**1.36**	**0.030**	**0.256**	**0.007**	**0.092**	**0.027**	**0.43994**	**6.42**	**0.62**	**216.7**	**0.053**
	21-1333	9.52	8.65	16.2	48.2	55.7	18.7	33.6	1095	22.9	13.2	8.2	0.02	0.2	0.89	9.4	7.96	83.6	0.56	5.9	0.09	0.9	0.02	0.2	0.2266	2.62	51.5	23.1	1095	0.11
1.09 mg/kg-d	21-1334	6.51	8.68	16.0	48.3	55.6	18.4	33.1	1098	22.4	12.8	7.6	0.00	0.0	0.85	13.0	5.11	78.5	0.51	7.8	0.03	0.5	0.01	0.2	0.1623	1.87	40.9	22.3	1098	0.17
	21-1335	11.87	8.42	15.8	47.0	55.8	18.8	33.6	1271	22.5	12.7	8.5	0.00	0.0	1.90	16.0	8.58	72.3	1.22	10.3	0.13	1.1	0.04	0.3	0.2273	2.70	41.6	22.8	1271	0.22
	21-1336	3.63	8.55	16.6	48.4	56.6	19.4	34.3	1229	23.6	13.2	8.1	0.00	0.0	0.24	6.5	3.20	88.2	0.17	4.7	0.02	0.6	0.00	0.0	0.2155	2.52	46.5	31.7	1229	0.08
	21-1341	9.21	8.95	16.7	50.1	56.0	18.7	33.3	1180	21.9	12.8	8.0	0.00	0.0	1.26	13.6	6.81	73.9	1.00	10.9	0.08	0.9	0.06	0.7	0.2327	2.60	52.3	22.9	1180	0.19
	21-1342	16.98	8.60	16.1	48.7	56.6	18.7	33.1	1361	25.5	14.5	7.9	0.02	0.1	1.62	9.5	14.07	82.9	1.14	6.7	0.08	0.5	0.07	0.4	0.3199	3.72	43.0	22.3	1361	0.12
	21-1371	8.17	8.27	15.8	46.9	56.7	19.1	33.7	1268	22.4	11.8	7.9	0.00	0.0	0.66	8.1	6.73	82.4	0.67	8.2	0.09	1.1	0.02	0.2	0.1869	2.26	47.0	23.0	1268	0.10
	21-1372	7.43	7.67	15.0	44.6	58.1	19.6	33.6	919	25.6	12.5	8.3	0.02	0.3	1.16	15.6	5.31	71.5	0.88	11.8	0.06	0.8	0.02	0.3	0.2792	3.64	46.0	23.1	919	0.22
	21-1373	6.40	8.19	15.6	47.4	57.9	19.0	32.9	1355	25.2	13.8	8.4	0.00	0.0	0.44	6.8	5.38	84.1	0.49	7.7	0.07	1.1	0.02	0.3	0.2744	3.35	52.7	22.7	1355	0.08
	21-1374	7.98	8.00	15.6	46.7	58.4	19.5	33.4	1529	23.3	11.8	8.5	0.02	0.3	0.58	7.5	6.72	84.2	0.58	7.3	0.08	1.0	0.02	0.3	0.2144	2.68	43.7	23.5	1529	0.09
	Mean	**8.77**	**8.40**	**15.9**	**47.6**	**56.7**	**19.0**	**33.5**	**1231**	**23.5**	**12.9**	**8.1**	**0.01**	**0.1**	**0.96**	**10.6**	**6.99**	**80.2**	**0.72**	**8.1**	**0.07**	**0.9**	**0.03**	**0.3**	**0.23**	**2.7960**	**46.5**	**23.7**	**1231**	**0.14**
	SD	**3.616**	**0.374**	**0.50**	**1.48**	**1.04**	**0.40**	**0.40**	**170.0**	**1.40**	**0.83**	**0.30**	**0.010**	**0.13**	**0.526**	**3.63**	**2.927**	**5.77**	**0.330**	**2.25**	**0.031**	**0.242**	**0.022**	**0.179**	**0.046**	**0.59498**	**4.38**	**2.82**	**170.0**	**0.057**
	21-1339	9.08	8.29	15.8	46.3	55.9	19.1	34.1	1391	23.3	12.7	7.6	0.00	0.0	1.46	16.1	6.92	76.2	0.59	6.5	0.10	1.1	0.01	0.1	0.1699	2.05	39.3	22.6	1391	0.21
4.38 mg/kg-d	21-1340	5.89	8.26	15.9	47.3	57.3	19.2	33.6	1129	23.5	13.2	8.0	0.00	0.0	0.73	12.5	4.42	75.0	0.68	11.5	0.06	1.0	0.00	0.0	0.2800	3.39	56.4	23.1	1129	0.17
	21-1351	12.45	8.51	16.3	48.9	57.5	19.2	33.3	1265	24.0	13.1	8.2	0.00	0.0	0.90	7.4	10.70	85.9	0.74	5.9	0.08	0.6	0.03	0.2	0.2170	2.55	40.8	22.8	1265	0.08
	21-1352	8.02	8.58	15.6	46.7	54.4	18.2	33.4	1243	22.6	13.6	7.7	0.07	0.9	0.97	12.1	6.07	75.7	0.83	10.3	0.12	1.5	0.03	0.4	0.2360	2.75	58.1	22.3	1243	0.16
	21-1355	7.27	8.23	15.4	45.8	55.7	18.7	33.6	1014	23.2	12.8	8.3	0.00	0.0	0.64	8.8	6.11	84.0	0.47	6.5	0.04	0.6	0.01	0.1	0.1646	2.00	44.4	22.4	1014	0.10
	21-1356	7.56	8.29	15.4	46.6	56.2	18.6	33.0	1108	22.5	12.1	8.1	0.00	0.0	0.89	11.8	5.98	79.1	0.60	7.9	0.07	0.9	0.02	0.3	0.1948	2.35	49.1	22.1	1108	0.15
	21-1357	8.07	7.76	14.7	44.2	57.0	18.9	33.3	1221	26.3	13.8	8.3	0.00	0.0	1.02	12.6	6.01	74.5	0.96	11.9	0.07	0.9	0.01	0.1	0.1901	2.45	47.3	22.3	1221	0.17
	21-1358	11.13	8.37	15.2	45.8	54.7	18.2	33.2	1125	24.0	13.5	8.3	0.00	0.0	0.84	7.5	9.68	87.0	0.51	4.6	0.07	0.6	0.03	0.3	0.1984	2.37	46.6	22.3	1125	0.09
	21-1359	8.14	8.42	16.1	47.3	56.2	19.1	34.0	1032	24.1	13.5	8.4	0.02	0.2	1.21	14.8	5.95	73.1	0.90	11.1	0.07	0.9	0.01	0.1	0.2223	2.64	50.9	23.1	1032	0.20
	21-1360	8.61	7.65	15.0	45.4	59.3	19.6	33.0	943	25.8	12.6	8.7	0.00	0.0	0.89	10.4	7.03	81.6	0.64	7.4	0.04	0.5	0.01	0.1	0.3060	4.00	43.6	23.3	943	0.13
	Mean	**8.62**	**8.24**	**15.5**	**46.4**	**56.4**	**18.9**	**33.5**	**1147**	**23.9**	**13.1**	**8.2**	**0.01**	**0.1**	**0.96**	**11.4**	**6.89**	**79.2**	**0.69**	**8.4**	**0.07**	**0.9**	**0.02**	**0.2**	**0.22**	**2.6550**	**47.7**	**22.6**	**1147**	**0.15**
	SD	**1.899**	**0.302**	**0.50**	**1.27**	**1.43**	**0.45**	**0.38**	**134.6**	**1.25**	**0.53**	**0.33**	**0.022**	**0.28**	**0.235**	**2.90**	**1.891**	**5.09**	**0.163**	**2.62**	**0.024**	**0.303**	**0.011**	**0.125**	**0.046**	**0.61290**	**6.18**	**0.42**	**134.6**	**0.045**
	21-1327	14.11	7.85	15.1	44.6	56.8	19.2	33.9	1162	26.0	13.6	8.9	0.03	0.2	2.43	17.2	9.95	70.5	1.55	11.0	0.13	0.9	0.05	0.4	0.2669	3.40	49.2	23.2	1162	0.24
17.5 mg/kg-d	21-1328	13.51	7.36	15.1	44.4	60.3	20.5	34.0	941	26.6	12.3	9.0	0.00	0.0	0.70	5.2	11.82	87.5	0.89	6.6	0.07	0.5	0.03	0.2	0.2112	2.87	34.3	23.9	941	0.06
	21-1329	16.06	8.30	16.0	47.1	56.7	19.3	34.0	1231	24.6	13.7	8.5	0.00	0.0	3.03	18.8	11.38	70.9	1.47	9.2	0.12	0.7	0.06	0.4	0.1984	2.39	49.0	23.5	1231	0.27
	21-1330	9.79	8.07	15.1	44.3	54.9	18.7	34.1	1048	23.3	12.8	7.9	0.00	0.0	1.98	20.2	6.76	69.1	0.93	9.5	0.09	0.9	0.03	0.3	0.1566	1.94	36.3	22.4	1048	0.29
	21-1343	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1344	9.44	8.76	16.5	49.1	56.1	18.8	33.6	1457	24.4	15.2	8.6	0.00	0.0	1.49	15.8	6.93	73.4	0.88	9.3	0.10	1.1	0.04	0.4	0.2759	3.15	54.0	23.4	1457	0.22
	21-1353	5.41	8.33	15.3	46.0	55.2	18.4	33.3	1164	23.8	13.2	8.3	0.02	0.4	0.56	10.3	4.60	85.0	0.22	4.1	0.02	0.4	0.01	0.2	0.2132	2.56	50.9	22.2	1164	0.12
	21-1354	7.14	7.90	15.0	43.7	55.3	19.0	34.3	1018	24.8	13.7	8.2	0.00	0.0	1.81	25.5	4.88	68.3	0.41	5.7	0.03	0.4	0.01	0.1	0.2157	2.73	49.4	22.8	1018	0.37
	21-1367	4.33	8.14	15.4	46.1	56.6	18.9	33.4	963	24.9	13.2	8.5	0.00	0.0	0.42	9.6	3.64	84.1	0.25	5.8	0.02	0.5	0.00	0.0	0.1726	2.12	45.7	22.2	963	0.12
	21-1368	10.49	7.83	14.5	42.9	54.8	18.5	33.8	1308	23.6	13.2	8.7	0.00	0.0	2.21	21.0	6.92	66.0	1.16	11.1	0.18	1.7	0.02	0.2	0.1707	2.18	37.2	21.5	1308	0.32
	Mean	**10.03**	**8.06**	**15.3**	**45.4**	**56.3**	**19.0**	**33.8**	**1144**	**24.7**	**13.4**	**8.5**	**0.01**	**0.1**	**1.63**	**16.0**	**7.43**	**75.0**	**0.86**	**8.0**	**0.08**	**0.8**	**0.03**	**0.2**	**0.21**	**2.5933**	**45.1**	**22.8**	**1144**	**0.22**
	SD	**3.999**	**0.394**	**0.59**	**1.92**	**1.69**	**0.62**	**0.33**	**170.4**	**1.09**	**0.80**	**0.34**	**0.011**	**0.14**	**0.907**	**6.44**	**2.980**	**8.21**	**0.491**	**2.53**	**0.055**	**0.423**	**0.020**	**0.142**	**0.041**	**0.48990**	**7.25**	**0.77**	**170.4**	**0.104**
	21-1337	25.21	6.25	12.2	35.9	57.4	19.5	34.0	678	25.0	11.8	9.9	0.03	0.1	3.08	12.2	20.42	81.0	1.61	6.4	0.04	0.2	0.06	0.2	0.2081	3.33	50.0	22.8	678	0.15
70 mg/kg-d	21-1338	11.65	6.41	12.5	37.4	58.3	19.5	33.4	778	26.4	12.3	9.2	0.00	0.0	1.41	12.0	9.12	78.3	1.00	8.6	0.10	0.9	0.02	0.2	0.2263	3.53	49.0	23.3	778	0.15
	21-1349	6.26	6.36	11.6	35.2	55.3	18.2	33.0	831	27.5	13.5	9.7	0.00	0.0	0.64	10.1	5.29	84.5	0.31	5.0	0.01	0.2	0.01	0.2	0.2881	4.53	57.3	20.7	831	0.12
	21-1350	4.46	6.77	12.6	37.3	55.1	18.6	33.8	459	23.5	11.7	10.2	0.00	0.0	0.89	20.0	3.20	71.7	0.33	7.4	0.03	0.7	0.01	0.2	0.2139	3.16	48.1	22.4	459	0.28
	21-1361	9.88	6.07	12.0	36.3	59.8	19.8	33.1	850	26.6	11.9	10.2	0.00	0.0	0.76	7.7	8.48	85.8	0.62	6.3	0.01	0.1	0.01	0.1	0.1839	3.03	40.3	22.1	850	0.09
	21-1362	21.39	5.96	11.3	33.3	55.9	19.0	33.9	747	25.5	12.2	9.7	0.02	0.1	3.09	14.4	16.76	78.4	1.47	6.9	0.02	0.1	0.05	0.2	0.1627	2.73	44.7	21.9	747	0.18
	21-1365	16.66	6.15	11.9	35.7	58.0	19.3	33.3	854	26.2	12.1	9.8	0.00	0.0	2.45	14.7	12.92	77.6	1.24	7.4	0.01	0.1	0.04	0.2	0.1599	2.60	38.2	21.8	854	0.19
	21-1366	13.07	7.51	14.2	42.5	56.6	18.9	33.4	846	26.9	13.4	8.6	0.02	0.2	1.10	8.4	10.72	82.0	1.10	8.4	0.10	0.8	0.05	0.4	0.3109	4.14	49.7	22.0	846	0.10
	21-1369	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1370	4.45	6.44	12.5	36.7	57.0	19.4	34.1	793	24.9	11.8	8.7	0.00	0.0	0.50	11.2	3.63	81.6	0.31	7.0	0.01	0.2	0.00	0.0	0.1346	2.09	33.9	22.1	793	0.14
	Mean	**12.56**	**6.44**	**12.3**	**36.7**	**57.0**	**19.1**	**33.6**	**760**	**25.8**	**12.3**	**9.6**	**0.01**	**0.0**	**1.55**	**12.3**	**10.06**	**80.1**	**0.89**	**7.0**	**0.04**	**0.4**	**0.03**	**0.2**	**0.21**	**3.2378**	**45.7**	**22.1**	**760**	**0.16**
	SD	**7.367**	**0.467**	**0.83**	**2.50**	**1.52**	**0.50**	**0.40**	**126.6**	**1.23**	**0.68**	**0.59**	**0.012**	**0.07**	**1.045**	**3.74**	**5.867**	**4.21**	**0.511**	**1.10**	**0.037**	**0.332**	**0.022**	**0.105**	**0.059**	**0.75903**	**7.17**	**0.72**	**126.6**	**0.057**

Table S-3
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Hematology Summary
Male Rats

Group	Animal ID	WBC (K/uL)	RBC (M/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT (K/uL)	RDW-SD (fL)	RDW-CV (%)	MPV (fL)	NRBC (K/uL)	NRBC (%)	NEUT (K/uL)	NEUT (%)	LYMPH (K/uL)	LYMPH (%)	MONO (K/uL)	MONO (%)	EO (K/uL)	EO (%)	BASO (K/uL)	BASO (%)	RET (K/uL)	RET (%)	IRF (%)	RET-He (pg)	PLT-F (K/uL)	NEU/LYM Ratio
Corn Oil Control	**Mean**	13.13	8.91	16.3	49.4	55.5	18.3	33.0	1081	25.9	16.0	8.2	0.01	0.1	1.99	16.1	9.88	74.5	1.12	8.5	0.11	0.8	0.03	0.2	0.25	2.8180	50.4	21.7	1054	0.22
	SD	4.257	0.412	0.41	1.26	1.87	0.66	0.57	108.7	1.70	0.70	0.35	0.017	0.11	0.673	4.34	3.375	4.32	0.394	1.29	0.056	0.281	0.014	0.088	0.056	0.73815	6.70	0.71	160.9	0.073
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1.09 mg/kg-d	**Mean**	15.56	8.90	16.6	50.0	56.2	18.6	33.1	1124	26.4	16.1	8.3	0.01	0.1	2.02	12.9	12.09	77.9	1.31	7.5	0.10	0.6	0.05	0.3*	0.27	2.9860	51.1	22.2	1124	0.17
	SD	4.854	0.381	0.95	2.72	1.79	0.67	0.24	109.1	1.25	0.56	0.29	0.013	0.09	0.724	2.52	3.821	3.52	0.498	2.96	0.043	0.225	0.024	0.115	0.033	0.40064	4.78	0.75	109.1	0.038
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
4.38 mg/kg-d	**Mean**	13.13	8.66	16.1	48.4	56.0	18.6	33.3	1101	26.8	16.1	8.1	0.01	0.1	2.17	16.6	9.77	74.3	1.09	8.3	0.08	0.6	0.03	0.2	0.24	2.8270	50.9	22.0	1090	0.23
	SD	3.627	0.513	0.57	1.57	2.56	0.99	0.40	98.3	1.76	0.70	0.29	0.012	0.13	0.783	3.52	2.864	3.75	0.286	1.11	0.030	0.123	0.012	0.074	0.046	0.67945	5.02	0.97	106.4	0.057
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
17.5 mg/kg-d	**Mean**	15.12	8.79	15.5*	47.0	53.5	17.7	33.0	1032	25.8	16.4	8.3	0.01	0.1	1.82	12.3	11.89	78.1	1.29	8.7	0.09	0.6	0.04	0.3	0.26	2.9260	53.4	21.6	1032	0.16
	SD	4.612	0.471	0.46	1.53	1.55	0.50	0.41	122.9	1.67	0.97	0.24	0.016	0.13	0.594	3.32	3.944	4.86	0.413	2.58	0.030	0.152	0.019	0.082	0.042	0.56131	4.74	2.95	122.9	0.053
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
70 mg/kg-d	**Mean**	24.63*	8.02*	14.2*	42.5*	53.1*	17.7	33.4	627*	27.9	16.7	9.8*	0.02	0.1	3.68*	15.4	18.38*	74.1	2.46*	10.1	0.03*	0.1*	0.07*	0.3	0.28	3.5367	54.2	20.7	627	0.21
	SD	7.927	0.569	0.96	2.87	2.12	0.75	0.37	85.2	2.50	1.70	0.53	0.017	0.07	1.614	5.32	6.309	5.90	0.810	1.75	0.033	0.093	0.031	0.071	0.047	0.67396	5.06	0.93	85.2	0.090
	N	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9

* p<0.05 compared to controls

Table S-4
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Hematology Summary
Female Rats

Group	Animal ID	WBC (K/uL)	RBC (M/uL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT (K/uL)	RDW-SD (fL)	RDW-CV (%)	MPV (fL)	NRBC (K/uL)	NRBC (%)	NEUT (K/uL)	NEUT (%)	LYMPH (K/uL)	LYMPH (%)	MONO (K/uL)	MONO (%)	EO (K/uL)	EO (%)	BASO (K/uL)	BASO (%)	RET (K/uL)	RET (%)	IRF (%)	RET-He (pg)	PLT-F (K/uL)	NEU/LYM Ratio
Corn Oil Control	**Mean**	9.92	8.31	15.8	47.1	56.7	19.0	33.5	1169	23.8	13.0	8.1	0.00	0.0	1.26	12.5	7.72	78.0	0.84	8.5	0.08	0.8	0.02	0.2	0.22	2.7010	46.4	22.9	1169	0.16
	SD	2.077	0.495	0.71	2.12	1.27	0.46	0.46	216.7	1.71	0.74	0.43	0.000	0.00	0.508	3.53	1.624	4.66	0.228	1.36	0.030	0.256	0.007	0.092	0.027	0.43994	6.42	0.62	216.7	0.053
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
1.09 mg/kg-d	**Mean**	8.77	8.40	15.9	47.6	56.7	19.0	33.5	1231	23.5	12.9	8.1	0.01	0.1	0.96	10.6	6.99	80.2	0.72	8.1	0.07	0.9	0.03	0.3	0.23	2.7960	46.5	23.7	1231	0.14
	SD	3.616	0.374	0.50	1.48	1.04	0.40	0.40	170.0	1.40	0.83	0.30	0.010	0.13	0.526	3.63	2.927	5.77	0.330	2.25	0.031	0.242	0.022	0.179	0.046	0.59498	4.38	2.82	170.0	0.057
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
4.38 mg/kg-d	**Mean**	8.62	8.24	15.5	46.4	56.4	18.9	33.5	1147	23.9	13.1	8.2	0.01	0.1	0.96	11.4	6.89	79.2	0.69	8.4	0.07	0.9	0.02	0.2	0.22	2.6550	47.7	22.6	1147	0.15
	SD	1.899	0.302	0.50	1.27	1.43	0.45	0.38	134.6	1.25	0.53	0.33	0.022	0.28	0.235	2.90	1.891	5.09	0.163	2.62	0.024	0.303	0.011	0.125	0.046	0.61290	6.18	0.42	134.6	0.045
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
17.5 mg/kg-d	**Mean**	10.03	8.06	15.3	45.4	56.3	19.0	33.8	1144	24.7	13.4	8.5*	0.01	0.1	1.63	16.0	7.43	75.0	0.86	8.0	0.08	0.8	0.03	0.2	0.21	2.5933	45.1	22.8	1144	0.22
	SD	3.999	0.394	0.59	1.92	1.69	0.62	0.33	170.4	1.09	0.80	0.34	0.011	0.14	0.907	6.44	2.980	8.21	0.491	2.53	0.055	0.423	0.020	0.142	0.041	0.48990	7.25	0.77	170.4	0.104
	N	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
70 mg/kg-d	**Mean**	12.56	6.44*	12.3*	36.7*	57.0	19.1	33.6	760*	25.8*	12.3	9.6*	0.01	0.0	1.55	12.3	10.06	80.1	0.89	7.0	0.04	0.4*	0.03	0.2	0.21	3.2378	45.7	22.1	760	0.16
	SD	7.367	0.467	0.83	2.50	1.52	0.50	0.40	126.6	1.23	0.68	0.59	0.012	0.07	1.045	3.74	5.867	4.21	0.511	1.10	0.037	0.332	0.022	0.105	0.059	0.75903	7.17	0.72	126.6	0.057
	N	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9

* p<0.05 compared to controls

Appendix T

Subchronic Individual and Summary of Electrolytes and Prothrombin Time

Abbreviations:

mg/kg-d: milligrams per kilogram per day
(f): animal died on study
mmol/L: millimoles per liter
mg/dl: milligrams per deciliter
sec: second
Na: sodium
K: potassium
Cl: chloride
iCa: ionized calcium
iMg: ionized magnesium
Glu: glucose
Lac: lactate
AVG PT: average prothrombin time
SD: standard deviation

Table T-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Electrolytes and Prothrombin Time
Male Rats

Group	Animal ID	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	iCa (mmol/L)	iMg (mmol/L)	Glu (mg/dL)	Lac (mmol/L)	Avg. PT (sec)
	21-1281	152.7	6.94	102.8	1.62	0.89	219	5.3	9.9
Corn Oil	21-1282	153.3	6.28	102.3	1.53	0.71	200	3.5	10.1
Control	21-1295	154.1	6.85	104.1	1.54	0.74	247	6.3	10.2
	21-1296	154.7	6.76	104.8	1.60	0.84	230	5.7	10.2
	21-1297	152.1	7.79	104.6	1.56	0.73	260	4.9	10.5
	21-1298	157.4	6.55	104.7	1.61	0.90	245	4.8	9.2
	21-1299	154.7	7.84	103.2	1.51	0.78	98	3.5	10.8
	21-1300	154.9	8.26	104.4	1.61	0.89	255	7.9	9.5
	21-1309	156.5	7.18	106.0	1.63	0.91	236	6.3	9.4
	21-1310	156.4	7.58	103.2	1.61	0.86	226	5.8	9.6
	Mean	**154.7**	**7.20**	**104.0**	**1.58**	**0.83**	**222**	**5.4**	**9.9**
	SD	**1.72**	**0.639**	**1.12**	**0.043**	**0.078**	**46.9**	**1.33**	**0.50**
	21-1293	155.2	8.11	104.7	1.68	0.85	286	6.1	9.9
1.09 mg/kg-d	21-1294	154.1	7.06	105.2	1.63	0.85	256	4.6	8.2
	21-1315	158.8	7.52	103.9	1.55	0.76	157	5.1	10.4
	21-1316	153.2	8.43	104.6	1.63	0.86	244	5.8	10.5
	21-1317	152.3	9.13	104.9	1.74	1.09	402	9.3	10.2
	21-1318	157.9	6.87	104.4	1.60	0.82	149	5.3	10.5
	21-1321	154.0	7.28	103.3	1.61	0.84	232	5.7	9.2
	21-1322	153.3	7.10	104.1	1.60	0.79	181	5.4	9.6
	21-1323	154.2	7.55	103.8	1.62	0.85	252	6.8	9.7
	21-1324	155.4	7.78	102.3	1.71	0.99	304	7.5	9.6
	Mean	**154.8**	**7.68**	**104.1**	**1.64**	**0.87**	**246**	**6.2**	**9.8**
	SD	**2.07**	**0.702**	**0.85**	**0.057**	**0.098**	**75.4**	**1.39**	**0.72**
	21-1275	154.9	8.56	100.1	1.64	0.81	192	5.2	9.6
4.38 mg/kg-d	21-1276	155.3	7.00	101.9	1.65	0.77	205	4.7	10.3
	21-1277	152.2	9.39	102.2	1.66	0.97	306	8.7	9.9
	21-1278	155.9	7.66	101.8	1.61	0.84	202	4.6	10.6
	21-1279	152.0	7.78	105.0	1.49	0.82	228	5.5	10.2
	21-1280	152.8	8.28	104.6	1.58	0.88	204	7.8	10.3
	21-1291	154.7	6.57	104.4	1.57	0.82	133	3.6	10.1
	21-1292	156.8	7.18	103.7	1.62	0.82	225	6.0	9.9
	21-1313	153.1	5.48	102.0	1.62	0.67	178	4.1	9.1
	21-1314	152.8	7.82	104.5	1.62	0.82	245	7.7	9.8
	Mean	**154.1**	**7.57**	**103.0**	**1.61**	**0.82**	**212**	**5.8**	**9.9**
	SD	**1.68**	**1.093**	**1.63**	**0.049**	**0.076**	**45.2**	**1.73**	**0.42**
	21-1283	151.6	8.35	104.0	1.62	0.77	211	6.7	9.7
17.5 mg/kg-d	21-1284	153.3	7.25	102.4	1.61	0.74	177	4.9	10.9
	21-1289	152.8	7.38	105.0	1.62	0.87	228	5.0	10.3
	21-1290	151.7	8.27	105.9	1.72	0.88	274	7.0	10.0
	21-1301	154.2	6.51	103.6	1.56	0.76	112	3.6	9.8
	21-1302	154.4	5.80	103.8	1.60	0.74	180	3.8	10.2
	21-1305	151.0	8.00	104.4	1.64	0.84	200	6.4	10.1
	21-1306	154.8	7.38	103.9	1.60	0.83	236	6.1	10.4
	21-1311	151.2	9.01	105.2	1.60	0.94	277	6.6	9.3
	21-1312	153.1	9.23	104.5	1.64	0.93	266	6.8	10.0
	Mean	**152.8**	**7.72**	**104.3**	**1.62**	**0.83**	**216**	**5.7**	**10.0**
	SD	**1.39**	**1.071**	**0.97**	**0.042**	**0.075**	**51.7**	**1.27**	**0.42**
	21-1285	150.0	7.97	103.3	1.60	0.90	161	4.7	10.0
70 mg/kg-d	21-1286	150.6	6.73	104.5	1.61	0.82	141	2.9	10.1
	21-1287	146.5	8.42	102.9	1.59	0.87	164	3.9	10.7
	21-1288	152.5	7.66	103.0	1.61	0.99	196	4.9	9.6
	21-1303	150.0	7.71	106.2	1.56	0.88	132	2.7	6.8
	21-1304	153.2	7.59	103.9	1.62	0.84	213	5.1	6.9
	21-1307	150.0	6.66	103.2	1.46	0.83	96	3.4	11.1
	21-1308	149.5	8.64	105.3	1.57	0.92	154	4.7	10.2
	21-1319	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1320	153.0	8.29	102.9	1.62	0.86	164	4.3	9.6
	Mean	**150.6**	**7.74**	**103.9**	**1.58**	**0.88**	**158**	**4.1**	**9.4**
	SD	**2.10**	**0.693**	**1.19**	**0.050**	**0.053**	**34.2**	**0.89**	**1.55**

Table T-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Electrolytes and Prothrombin Time
Female Rats

Group	Animal ID	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	iCa (mmol/L)	iMg (mmol/L)	Glu (mg/dL)	Lac (mmol/L)	Avg. PT (sec)
	21-1325	149.9	9.50	103.4	1.67	1.02	200	8.3	9.6
Corn Oil	21-1326	152.6	9.98	104.0	1.66	1.01	185	6.8	8.9
Control	21-1331	148.5	10.71	104.5	1.58	0.99	180	5.0	9.1
	21-1332	154.1	8.45	101.5	1.77	1.11	309	9.9	9.7
	21-1345	148.0	7.27	103.7	1.56	0.89	191	5.5	9.1
	21-1346	151.1	6.39	104.4	1.55	0.86	153	3.8	8.9
	21-1347	153.0	8.33	103.9	1.63	0.91	188	4.0	8.7
	21-1348	150.7	7.71	104.3	1.64	0.98	238	6.4	8.7
	21-1363	148.7	8.00	103.6	1.68	0.99	254	7.6	8.5
	21-1364	154.6	7.38	104.1	1.65	0.93	227	4.4	8.6
	Mean	**151.1**	**8.37**	**103.7**	**1.64**	**0.97**	**213**	**6.2**	**9.0**
	SD	**2.38**	**1.335**	**0.86**	**0.065**	**0.073**	**45.3**	**2.01**	**0.40**
	21-1333	154.6	6.75	103.6	1.63	0.82	187	4.1	9.7
1.09 mg/kg-d	21-1334	152.8	6.84	103.5	1.59	0.83	149	4.7	9.9
	21-1335	149.7	10.18	102.7	1.73	1.03	259	7.2	8.8
	21-1336	153.6	6.26	104.7	1.60	0.88	127	3.9	9.3
	21-1341	147.8	9.44	105.0	1.67	0.95	258	6.3	9.3
	21-1342	149.8	8.02	104.5	1.54	0.83	218	4.4	9.3
	21-1371	152.3	7.66	101.1	1.64	0.89	163	4.2	9.1
	21-1372	147.5	7.04	103.8	1.59	1.02	176	5.5	8.5
	21-1373	153.8	8.54	104.3	1.71	1.15	314	10.4	10.0
	21-1374	151.6	8.30	103.7	1.70	1.09	266	9.1	9.6
	Mean	**151.4**	**7.90**	**103.7**	**1.64**	**0.95**	**212**	**6.0**	**9.3**
	SD	**2.52**	**1.251**	**1.13**	**0.062**	**0.118**	**60.7**	**2.27**	**0.47**
	21-1339	150.4	5.67	104.5	1.59	0.79	170	3.8	9.1
4.38 mg/kg-d	21-1340	148.2	8.45	104.5	1.64	0.87	221	5.2	9.2
	21-1351	150.7	8.71	104.3	1.61	0.86	170	3.5	9.0
	21-1352	147.9	8.48	103.4	1.57	0.92	208	4.7	9.6
	21-1355	149.7	6.98	102.8	1.65	0.88	215	7.5	9.9
	21-1356	153.1	8.47	105.6	1.66	0.92	219	6.2	9.2
	21-1357	153.9	6.53	103.2	1.71	0.93	265	5.8	9.3
	21-1358	153.4	6.51	103.9	1.64	0.93	199	7.4	9.1
	21-1359	148.4	7.38	102.9	1.60	0.92	180	4.7	8.7
	21-1360	152.5	6.73	103.8	1.56	0.95	164	4.5	8.7
	Mean	**150.8**	**7.39**	**103.9**	**1.62**	**0.90**	**201**	**5.3**	**9.2**
	SD	**2.28**	**1.070**	**0.86**	**0.046**	**0.048**	**31.3**	**1.38**	**0.37**
	21-1327	150.3	8.11	103.6	1.71	1.02	278	8.1	9.4
17.5 mg/kg-d	21-1328	149.2	7.97	105.4	1.63	0.89	193	3.8	9.4
	21-1329	149.6	7.73	105.2	1.59	0.85	166	5.0	9.3
	21-1330	148.6	10.01	104.5	1.61	0.84	196	5.6	9.8
	21-1343	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1344	150.1	9.93	103.5	1.72	0.94	248	7.6	8.9
	21-1353	152.5	6.84	104.7	1.63	0.90	176	5.3	9.0
	21-1354	145.6	7.23	106.2	1.61	0.91	158	6.0	9.7
	21-1367	154.2	6.11	103.4	1.66	0.89	188	4.4	9.1
	21-1368	151.0	6.96	105.1	1.61	0.91	174	7.3	8.8
	Mean	**150.1**	**7.88**	**104.6**	**1.64**	**0.91**	**197**	**5.9**	**9.3**
	SD	**2.42**	**1.337**	**0.97**	**0.046**	**0.053**	**39.9**	**1.48**	**0.35**
	21-1337	145.0	9.03	105.8	1.56	0.91	136	4.2	9.2
70 mg/kg-d	21-1338	148.2	8.41	104.6	1.57	0.84	140	3.6	9.6
	21-1349	153.1	4.75	105.1	1.53	0.96	97	3.0	9.4
	21-1350	144.3	6.89	104.9	1.54	0.92	106	3.8	11.0
	21-1361	155.4	6.56	105.6	1.56	0.85	146	3.9	9.3
	21-1362	146.4	6.83	103.7	1.52	0.88	143	3.0	9.6
	21-1365	147.0	8.39	103.5	1.65	1.02	185	5.4	8.9
	21-1366	149.6	8.37	105.7	1.62	1.05	196	4.7	9.2
	21-1369	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1370	151.3	4.99	102.3	1.58	0.84	108	2.1	9.1
	Mean	**148.9**	**7.14**	**104.6**	**1.57**	**0.92**	**140**	**3.7**	**9.5**
	SD	**3.76**	**1.545**	**1.19**	**0.042**	**0.077**	**34.0**	**0.98**	**0.62**

Table T-3
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Electrolytes and Prothrombin Time Summary
Male Rats

Group	Animal ID	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	iCa (mmol/L)	iMg (mmol/L)	Glu (mg/dL)	Lac (mmol/L)	Avg. PT (sec)
Corn Oil Control	**Mean**	154.7	7.20	104.0	1.58	0.83	222	5.4	9.9
	SD	1.72	0.639	1.12	0.043	0.078	46.9	1.33	0.50
	N	10	10	10	10	10	10	10	10
1.09 mg/kg-d	**Mean**	154.8	7.68	104.1	1.64	0.87	246	6.2	9.8
	SD	2.07	0.702	0.85	0.057	0.098	75.4	1.39	0.72
	N	10	10	10	10	10	10	10	10
4.38 mg/kg-d	**Mean**	154.1	7.57	103.0	1.61	0.82	212	5.8	9.9
	SD	1.68	1.093	1.63	0.049	0.076	45.2	1.73	0.42
	N	10	10	10	10	10	10	10	10
17.5 mg/kg-d	**Mean**	152.8	7.72	104.3	1.62	0.83	216	5.7	10.0
	SD	1.39	1.071	0.97	0.042	0.075	51.7	1.27	0.42
	N	10	10	10	10	10	10	10	10
70 mg/kg-d	**Mean**	150.6*	7.74	103.9	1.58	0.88	158*	4.1	9.4
	SD	2.10	0.693	1.19	0.050	0.053	34.2	0.89	1.55
	N	9	9	9	9	9	9	9	9

* $p<0.05$ compared to controls

Table T-4
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Electrolytes and Prothrombin Time Summary
Female Rats

Group	Animal ID	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	iCa (mmol/L)	iMg (mmol/L)	Glu (mg/dL)	Lac (mmol/L)	Avg. PT (sec)
Corn Oil Control	**Mean**	151.1	8.37	103.7	1.64	0.97	213	6.2	9.0
	SD	2.38	1.335	0.86	0.065	0.073	45.3	2.01	0.40
	N	10	10	10	10	10	10	10	10
1.09 mg/kg-d	**Mean**	151.4	7.90	103.7	1.64	0.95	212	6.0	9.3
	SD	2.52	1.251	1.13	0.062	0.118	60.7	2.27	0.47
	N	10	10	10	10	10	10	10	10
4.38 mg/kg-d	**Mean**	150.8	7.39	103.9	1.62	0.90	201	5.3	9.2
	SD	2.28	1.070	0.86	0.046	0.048	31.3	1.38	0.37
	N	10	10	10	10	10	10	10	10
17.5 mg/kg-d	**Mean**	150.1	7.88	104.6	1.64	0.91	197	5.9	9.3
	SD	2.42	1.337	0.97	0.046	0.053	39.9	1.48	0.35
	N	9	9	9	9	9	9	9	9
70 mg/kg-d	**Mean**	148.9	7.14	104.6	1.57*	0.92	140*	3.7*	9.5
	SD	3.76	1.545	1.19	0.042	0.077	34.0	0.98	0.62
	N	9	9	9	9	9	9	9	9

* $p<0.05$ compared to controls

Appendix U

Subchronic Individual and Summary of Organ Mass and Mass Ratios

Abbreviations:

mg/kg-d: milligrams per kilogram per day
(f): animal died on study
ND: no data
N/A: not applicable
SD: standard deviation

Table U-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Organ Mass
Male Rats

Group	Animal ID	Body Weight[1]	Body Weight[2]	Brain	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Testes	Epididymides	Prostate	Seminal Vesicles	Thyroid	Pituitary
	21-1281	613	595	2.206	0.08720	3.629	0.823	1.781	0.514	19.567	3.209	1.529	1.896	1.873	0.029	0.010
Corn Oil	21-1282	520	503	2.400	0.07280	3.134	0.790	1.787	0.365	14.894	3.609	1.404	1.836	1.174	0.021	0.011
Control	21-1295	653	643	2.212	0.06443	3.322	0.785	1.920	0.614	20.684	3.900	1.343	2.628	1.828	0.041	0.016
	21-1296	626	609	2.062	0.08001	3.690	0.781	1.970	0.431	20.713	3.483	1.330	2.099	1.496	0.023	0.027
	21-1297	628	617	2.204	0.07134	3.952	0.943	1.687	0.459	19.004	3.405	1.396	1.657	2.519	0.020	0.017
	21-1298	553	537	2.186	3.262*	3.274	0.784	1.980	0.448	16.603	3.512	1.304	2.328	1.164	0.038	0.014
	21-1299	453	438	2.230	0.06153	2.972	0.698	1.524	0.300	13.159	3.919	1.304	2.271	1.770	0.033	0.016
	21-1300	656	633	2.241	0.08287	4.053	0.863	1.872	0.412	21.040	3.538	1.626	2.933	1.650	0.014	0.017
	21-1309	725	710	2.372	0.09155	3.775	1.003	2.176	0.468	21.655	3.883	1.741	2.753	1.764	0.035	0.016
	21-1310	575	558	2.175	0.06556	3.559	0.673	1.909	0.471	17.510	3.714	1.463	2.373	1.733	0.035	0.016
	Mean	**600.2**	**584.3**	**2.229**	**0.07525**	**3.536**	**0.814**	**1.861**	**0.448**	**18.483**	**3.617**	**1.444**	**2.277**	**1.697**	**0.029**	**0.016**
	SD	**77.49**	**77.71**	**0.0966**	**0.010664**	**0.3535**	**0.1009**	**0.1785**	**0.0839**	**2.8591**	**0.2353**	**0.1473**	**0.4147**	**0.3852**	**0.0089**	**0.0046**
	21-1293	540	529	2.189	0.06867	2.914	0.657	1.510	0.418	17.059	3.307	1.429	2.128	1.887	N/A	N/A
1.09 mg/kg-d	21-1294	572	558	2.210	0.08196	3.388	0.843	1.960	0.480	16.821	3.870	1.602	2.210	1.275	N/A	N/A
	21-1315	572	559	2.315	0.05672	3.426	0.360	1.890	0.828	15.710	3.527	1.362	1.870	1.830	N/A	N/A
	21-1316	603	584	2.166	0.08431	3.538	0.861	1.951	0.426	17.432	3.561	1.401	1.549	1.667	N/A	N/A
	21-1317	497	485	2.149	0.07613	3.403	0.698	1.764	0.520	13.905	3.328	1.431	1.602	1.690	N/A	N/A
	21-1318	496	483	2.314	0.06533	2.937	0.783	1.561	0.387	14.960	3.101	1.277	1.523	1.957	N/A	N/A
	21-1321	643	627	2.334	0.07876	3.904	0.898	1.871	0.289	18.470	3.474	1.340	2.460	1.555	N/A	N/A
	21-1322	655	630	2.399	0.07364	3.986	1.002	2.084	0.378	19.618	3.671	1.541	2.829	1.395	N/A	N/A
	21-1323	680	664	2.177	0.07280	3.816	1.122	2.352	0.690	20.204	3.804	1.521	3.122	1.413	N/A	N/A
	21-1324	645	630	2.200	0.08057	4.075	0.730	1.897	0.47	20.402	3.484	1.453	2.116	1.479	N/A	N/A
	Mean	**590.3**	**574.9**	**2.245**	**0.07389**	**3.539**	**0.795**	**1.884**	**0.489**	**17.458**	**3.513**	**1.436**	**2.141**	**1.615**		
	SD	**65.79**	**63.23**	**0.0868**	**0.008457**	**0.4088**	**0.2079**	**0.2423**	**0.1593**	**2.2207**	**0.2329**	**0.0985**	**0.5415**	**0.2291**		
	21-1275	562	549	2.128	0.06853	3.637	0.743	1.792	0.355	17.259	3.446	1.296	1.817	1.913	N/A	N/A
4.38 mg/kg-d	21-1276	534	520	2.286	0.06558	2.917	0.806	1.735	0.355	15.898	3.226	1.511	2.359	1.604	N/A	N/A
	21-1277	475	466	2.064	0.06849	3.152	0.600	1.557	0.318	14.949	3.620	1.341	1.447	1.388	N/A	N/A
	21-1278	460	448	2.253	0.06119	2.657	0.600	1.419	0.324	12.759	3.182	1.322	1.718	1.617	N/A	N/A
	21-1279	599	577	2.406	0.07030	3.236	0.758	1.742	0.340	17.740	3.497	1.405	2.329	1.151	N/A	N/A
	21-1280	590	569	2.281	0.07707	3.207	0.796	1.747	0.384	17.687	3.018	1.291	2.244	1.914	N/A	N/A
	21-1291	561	539	2.344	0.07704	3.025	0.871	1.978	0.43	16.404	3.613	1.465	2.095	1.346	N/A	N/A
	21-1292	631	615	2.237	0.07405	3.694	0.728	1.940	0.258	19.492	3.146	1.168	2.547	1.690	N/A	N/A
	21-1313	684	668	2.302	0.06108	3.704	0.987	2.217	0.529	20.429	3.464	1.370	1.782	2.288	N/A	N/A
	21-1314	606	586	2.315	0.07213	3.298	0.765	1.751	0.340	18.110	3.632	1.583	2.406	1.222	N/A	N/A
	Mean	**570.2**	**553.7**	**2.262**	**0.06955**	**3.253**	**0.765**	**1.788**	**0.363**	**17.073**	**3.384**	**1.375**	**2.074**	**1.613**		
	SD	**68.17**	**65.73**	**0.1004**	**0.005770**	**0.3464**	**0.1152**	**0.2213**	**0.0732**	**2.2110**	**0.2234**	**0.1206**	**0.3622**	**0.3544**		
	21-1283	617	598	2.168	0.06841	3.817	0.972	1.844	0.622	19.194	3.696	1.428	2.545	1.245	0.073	N/A
17.5 mg/kg-d	21-1284	660	642	2.322	0.05877	3.923	1.106	1.999	0.598	21.788	3.420	1.510	2.378	2.337	0.062	N/A
	21-1289	507	493	2.246	0.06640	2.940	0.829	1.698	0.512	14.541	2.903	1.169	1.625	1.190	0.035	N/A
	21-1290	728	714	2.342	0.07467	4.153	1.096	2.325	0.609	22.421	3.723	1.512	1.949	1.270	0.037	N/A
	21-1301	488	473	2.162	0.06704	3.138	0.864	1.825	0.427	14.734	3.093	1.211	1.865	2.486	0.023	N/A
	21-1302	476	464	2.202	0.06428	2.756	0.754	1.607	0.286	13.009	3.250	1.243	1.819	1.287	0.018	N/A
	21-1305	595	579	2.250	0.09593	3.709	0.836	2.093	0.425	16.418	3.793	1.528	1.833	2.550	0.017	N/A
	21-1306	651	625	2.206	0.05811	3.451	1.003	2.218	0.500	20.102	3.579	1.421	2.055	2.053	0.029	N/A
	21-1311	447	431	2.083	0.06543	2.888	0.799	1.791	0.296	13.087	3.803	1.493	1.689	1.257	0.029	N/A
	21-1312	537	521	2.214	0.06969	3.534	0.887	1.796	0.238	15.785	3.440	1.390	1.362	2.469	0.026	N/A
	Mean	**570.6**	**554.0**	**2.220**	**0.06887**	**3.431**	**0.915**	**1.920**	**0.451**	**17.108**	**3.470**	**1.391**	**1.912**	**1.814**	**0.035**	
	SD	**93.22**	**91.62**	**0.0762**	**0.010682**	**0.4805**	**0.1232**	**0.2317**	**0.1413**	**3.5098**	**0.3087**	**0.1349**	**0.3482**	**0.6101**	**0.0184**	
	21-1285	415	391	2.259	0.608*	2.731	1.330	1.444	0.333	12.888	1.778	0.707	1.370	1.002	0.048	0.015
70 mg/kg-d	21-1286	428	409	2.494	0.07000	2.831	0.924	1.359	0.372	12.354	1.324	0.805	1.738	1.145	0.065	0.012
	21-1287	442	426	2.220	0.06544	2.861	1.125	1.526	0.308	14.332	1.515	0.802	2.093	1.241	0.062	0.014
	21-1288	531	506	2.318	0.06755	3.651	0.945	1.800	0.333	16.384	4.090	0.954	2.494	1.411	0.065	0.012
	21-1303	470	437	2.317	0.06214	2.784	1.204	1.755	0.307	13.825	1.635	0.935	1.612	1.735	0.051	0.015
	21-1304	526	498	2.192	0.06817	3.344	1.522	1.866	0.324	19.358	3.387	1.152	2.161	1.256	0.073	0.010
	21-1307	402	386	2.319	0.07018	2.693	0.979	1.387	0.178	10.615	1.147	0.794	1.819	1.354	0.055	0.013
	21-1308	407	387	2.310	0.06483	3.026	1.072	1.575	0.327	12.464	2.665	1.019	1.795	2.588	0.061	0.011
	21-1319	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1320	482	458	2.435	0.06849	3.641	1.217	1.786	0.236	15.234	2.920	1.112	1.404	2.116	0.077	0.010
	Mean	**455.9**	**433.1**	**2.318**	**0.06710**	**3.062**	**1.146**	**1.611**	**0.302**	**14.162**	**2.273**	**0.920**	**1.832**	**1.539**	**0.062**	**0.012**
	SD	**49.21**	**45.97**	**0.0960**	**0.002769**	**0.3840**	**0.1959**	**0.1944**	**0.0589**	**2.5880**	**1.0314**	**0.1542**	**0.3657**	**0.5166**	**0.0096**	**0.0019**

[1] Non-fasted Day 90 Body Weight
[2] Fasted Day 91 Body Weight
* Outlier

Table U-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Organ to Body Mass Ratios
Male Rats

Group	Animal ID	Brain	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Testes	Epididymides	Prostate	Seminal Vesicles	Thyroid	Pituitary
	21-1281	0.0036	0.00014	0.0059	0.0013	0.0029	0.0008	0.0319	0.0052	0.0025	0.0031	0.0031	0.00005	0.00002
Corn Oil	21-1282	0.0046	0.00014	0.0060	0.0015	0.0034	0.0007	0.0286	0.0069	0.0027	0.0035	0.0023	0.00004	0.00002
Control	21-1295	0.0034	0.00010	0.0051	0.0012	0.0029	0.0009	0.0317	0.0060	0.0021	0.0040	0.0028	0.00006	0.00002
	21-1296	0.0033	0.00013	0.0059	0.0012	0.0031	0.0007	0.0331	0.0056	0.0021	0.0034	0.0024	0.00004	0.00004
	21-1297	0.0035	0.00011	0.0063	0.0015	0.0027	0.0007	0.0303	0.0054	0.0022	0.0026	0.0040	0.00003	0.00003
	21-1298	0.0040	ND	0.0059	0.0014	0.0036	0.0008	0.0300	0.0064	0.0024	0.0042	0.0021	0.00007	0.00003
	21-1299	0.0049	0.00014	0.0066	0.0015	0.0034	0.0007	0.0290	0.0087	0.0029	0.0050	0.0039	0.00007	0.00004
	21-1300	0.0034	0.00013	0.0062	0.0013	0.0029	0.0006	0.0321	0.0054	0.0025	0.0045	0.0025	0.00002	0.00003
	21-1309	0.0033	0.00013	0.0052	0.0014	0.0030	0.0006	0.0299	0.0054	0.0024	0.0038	0.0024	0.00005	0.00002
	21-1310	0.0038	0.00011	0.0062	0.0012	0.0033	0.0008	0.0305	0.0065	0.0025	0.0041	0.0030	0.00006	0.00003
	Mean	**0.0038**	**0.00012**	**0.0059**	**0.0014**	**0.0031**	**0.0007**	**0.0307**	**0.0061**	**0.0024**	**0.0038**	**0.0028**	**0.00005**	**0.00003**
	SD	**0.00057**	**0.000014**	**0.00046**	**0.00013**	**0.00029**	**0.00010**	**0.00143**	**0.00105**	**0.00025**	**0.00070**	**0.00066**	**0.000017**	**0.000008**
	21-1293	0.0041	0.00013	0.0054	0.0012	0.0028	0.0008	0.0316	0.0061	0.0026	0.0039	0.0035	N/A	N/A
1.09 mg/kg-d	21-1294	0.0039	0.00014	0.0059	0.0015	0.0034	0.0008	0.0294	0.0068	0.0028	0.0039	0.0022	N/A	N/A
	21-1315	0.0040	0.00010	0.0060	0.0006	0.0033	0.0014	0.0275	0.0062	0.0024	0.0033	0.0032	N/A	N/A
	21-1316	0.0036	0.00014	0.0059	0.0014	0.0032	0.0007	0.0289	0.0059	0.0023	0.0026	0.0028	N/A	N/A
	21-1317	0.0043	0.00015	0.0068	0.0014	0.0035	0.0010	0.0280	0.0067	0.0029	0.0032	0.0034	N/A	N/A
	21-1318	0.0047	0.00013	0.0059	0.0016	0.0031	0.0008	0.0302	0.0063	0.0026	0.0031	0.0039	N/A	N/A
	21-1321	0.0036	0.00012	0.0061	0.0014	0.0029	0.0004	0.0287	0.0054	0.0021	0.0038	0.0024	N/A	N/A
	21-1322	0.0037	0.00011	0.0061	0.0015	0.0032	0.0006	0.0300	0.0056	0.0024	0.0043	0.0021	N/A	N/A
	21-1323	0.0032	0.00011	0.0056	0.0017	0.0035	0.0010	0.0297	0.0056	0.0022	0.0046	0.0021	N/A	N/A
	21-1324	0.0034	0.00012	0.0063	0.0011	0.0029	0.0007	0.0316	0.0054	0.0023	0.0033	0.0023	N/A	N/A
	Mean	**0.0038**	**0.00013**	**0.0060**	**0.0013**	**0.0032**	**0.0008**	**0.0296**	**0.0060**	**0.0025**	**0.0036**	**0.0028**		
	SD	**0.00044**	**0.000017**	**0.00039**	**0.00030**	**0.00025**	**0.00028**	**0.00137**	**0.00050**	**0.00026**	**0.00062**	**0.00067**		
	21-1275	0.0038	0.00012	0.0065	0.0013	0.0032	0.0006	0.0307	0.0061	0.0023	0.0032	0.0034	N/A	N/A
4.38 mg/kg-d	21-1276	0.0043	0.00012	0.0055	0.0015	0.0032	0.0007	0.0298	0.0060	0.0028	0.0044	0.0030	N/A	N/A
	21-1277	0.0043	0.00014	0.0066	0.0013	0.0033	0.0007	0.0315	0.0076	0.0028	0.0030	0.0029	N/A	N/A
	21-1278	0.0049	0.00013	0.0058	0.0013	0.0031	0.0007	0.0277	0.0069	0.0029	0.0037	0.0035	N/A	N/A
	21-1279	0.0040	0.00012	0.0054	0.0013	0.0029	0.0006	0.0296	0.0058	0.0023	0.0039	0.0019	N/A	N/A
	21-1280	0.0039	0.00013	0.0054	0.0013	0.0030	0.0007	0.0300	0.0051	0.0022	0.0038	0.0032	N/A	N/A
	21-1291	0.0042	0.00014	0.0054	0.0016	0.0035	0.0008	0.0292	0.0064	0.0026	0.0037	0.0024	N/A	N/A
	21-1292	0.0035	0.00012	0.0059	0.0012	0.0031	0.0004	0.0309	0.0050	0.0019	0.0040	0.0027	N/A	N/A
	21-1313	0.0034	0.00009	0.0054	0.0014	0.0032	0.0008	0.0299	0.0051	0.0020	0.0026	0.0033	N/A	N/A
	21-1314	0.0038	0.00012	0.0054	0.0013	0.0029	0.0006	0.0299	0.0060	0.0026	0.0040	0.0020	N/A	N/A
	Mean	**0.0040**	**0.00012**	**0.0057**	**0.0013**	**0.0031**	**0.0006**	**0.0299**	**0.0060**	**0.0024**	**0.0036**	**0.0028**		
	SD	**0.00044**	**0.000015**	**0.00047**	**0.00012**	**0.00020**	**0.00011**	**0.00102**	**0.00084**	**0.00036**	**0.00053**	**0.00057**		
	21-1283	0.0035	0.00011	0.0062	0.0016	0.0030	0.0010	0.0311	0.0060	0.0023	0.0041	0.0020	0.00012	N/A
17.5 mg/kg-d	21-1284	0.0035	0.00009	0.0059	0.0017	0.0030	0.0009	0.0330	0.0052	0.0023	0.0036	0.0035	0.00009	N/A
	21-1289	0.0044	0.00013	0.0058	0.0016	0.0033	0.0010	0.0287	0.0057	0.0023	0.0032	0.0023	0.00007	N/A
	21-1290	0.0032	0.00010	0.0057	0.0015	0.0032	0.0008	0.0308	0.0051	0.0021	0.0027	0.0017	0.00005	N/A
	21-1301	0.0044	0.00014	0.0064	0.0018	0.0037	0.0009	0.0302	0.0063	0.0025	0.0038	0.0051	0.00005	N/A
	21-1302	0.0046	0.00014	0.0058	0.0016	0.0034	0.0006	0.0273	0.0068	0.0026	0.0038	0.0027	0.00004	N/A
	21-1305	0.0038	0.00016	0.0062	0.0014	0.0035	0.0007	0.0276	0.0064	0.0026	0.0031	0.0043	0.00003	N/A
	21-1306	0.0034	0.00009	0.0053	0.0015	0.0034	0.0008	0.0309	0.0055	0.0022	0.0032	0.0032	0.00004	N/A
	21-1311	0.0047	0.00015	0.0065	0.0018	0.0040	0.0007	0.0293	0.0085	0.0033	0.0038	0.0028	0.00006	N/A
	21-1312	0.0041	0.00013	0.0066	0.0017	0.0033	0.0004	0.0294	0.0064	0.0026	0.0025	0.0046	0.00005	N/A
	Mean	**0.0040**	**0.00012**	**0.0060**	**0.0016**	**0.0034**	**0.0008**	**0.0298**	**0.0062**	**0.0025**	**0.0034**	**0.0032**	**0.00006**	
	SD	**0.00055**	**0.000024**	**0.00040**	**0.00012**	**0.00031**	**0.00018**	**0.00173**	**0.00099**	**0.00035**	**0.00053**	**0.00113**	**0.000027**	
	21-1285	0.0054	ND	0.0066	0.0032	0.0035	0.0008	0.0311	0.0043	0.0017	0.0033	0.0024	0.00012	0.00004
70 mg/kg-d	21-1286	0.0058	0.00016	0.0066	0.0022	0.0032	0.0009	0.0289	0.0031	0.0019	0.0041	0.0027	0.00015	0.00003
	21-1287	0.0050	0.00015	0.0065	0.0025	0.0035	0.0007	0.0324	0.0034	0.0018	0.0047	0.0028	0.00014	0.00003
	21-1288	0.0044	0.00013	0.0069	0.0018	0.0034	0.0006	0.0309	0.0077	0.0018	0.0047	0.0027	0.00012	0.00002
	21-1303	0.0049	0.00013	0.0059	0.0026	0.0037	0.0007	0.0294	0.0035	0.0020	0.0034	0.0037	0.00011	0.00003
	21-1304	0.0042	0.00013	0.0064	0.0029	0.0035	0.0006	0.0368	0.0064	0.0022	0.0041	0.0024	0.00014	0.00002
	21-1307	0.0058	0.00017	0.0067	0.0024	0.0035	0.0004	0.0264	0.0029	0.0020	0.0045	0.0034	0.00014	0.00003
	21-1308	0.0057	0.00016	0.0074	0.0026	0.0039	0.0008	0.0306	0.0065	0.0025	0.0044	0.0064	0.00015	0.00003
	21-1319	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1320	0.0051	0.00014	0.0076	0.0025	0.0037	0.0005	0.0316	0.0061	0.0023	0.0029	0.0044	0.00016	0.00002
	Mean	**0.0051**	**0.00015**	**0.0067**	**0.0025**	**0.0035**	**0.0007**	**0.0309**	**0.0049**	**0.0020**	**0.0040**	**0.0034**	**0.00014**	**0.00003**
	SD	**0.00060**	**0.000017**	**0.00051**	**0.00040**	**0.00021**	**0.00014**	**0.00284**	**0.00181**	**0.00026**	**0.00066**	**0.00129**	**0.000017**	**0.000006**

* Outlier

Table U-3
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Organ to Brain Mass Ratios
Male Rats

Group	Animal ID	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Testes	Epididymides	Prostate	Seminal Vesicles	Thyroid	Pituitary
	21-1281	0.03953	1.6451	0.3731	0.8073	0.2330	8.8699	1.4547	0.6931	0.8595	0.8490	0.0131	0.0045
Corn Oil	21-1282	0.03033	1.3058	0.3292	0.7446	0.1521	6.2058	1.5038	0.5850	0.7650	0.4892	0.0088	0.0046
Control	21-1295	0.02913	1.5018	0.3549	0.8680	0.2776	9.3508	1.7631	0.6071	1.1881	0.8264	0.0185	0.0072
	21-1296	0.03880	1.7895	0.3788	0.9554	0.2090	10.0451	1.6891	0.6450	1.0179	0.7255	0.0112	0.0131
	21-1297	0.03237	1.7931	0.4279	0.7654	0.2083	8.6225	1.5449	0.6334	0.7518	1.1429	0.0091	0.0077
	21-1298	ND	1.4977	0.3586	0.9058	0.2049	7.5952	1.6066	0.5965	1.0650	0.5325	0.0174	0.0064
	21-1299	0.02759	1.3327	0.3130	0.6834	0.1345	5.9009	1.7574	0.5848	1.0184	0.7937	0.0148	0.0072
	21-1300	0.03698	1.8086	0.3851	0.8353	0.1838	9.3887	1.5788	0.7256	1.3088	0.7363	0.0062	0.0076
	21-1309	0.03860	1.5915	0.4228	0.9174	0.1973	9.1294	1.6370	0.7340	1.1606	0.7437	0.0148	0.0067
	21-1310	0.03014	1.6363	0.3094	0.8777	0.2166	8.0506	1.7076	0.6726	1.0910	0.7968	0.0161	0.0074
	Mean	**0.03372**	**1.5902**	**0.3653**	**0.8360**	**0.2017**	**8.3159**	**1.6243**	**0.6477**	**1.0226**	**0.7636**	**0.0130**	**0.0072**
	SD	**0.004726**	**0.18173**	**0.04106**	**0.08560**	**0.03997**	**1.38039**	**0.10556**	**0.05633**	**0.18292**	**0.17903**	**0.00406**	**0.00236**
	21-1293	0.03137	1.3312	0.3001	0.6898	0.1910	7.7931	1.5107	0.6528	0.9721	0.8620	N/A	N/A
1.09 mg/kg-d	21-1294	0.03709	1.5330	0.3814	0.8869	0.2172	7.6113	1.7511	0.7249	1.0000	0.5769	N/A	N/A
	21-1315	0.02450	1.4799	0.1555	0.8164	0.3577	6.7862	1.5235	0.5883	0.8078	0.7905	N/A	N/A
	21-1316	0.03892	1.6334	0.3975	0.9007	0.1967	8.0480	1.6440	0.6468	0.7151	0.7696	N/A	N/A
	21-1317	0.03543	1.5835	0.3248	0.8208	0.2420	6.4705	1.5486	0.6659	0.7455	0.7864	N/A	N/A
	21-1318	0.02823	1.2692	0.3384	0.6746	0.1672	6.4650	1.3401	0.5519	0.6582	0.8457	N/A	N/A
	21-1321	0.03374	1.6727	0.3847	0.8016	0.1238	7.9135	1.4884	0.5741	1.0540	0.6662	N/A	N/A
	21-1322	0.03070	1.6615	0.4177	0.8687	0.1576	8.1776	1.5302	0.6424	1.1792	0.5815	N/A	N/A
	21-1323	0.03344	1.7529	0.5154	1.0804	0.3169	9.2807	1.7474	0.6987	1.4341	0.6491	N/A	N/A
	21-1324	0.03662	1.8523	0.3318	0.8623	0.2136	9.2736	1.5836	0.6605	0.9618	0.6723	N/A	N/A
	Mean	**0.03300**	**1.5770**	**0.3547**	**0.8402**	**0.2184**	**7.7819**	**1.5668**	**0.6406**	**0.9528**	**0.7200**		
	SD	**0.004403**	**0.18035**	**0.09284**	**0.11417**	**0.07163**	**1.01056**	**0.12340**	**0.05449**	**0.23644**	**0.10418**		
	21-1275	0.03220	1.7091	0.3492	0.8421	0.1668	8.1104	1.6194	0.6090	0.8539	0.8990	N/A	N/A
4.38 mg/kg-d	21-1276	0.02869	1.2760	0.3526	0.7590	0.1553	6.9545	1.4112	0.6610	1.0319	0.7017	N/A	N/A
	21-1277	0.03318	1.5271	0.2907	0.7544	0.1541	7.2427	1.7539	0.6497	0.7011	0.6725	N/A	N/A
	21-1278	0.02716	1.1793	0.2663	0.6298	0.1438	5.6631	1.4123	0.5868	0.7625	0.7177	N/A	N/A
	21-1279	0.02922	1.3450	0.3150	0.7240	0.1413	7.3732	1.4534	0.5840	0.9680	0.4784	N/A	N/A
	21-1280	0.03379	1.4060	0.3490	0.7659	0.1683	7.7541	1.3231	0.5660	0.9838	0.8391	N/A	N/A
	21-1291	0.03287	1.2905	0.3716	0.8439	0.1834	6.9983	1.5414	0.6250	0.8938	0.5742	N/A	N/A
	21-1292	0.03310	1.6513	0.3254	0.8672	0.1153	8.7135	1.4063	0.5221	1.1386	0.7555	N/A	N/A
	21-1313	0.02653	1.6090	0.4288	0.9631	0.2298	8.8745	1.5048	0.5951	0.7741	0.9939	N/A	N/A
	21-1314	0.03116	1.4246	0.3305	0.7564	0.1469	7.8229	1.5689	0.6838	1.0393	0.5279	N/A	N/A
	Mean	**0.03079**	**1.4418**	**0.3379**	**0.7906**	**0.1605**	**7.5507**	**1.4995**	**0.6082**	**0.9147**	**0.7160**		
	SD	**0.002681**	**0.17664**	**0.04465**	**0.09158**	**0.03050**	**0.93589**	**0.12604**	**0.04821**	**0.14130**	**0.16380**		
	21-1283	0.03155	1.7606	0.4483	0.8506	0.2869	8.8533	1.7048	0.6587	1.1739	0.5743	0.0336	N/A
17.5 mg/kg-d	21-1284	0.02531	1.6895	0.4763	0.8609	0.2575	9.3833	1.4729	0.6503	1.0241	1.0065	0.0265	N/A
	21-1289	0.02956	1.3090	0.3691	0.7560	0.2280	6.4742	1.2925	0.5205	0.7235	0.5298	0.0156	N/A
	21-1290	0.03188	1.7733	0.4680	0.9927	0.2600	9.5734	1.5897	0.6456	0.8322	0.5423	0.0158	N/A
	21-1301	0.03101	1.4514	0.3996	0.8441	0.1975	6.8150	1.4306	0.5601	0.8626	1.1499	0.0108	N/A
	21-1302	0.02919	1.2516	0.3424	0.7298	0.1299	5.9078	1.4759	0.5645	0.8261	0.5845	0.0080	N/A
	21-1305	0.04264	1.6484	0.3716	0.9302	0.1889	7.2969	1.6858	0.6791	0.8147	1.1333	0.0075	N/A
	21-1306	0.02634	1.5644	0.4547	1.0054	0.2267	9.1124	1.6224	0.6442	0.9316	0.9306	0.0131	N/A
	21-1311	0.03141	1.3865	0.3836	0.8598	0.1421	6.2828	1.8257	0.7168	0.8108	0.6035	0.0138	N/A
	21-1312	0.03148	1.5962	0.4006	0.8112	0.1075	7.1296	1.5537	0.6278	0.6152	1.1152	0.0119	N/A
	Mean	**0.03104**	**1.5431**	**0.4114**	**0.8641**	**0.2025**	**7.6829**	**1.5654**	**0.6268**	**0.8615**	**0.8170**	**0.0157**	
	SD	**0.004670**	**0.18524**	**0.04692**	**0.09069**	**0.06042**	**1.40078**	**0.15451**	**0.06026**	**0.15475**	**0.27185**	**0.00824**	
	21-1285	ND	1.2089	0.5888	0.6392	0.1474	5.7052	0.7871	0.3130	0.6065	0.4436	0.0212	0.0066
70 mg/kg-d	21-1286	0.02807	1.1351	0.3705	0.5449	0.1492	4.9535	0.5309	0.3228	0.6969	0.4591	0.0261	0.0048
	21-1287	0.02948	1.2887	0.5068	0.6874	0.1387	6.4559	0.6824	0.3613	0.9428	0.5590	0.0279	0.0063
	21-1288	0.02914	1.5751	0.4077	0.7765	0.1437	7.0682	1.7645	0.4116	1.0759	0.6087	0.0280	0.0052
	21-1303	0.02682	1.2016	0.5196	0.7574	0.1325	5.9668	0.7057	0.4035	0.6957	0.7488	0.0220	0.0065
	21-1304	0.03110	1.5255	0.6943	0.8513	0.1478	8.8312	1.5452	0.5255	0.9859	0.5730	0.0333	0.0046
	21-1307	0.03026	1.1613	0.4222	0.5981	0.0768	4.5774	0.4946	0.3424	0.7844	0.5839	0.0237	0.0056
	21-1308	0.02806	1.3100	0.4641	0.6818	0.1416	5.3957	1.1537	0.4411	0.7771	1.1203	0.0264	0.0048
	21-1319	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1320	0.02813	1.4953	0.4998	0.7335	0.0969	6.2563	1.1992	0.4567	0.5766	0.8690	0.0316	0.0041
	Mean	**0.02888**	**1.3224**	**0.4971**	**0.6967**	**0.1305**	**6.1344**	**0.9848**	**0.3975**	**0.7935**	**0.6628**	**0.0267**	**0.0054**
	SD	**0.001384**	**0.16763**	**0.09915**	**0.09466**	**0.02578**	**1.26687**	**0.45430**	**0.06992**	**0.17333**	**0.21703**	**0.00407**	**0.00092**

* Outlier

Table U-4
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Organ Mass
Female Rats

Group	Animal ID	Body Weight[1]	Body Weight[2]	Brain	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Uterus	Ovaries	Thyroid	Pituitary
	21-1325	284	279	1.993	0.06695	1.916	0.471	1.152	0.189	8.829	0.528	0.129	0.022	0.020
Corn Oil	21-1326	285	264	2.204	0.06421	1.857	0.514	1.102	0.284	7.869	0.309	0.100	0.024	0.024
Control	21-1331	310	296	2.088	0.07603	1.886	0.483	1.197	0.183	10.076	0.598	0.121	0.034	ND
	21-1332	308	294	1.997	0.07228	2.172	0.418	1.087	0.234	10.181	0.754	0.090	0.017	0.026
	21-1345	344	323	2.046	0.08250	2.185	0.591	1.370	0.220	9.880	0.615	0.142	0.038	0.023
	21-1346	306	287	2.067	0.07134	1.909	0.484	1.218	0.246	9.355	1.080	0.156	0.036	0.015
	21-1347	286	270	1.944	0.06551	1.807	0.469	1.077	0.233	7.588	0.651	0.112	0.018	0.012
	21-1348	325	310	2.000	0.08310	1.894	0.588	1.200	0.221	9.043	0.728	0.109	0.021	0.024
	21-1363	348	334	2.098	0.07926	2.018	0.489	1.295	0.319	8.873	0.428	0.159	0.031	0.018
	21-1364	330	312	2.070	0.08219	2.045	0.575	1.246	0.232	10.537	0.642	0.161	0.028	0.011
	Mean	**312.6**	**296.9**	**2.051**	**0.07434**	**1.969**	**0.508**	**1.194**	**0.236**	**9.223**	**0.633**	**0.128**	**0.027**	**0.019**
	SD	**23.70**	**22.83**	**0.0730**	**0.007306**	**0.1307**	**0.0581**	**0.0942**	**0.0406**	**0.9797**	**0.2064**	**0.0257**	**0.0076**	**0.0055**
	21-1333	300	285	2.043	0.07793	1.890	0.482	1.133	0.229	7.748	0.508	0.136	N/A	N/A
1.09 mg/kg-d	21-1334	264	256	2.043	0.08232	1.808	0.469	1.196	0.311	8.423	0.488	0.151	N/A	N/A
	21-1335	287	279	1.996	0.05492	1.829	0.526	1.068	0.243	8.372	0.527	0.149	N/A	N/A
	21-1336	280	274	2.071	0.07291	1.827	0.463	1.164	0.187	8.048	0.650	0.131	N/A	N/A
	21-1341	293	277	1.987	0.08450	1.872	0.593	1.098	0.200	9.160	0.853	0.159	N/A	N/A
	21-1342	342	324	2.056	0.08581	2.176	0.694	1.304	0.176	10.969	0.551	0.178	N/A	N/A
	21-1371	291	274	1.975	0.07345	2.061	0.584	1.036	0.201	9.088	0.578	0.146	N/A	N/A
	21-1372	303	288	1.990	0.07395	1.865	0.657	1.182	0.266	9.902	0.666	0.109	N/A	N/A
	21-1373	287	269	1.928	0.06686	1.916	0.445	1.038	0.271	9.052	1.089	0.106	N/A	N/A
	21-1374	306	299	1.977	0.07300	2.091	0.486	1.07	0.307	9.651	0.641	0.118	N/A	N/A
	Mean	**295.3**	**282.5**	**2.007**	**0.07457**	**1.934**	**0.540**	**1.129**	**0.239**	**9.041**	**0.655**	**0.138**		
	SD	**20.42**	**18.57**	**0.0448**	**0.009121**	**0.1285**	**0.0873**	**0.0845**	**0.0487**	**0.9623**	**0.1858**	**0.0228**		
	21-1339	291	281	2.068	0.07440	1.687	0.490	1.236	0.221	8.571	0.359	0.141	N/A	N/A
4.38 mg/kg-d	21-1340	321	309	1.986	0.06669	1.980	0.657	1.217	0.309	9.625	0.790	0.150	N/A	N/A
	21-1351	286	271	2.106	0.06604	1.956	0.564	1.171	0.234	9.144	0.577	0.166	N/A	N/A
	21-1352	303	293	1.999	0.07567	2.026	0.604	1.056	0.218	9.537	1.055	0.171	N/A	N/A
	21-1355	351	337	2.048	0.06840	2.161	0.442	1.390	0.205	10.623	0.834	0.116	N/A	N/A
	21-1356	259	248	1.973	0.06110	1.705	0.426	1.054	0.308	7.664	0.456	0.117	N/A	N/A
	21-1357	319	311	2.077	0.07959	2.029	0.522	1.095	0.247	11.233	0.516	0.132	N/A	N/A
	21-1358	318	304	2.050	0.05965	1.906	0.457	1.071	0.240	8.625	0.502	0.124	N/A	N/A
	21-1359	306	295	2.093	0.06071	2.077	0.448	1.238	0.301	7.837	0.547	0.140	N/A	N/A
	21-1360	298	280	2.157	0.07223	1.438	0.592	1.224	0.213	9.664	0.632	0.122	N/A	N/A
	Mean	**305.2**	**292.9**	**2.056**	**0.06845**	**1.897**	**0.520**	**1.175**	**0.250**	**9.252**	**0.627**	**0.138**		
	SD	**24.64**	**24.64**	**0.0575**	**0.006882**	**0.2207**	**0.0802**	**0.1076**	**0.0409**	**1.1346**	**0.2083**	**0.0197**		
	21-1327	315	301	2.030	0.06192	1.992	0.615	1.232	0.291	9.085	0.433	0.129	0.027	N/A
17.5 mg/kg-d	21-1328	286	275	2.020	0.05589	1.712	0.647	1.165	0.328	8.489	0.433	0.122	0.026	N/A
	21-1329	284	275	1.857	0.06110	1.683	0.614	1.169	0.315	7.602	0.486	0.127	0.018	N/A
	21-1330	301	292	1.974	0.06227	1.703	0.504	1.162	0.263	7.764	0.425	0.133	0.023	N/A
	21-1343	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	N/A
	21-1344	301	288	1.969	0.06099	1.838	0.604	0.979	0.260	8.588	1.017	0.161	0.023	N/A
	21-1353	307	287	2.026	0.06791	1.880	0.554	1.228	0.367	8.116	0.450	0.105	0.018	N/A
	21-1354	335	320	2.126	0.08197	2.052	0.737	1.204	0.221	8.882	0.623	0.160	0.020	N/A
	21-1367	295	280	1.990	0.06373	2.008	0.426	1.144	0.193	7.579	0.797	0.095	0.023	N/A
	21-1368	322	305	1.969	0.06666	1.965	0.649	1.230	0.267	9.245	0.482	0.137	0.032	N/A
	Mean	**305.1**	**291.4**	**1.996**	**0.06472**	**1.870**	**0.594**	**1.168**	**0.278**	**8.372**	**0.572**	**0.130**	**0.023**	
	SD	**16.68**	**14.98**	**0.0714**	**0.007343**	**0.1436**	**0.0902**	**0.0784**	**0.0537**	**0.6372**	**0.2067**	**0.0220**	**0.0044**	
	21-1337	256	244	2.075	0.05938	1.640	0.666	0.980	0.247	7.627	0.443	0.128	0.065	0.012
70 mg/kg-d	21-1338	259	249	1.987	0.63810*	1.755	0.467	1.131	0.288	7.709	0.433	0.142	0.038	0.012
	21-1349	229	218	2.013	0.46000*	1.761	0.511	0.991	0.243	6.740	0.496	0.079	0.033	0.016
	21-1350	241	233	2.083	0.05533	1.661	0.671	0.967	0.247	7.679	0.415	0.129	0.037	0.016
	21-1361	255	242	2.214	0.06668	1.709	0.519	1.094	0.372	7.624	0.543	0.137	0.027	0.005
	21-1362	303	285	2.061	0.05786	1.991	0.708	1.209	0.267	9.091	0.430	0.108	0.036	0.018
	21-1365	298	286	2.133	0.06267	2.041	0.572	1.303	0.196	9.319	0.411	0.164	0.055	0.008
	21-1366	236	223	1.972	0.06395	1.799	0.579	0.960	0.208	7.624	0.973	0.114	0.036	0.019
	21-1369	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1370	273	259	2.035	0.05731	1.789	0.581	1.082	0.181	7.891	0.660	0.102	0.038	0.021
	Mean	**261.1**	**248.8**	**2.064**	**0.06045**	**1.794**	**0.586**	**1.080**	**0.250**	**7.923**	**0.534**	**0.123**	**0.041**	**0.014**
	SD	**25.96**	**24.32**	**0.0755**	**0.004081**	**0.1374**	**0.0814**	**0.1195**	**0.0571**	**0.7973**	**0.1833**	**0.0250**	**0.0118**	**0.0053**

[1] Non-fasted Day 90 Body Weight
[2] Fasted Day 91 Body Weight
* Outlier

Table U-5
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Organ to Body Mass Ratios
Female Rats

Group	Animal ID	Brain	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Uterus	Ovaries	Thyroid	Pituitary
Corn Oil Control	21-1325	0.0070	0.00024	0.0067	0.0017	0.0041	0.0007	0.0311	0.0019	0.0005	0.00008	0.00007
	21-1326	0.0077	0.00023	0.0065	0.0018	0.0039	0.0010	0.0276	0.0011	0.0003	0.00008	0.00008
	21-1331	0.0067	0.00025	0.0061	0.0016	0.0039	0.0006	0.0325	0.0019	0.0004	0.00011	ND
	21-1332	0.0065	0.00023	0.0071	0.0014	0.0035	0.0008	0.0331	0.0024	0.0003	0.00006	0.00008
	21-1345	0.0059	0.00024	0.0064	0.0017	0.0040	0.0006	0.0287	0.0018	0.0004	0.00011	0.00007
	21-1346	0.0068	0.00023	0.0062	0.0016	0.0040	0.0008	0.0306	0.0035	0.0005	0.00012	0.00005
	21-1347	0.0068	0.00023	0.0063	0.0016	0.0038	0.0008	0.0265	0.0023	0.0004	0.00006	0.00004
	21-1348	0.0062	0.00026	0.0058	0.0018	0.0037	0.0007	0.0278	0.0022	0.0003	0.00006	0.00007
	21-1363	0.0060	0.00023	0.0058	0.0014	0.0037	0.0009	0.0255	0.0012	0.0005	0.00009	0.00005
	21-1364	0.0063	0.00025	0.0062	0.0017	0.0038	0.0007	0.0319	0.0019	0.0005	0.00008	0.00003
	Mean	**0.0066**	**0.00024**	**0.0063**	**0.0016**	**0.0038**	**0.0008**	**0.0295**	**0.0020**	**0.0004**	**0.00009**	**0.000062**
	SD	**0.00054**	**0.000010**	**0.00039**	**0.00015**	**0.00016**	**0.00013**	**0.00265**	**0.00068**	**0.00007**	**0.000022**	**0.0000185**
1.09 mg/kg-d	21-1333	0.0068	0.00026	0.0063	0.0016	0.0038	0.0008	0.0258	0.0017	0.0005	N/A	N/A
	21-1334	0.0077	0.00031	0.0068	0.0018	0.0045	0.0012	0.0319	0.0018	0.0006	N/A	N/A
	21-1335	0.0070	0.00019	0.0064	0.0018	0.0037	0.0008	0.0292	0.0018	0.0005	N/A	N/A
	21-1336	0.0074	0.00026	0.0065	0.0017	0.0042	0.0007	0.0287	0.0023	0.0005	N/A	N/A
	21-1341	0.0068	0.00029	0.0064	0.0020	0.0037	0.0007	0.0313	0.0029	0.0005	N/A	N/A
	21-1342	0.0060	0.00025	0.0064	0.0020	0.0038	0.0005	0.0321	0.0016	0.0005	N/A	N/A
	21-1371	0.0068	0.00025	0.0071	0.0020	0.0036	0.0007	0.0312	0.0020	0.0005	N/A	N/A
	21-1372	0.0066	0.00024	0.0062	0.0022	0.0039	0.0009	0.0327	0.0022	0.0004	N/A	N/A
	21-1373	0.0067	0.00023	0.0067	0.0016	0.0036	0.0009	0.0315	0.0038	0.0004	N/A	N/A
	21-1374	0.0065	0.00024	0.0068	0.0016	0.0035	0.0010	0.0315	0.0021	0.0004	N/A	N/A
	Mean	**0.0068**	**0.00025**	**0.0066**	**0.0018**	**0.0038**	**0.0008**	**0.0306**	**0.0022**	**0.0005**		
	SD	**0.00048**	**0.000032**	**0.00029**	**0.00022**	**0.00031**	**0.00019**	**0.00208**	**0.00066**	**0.00008**		
4.38 mg/kg-d	21-1339	0.0071	0.00026	0.0058	0.0017	0.0042	0.0008	0.0295	0.0012	0.0005	N/A	N/A
	21-1340	0.0062	0.00021	0.0062	0.0020	0.0038	0.0010	0.0300	0.0025	0.0005	N/A	N/A
	21-1351	0.0074	0.00023	0.0068	0.0020	0.0041	0.0008	0.0320	0.0020	0.0006	N/A	N/A
	21-1352	0.0066	0.00025	0.0067	0.0020	0.0035	0.0007	0.0315	0.0035	0.0006	N/A	N/A
	21-1355	0.0058	0.00019	0.0062	0.0013	0.0040	0.0006	0.0303	0.0024	0.0003	N/A	N/A
	21-1356	0.0076	0.00024	0.0066	0.0016	0.0041	0.0012	0.0296	0.0018	0.0005	N/A	N/A
	21-1357	0.0065	0.00025	0.0064	0.0016	0.0034	0.0008	0.0352	0.0016	0.0004	N/A	N/A
	21-1358	0.0064	0.00019	0.0060	0.0014	0.0034	0.0008	0.0271	0.0016	0.0004	N/A	N/A
	21-1359	0.0068	0.0002	0.0068	0.0015	0.0040	0.0010	0.0256	0.0018	0.0005	N/A	N/A
	21-1360	0.0072	0.00024	0.0048	0.0020	0.0041	0.0007	0.0324	0.0021	0.0004	N/A	N/A
	Mean	**0.0068**	**0.00023**	**0.0062**	**0.0017**	**0.0039**	**0.0008**	**0.0303**	**0.0020**	**0.0005**		
	SD	**0.00056**	**0.000026**	**0.00060**	**0.00028**	**0.00032**	**0.00017**	**0.00271**	**0.00063**	**0.00008**		
17.5 mg/kg-d	21-1327	0.0064	0.00020	0.0063	0.0020	0.0039	0.0009	0.0288	0.0014	0.0004	0.00009	N/A
	21-1328	0.0071	0.00020	0.0060	0.0023	0.0041	0.0011	0.0297	0.0015	0.0004	0.00009	N/A
	21-1329	0.0065	0.00022	0.0059	0.0022	0.0041	0.0011	0.0268	0.0017	0.0004	0.00006	N/A
	21-1330	0.0066	0.00021	0.0057	0.0017	0.0039	0.0009	0.0258	0.0014	0.0004	0.00008	N/A
	21-1343	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	N/A
	21-1344	0.0065	0.00020	0.0061	0.0020	0.0033	0.0009	0.0285	0.0034	0.0005	0.00007	N/A
	21-1353	0.0066	0.00022	0.0061	0.0018	0.0040	0.0012	0.0264	0.0015	0.0003	0.00006	N/A
	21-1354	0.0063	0.00024	0.0061	0.0022	0.0036	0.0007	0.0265	0.0019	0.0005	0.00006	N/A
	21-1367	0.0067	0.00022	0.0068	0.0014	0.0039	0.0007	0.0257	0.0027	0.0003	0.00008	N/A
	21-1368	0.0061	0.00021	0.0061	0.0020	0.0038	0.0008	0.0287	0.0015	0.0004	0.00010	N/A
	Mean	**0.0066**	**0.00021**	**0.0061**	**0.0019**	**0.0038**	**0.0009**	**0.0274**	**0.0019**	**0.0004**	**0.00008**	
	SD	**0.00026**	**0.000015**	**0.00031**	**0.00027**	**0.00027**	**0.00020**	**0.00150**	**0.00070**	**0.00006**	**0.000014**	
70 mg/kg-d	21-1337	0.0081	0.00023	0.0064	0.0026	0.0038	0.0010	0.0298	0.0017	0.0005	0.00025	0.00005
	21-1338	0.0077	ND	0.0068	0.0018	0.0044	0.0011	0.0298	0.0017	0.0006	0.00015	0.00005
	21-1349	0.0088	ND	0.0077	0.0022	0.0043	0.0011	0.0294	0.0022	0.0003	0.00014	0.00007
	21-1350	0.0086	0.00023	0.0069	0.0028	0.0040	0.0010	0.0319	0.0017	0.0005	0.00015	0.00007
	21-1361	0.0087	0.00026	0.0067	0.0020	0.0043	0.0015	0.0299	0.0021	0.0005	0.00011	0.00002
	21-1362	0.0068	0.00019	0.0066	0.0023	0.0040	0.0009	0.0300	0.0014	0.0004	0.00012	0.00006
	21-1365	0.0072	0.00021	0.0068	0.0019	0.0044	0.0007	0.0313	0.0014	0.0006	0.00018	0.00003
	21-1366	0.0084	0.00027	0.0076	0.0025	0.0041	0.0009	0.0323	0.0041	0.0005	0.00015	0.00008
	21-1369	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1370	0.0075	0.00021	0.0066	0.0021	0.0040	0.0007	0.0289	0.0024	0.0004	0.00014	0.00008
	Mean	**0.0080**	**0.00023**	**0.0069**	**0.0023**	**0.0041**	**0.0010**	**0.0304**	**0.0021**	**0.0005**	**0.00016**	**0.000055**
	SD	**0.00072**	**0.000029**	**0.00046**	**0.00032**	**0.00020**	**0.00024**	**0.00117**	**0.00084**	**0.00009**	**0.000043**	**0.0000215**

Table U-6
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Organ to Brain Mass Ratios
Female Rats

Group	Animal ID	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Uterus	Ovaries	Thyroid	Pituitary
Corn Oil Control	21-1325	0.03359	0.9614	0.2363	0.5780	0.0948	4.4300	0.2649	0.0647	0.01104	0.01004
	21-1326	0.02913	0.8426	0.2332	0.5000	0.1289	3.5703	0.1402	0.0452	0.01089	0.01089
	21-1331	0.03641	0.9033	0.2313	0.5733	0.0876	4.8257	0.2864	0.0579	0.01628	ND
	21-1332	0.03619	1.0876	0.2093	0.5443	0.1172	5.0981	0.3776	0.0452	0.00851	0.01302
	21-1345	0.04032	1.0679	0.2889	0.6696	0.1075	4.8289	0.3006	0.0693	0.01857	0.01124
	21-1346	0.03451	0.9236	0.2342	0.5893	0.1190	4.5259	0.5225	0.0753	0.01742	0.00726
	21-1347	0.03370	0.9295	0.2413	0.5540	0.1199	3.9033	0.3349	0.0578	0.00926	0.00617
	21-1348	0.04155	0.9470	0.2940	0.6000	0.1105	4.5215	0.3640	0.0543	0.01050	0.01200
	21-1363	0.03778	0.9619	0.2331	0.6173	0.1520	4.2293	0.2040	0.0760	0.01478	0.00858
	21-1364	0.03971	0.9879	0.2778	0.6019	0.1121	5.0903	0.3101	0.0777	0.01353	0.00531
	Mean	**0.03629**	**0.9613**	**0.2479**	**0.5828**	**0.1150**	**4.5023**	**0.3105**	**0.0623**	**0.01308**	**0.009390**
	SD	**0.003745**	**0.07314**	**0.02840**	**0.04559**	**0.01779**	**0.49667**	**0.10328**	**0.01219**	**0.003550**	**0.0026983**
1.09 mg/kg-d	21-1333	0.03814	0.9251	0.2359	0.5546	0.1121	3.7925	0.2487	0.0665	N/A	N/A
	21-1334	0.04029	0.8850	0.2296	0.5854	0.1522	4.1229	0.2389	0.0740	N/A	N/A
	21-1335	0.02752	0.9163	0.2635	0.5351	0.1217	4.1944	0.2640	0.0744	N/A	N/A
	21-1336	0.03521	0.8822	0.2236	0.5620	0.0903	3.8860	0.3139	0.0634	N/A	N/A
	21-1341	0.04253	0.9421	0.2984	0.5526	0.1007	4.6100	0.4293	0.0800	N/A	N/A
	21-1342	0.04174	1.0584	0.3375	0.6342	0.0856	5.3351	0.2680	0.0863	N/A	N/A
	21-1371	0.03719	1.0435	0.2957	0.5246	0.1018	4.6015	0.2927	0.0740	N/A	N/A
	21-1372	0.03716	0.9372	0.3302	0.5940	0.1337	4.9759	0.3347	0.0547	N/A	N/A
	21-1373	0.03468	0.9938	0.2308	0.5384	0.1406	4.6950	0.5648	0.0547	N/A	N/A
	21-1374	0.03692	1.0577	0.2458	0.5412	0.1553	4.8816	0.3242	0.0598	N/A	N/A
	Mean	**0.03714**	**0.9641**	**0.2691**	**0.5622**	**0.1194**	**4.5095**	**0.3279**	**0.0688**		
	SD	**0.004263**	**0.06897**	**0.04315**	**0.03341**	**0.02523**	**0.49914**	**0.09988**	**0.01070**		
4.38 mg/kg-d	21-1339	0.03598	0.8158	0.2369	0.5977	0.1069	4.1446	0.1736	0.0683	N/A	N/A
	21-1340	0.03358	0.9970	0.3308	0.6128	0.1556	4.8464	0.3978	0.0755	N/A	N/A
	21-1351	0.03136	0.9288	0.2678	0.5560	0.1111	4.3419	0.2740	0.0790	N/A	N/A
	21-1352	0.03785	1.0135	0.3022	0.5283	0.1091	4.7709	0.5278	0.0857	N/A	N/A
	21-1355	0.03340	1.0552	0.2158	0.6787	0.1001	5.1870	0.4072	0.0566	N/A	N/A
	21-1356	0.03097	0.8642	0.2159	0.5342	0.1561	3.8844	0.2311	0.0594	N/A	N/A
	21-1357	0.03832	0.9769	0.2513	0.5272	0.1189	5.4083	0.2484	0.0634	N/A	N/A
	21-1358	0.02910	0.9298	0.2229	0.5224	0.1171	4.2073	0.2449	0.0606	N/A	N/A
	21-1359	0.0290	0.9924	0.2140	0.5915	0.1438	3.7444	0.2613	0.0671	N/A	N/A
	21-1360	0.03349	0.6667	0.2745	0.5675	0.0987	4.4803	0.2930	0.0564	N/A	N/A
	Mean	**0.03330**	**0.9240**	**0.2532**	**0.5716**	**0.1217**	**4.5016**	**0.3059**	**0.0672**		
	SD	**0.003309**	**0.11527**	**0.04026**	**0.04963**	**0.02195**	**0.54544**	**0.10605**	**0.00999**		
17.5 mg/kg-d	21-1327	0.03050	0.9813	0.3030	0.6069	0.1433	4.4754	0.2133	0.0634	0.01334	N/A
	21-1328	0.02767	0.8475	0.3203	0.5767	0.1624	4.2025	0.2144	0.0602	0.01306	N/A
	21-1329	0.03290	0.9063	0.3306	0.6295	0.1696	4.0937	0.2617	0.0682	0.00982	N/A
	21-1330	0.03155	0.8627	0.2553	0.5887	0.1332	3.9331	0.2153	0.0673	0.01160	N/A
	21-1343	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	N/A
	21-1344	0.03098	0.9335	0.3068	0.4972	0.1320	4.3616	0.5165	0.0818	0.01146	N/A
	21-1353	0.03352	0.9279	0.2734	0.6061	0.1811	4.0059	0.2221	0.0518	0.00904	N/A
	21-1354	0.03856	0.9652	0.3467	0.5663	0.1040	4.1778	0.2930	0.0753	0.00938	N/A
	21-1367	0.03203	1.0090	0.2141	0.5749	0.0970	3.8085	0.4005	0.0476	0.01155	N/A
	21-1368	0.03385	0.9980	0.3296	0.6247	0.1356	4.6953	0.2448	0.0697	0.01609	N/A
	Mean	**0.03239**	**0.9368**	**0.2978**	**0.5857**	**0.1398**	**4.1949**	**0.2868**	**0.0650**	**0.01170**	
	SD	**0.002967**	**0.05725**	**0.04257**	**0.03987**	**0.02820**	**0.27860**	**0.10492**	**0.01077**	**0.002235**	
70 mg/kg-d	21-1337	0.02862	0.7904	0.3210	0.4723	0.1190	3.6757	0.2135	0.0616	0.0313	0.0058
	21-1338	ND	0.8832	0.2350	0.5692	0.1449	3.8797	0.2179	0.0717	0.0191	0.0060
	21-1349	ND	0.8748	0.2538	0.4923	0.1207	3.3482	0.2464	0.0391	0.0164	0.0079
	21-1350	0.02656	0.7974	0.3221	0.4642	0.1186	3.6865	0.1992	0.0620	0.0178	0.0077
	21-1361	0.03012	0.7719	0.2344	0.4941	0.1680	3.4435	0.2453	0.0620	0.0122	0.0023
	21-1362	0.02807	0.9660	0.3435	0.5866	0.1295	4.4110	0.2086	0.0526	0.0175	0.0087
	21-1365	0.02938	0.9569	0.2682	0.6109	0.0919	4.3690	0.1927	0.0769	0.0258	0.0038
	21-1366	0.03243	0.9123	0.2936	0.4868	0.1055	3.8661	0.4934	0.0579	0.0183	0.0096
	21-1369	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1370	0.02816	0.8791	0.2855	0.5317	0.0889	3.8776	0.3243	0.0503	0.0187	0.0103
	Mean	**0.02905**	**0.8702**	**0.2841**	**0.5231**	**0.1208**	**3.8397**	**0.2602**	**0.0593**	**0.01966**	**0.006905**
	SD	**0.001861**	**0.07077**	**0.03949**	**0.05372**	**0.02496**	**0.36384**	**0.09606**	**0.01128**	**0.005608**	**0.0026855**

Table U-7
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Organ Mass Summary
Male Rats

Group	Animal ID	Body Weight[1]	Body Weight[2]	Brain	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Testes	Epididymides	Prostate	Seminal Vesicles	Thyroid	Pituitary
Corn Oil Control	**Mean**	600.2	584.3	2.229	0.07525	3.536	0.814	1.861	0.448	18.483	3.617	1.444	2.277	1.697	0.029	0.016
	SD	77.49	77.71	0.0966	0.010664	0.3535	0.1009	0.1785	0.0839	2.8591	0.2353	0.1473	0.4147	0.3852	0.0089	0.0046
	N	10	10	10	9	10	10	10	10	10	10	10	10	10	10	10
1.09 mg/kg-d	**Mean**	590.3	574.9	2.245	0.07389	3.539	0.795	1.884	0.489	17.458	3.513	1.436	2.141	1.615	N/A	N/A
	SD	65.79	63.23	0.0868	0.008457	0.4088	0.2079	0.2423	0.1593	2.2207	0.2329	0.0985	0.5415	0.2291	N/A	N/A
	N	10	10	10	10	10	10	10	10	10	10	10	10	10		
4.38 mg/kg-d	**Mean**	570.2	553.7	2.262	0.06955	3.253	0.765	1.788	0.363	17.073	3.384	1.375	2.074	1.613	N/A	N/A
	SD	68.17	65.73	0.1004	0.005770	0.3464	0.1152	0.2213	0.0732	2.2110	0.2234	0.1206	0.3622	0.3544	N/A	N/A
	N	10	10	10	10	10	10	10	10	10	10	10	10	10		
17.5 mg/kg-d	**Mean**	570.6	554.0	2.220	0.06887	3.431	0.915	1.920	0.451	17.108	3.470	1.391	1.912	1.814	0.035	N/A
	SD	93.22	91.62	0.0762	0.010682	0.4805	0.1232	0.2317	0.1413	3.5098	0.3087	0.1349	0.3482	0.6101	0.0184	N/A
	N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	
70 mg/kg-d	**Mean**	455.9*	433.1*	2.318	0.06710	3.062	1.146*	1.611	0.302	14.162	2.273	0.920*	1.832	1.539	0.062*	0.012
	SD	49.21	45.97	0.0960	0.002769	0.3840	0.1959	0.1944	0.0589	2.5880	1.0314	0.1542	0.3657	0.5166	0.0096	0.0019
	N	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9

[1] Non-fasted Day 90 Body Weight
[2] Fasted Day 91 Body Weight
* $p<0.05$ compared to controls

Table U-8
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Organ to Body Mass Ratio Summary
Male Rats

Group	Animal ID	Brain	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Testes	Epididymides	Prostate	Seminal Vesicles	Thyroid	Pituitary
Corn Oil Control	**Mean**	0.0038	0.00012	0.0059	0.0014	0.0031	0.0007	0.0307	0.0061	0.0024	0.0038	0.0028	0.00005	0.00003
	SD	0.00057	0.000014	0.00046	0.00013	0.00029	0.00010	0.00143	0.00105	0.00025	0.00070	0.00066	0.000017	0.000008
	N	10	9	10	10	10	10	10	10	10	10	10	10	10
1.09 mg/kg-d	**Mean**	0.0038	0.00013	0.0060	0.0013	0.0032	0.0008	0.0296	0.0060	0.0025	0.0036	0.0028	N/A	N/A
	SD	0.00044	0.000017	0.00039	0.00030	0.00025	0.00028	0.00137	0.00050	0.00026	0.00062	0.00067	N/A	N/A
	N	10	10	10	10	10	10	10	10	10	10	10		
4.38 mg/kg-d	**Mean**	0.0040	0.00012	0.0057	0.0013	0.0031	0.0006	0.0299	0.0060	0.0024	0.0036	0.0028	N/A	N/A
	SD	0.00044	0.000015	0.00047	0.00012	0.00020	0.00011	0.00102	0.00084	0.00036	0.00053	0.00057	N/A	N/A
	N	10	10	10	10	10	10	10	10	10	10	10		
17.5 mg/kg-d	**Mean**	0.0040	0.00012	0.0060	0.0016*	0.0034	0.0008	0.0298	0.0062	0.0025	0.0034	0.0032	0.00006	N/A
	SD	0.00055	0.000024	0.00040	0.00012	0.00031	0.00018	0.00173	0.00099	0.00035	0.00053	0.00113	0.000027	N/A
	N	10	10	10	10	10	10	10	10	10	10	10	10	
70 mg/kg-d	**Mean**	0.0051*	0.00015	0.0067*	0.0025*	0.0035*	0.0007	0.0309	0.0049	0.0020*	0.0040	0.0034	0.00014*	0.00003
	SD	0.00060	0.000017	0.00051	0.00040	0.00021	0.00014	0.00284	0.00181	0.00026	0.00066	0.00129	0.000017	0.000006
	N	9	8	9	9	9	9	9	9	9	9	9	9	9

* $p<0.05$ compared to controls

Table U-9
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Organ to Brain Mass Ratio Summary
Male Rats

Group	Animal ID	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Testes	Epididymides	Prostate	Seminal Vesicles	Thyroid	Pituitary
Corn Oil Control	**Mean**	0.03372	1.5902	0.3653	0.8360	0.2017	8.3159	1.6243	0.6477	1.0226	0.7636	0.0130	0.0072
	SD	0.004726	0.18173	0.04106	0.08560	0.03997	1.38039	0.10556	0.05633	0.18292	0.17903	0.00406	0.00236
	N	9	10	10	10	10	10	10	10	10	10	10	10
1.09 mg/kg-d	**Mean**	0.03300	1.5770	0.3547	0.8402	0.2184	7.7819	1.5668	0.6406	0.9528	0.7200	N/A	N/A
	SD	0.004403	0.18035	0.09284	0.11417	0.07163	1.01056	0.12340	0.05449	0.23644	0.10418	N/A	N/A
	N	10	10	10	10	10	10	10	10	10	10		
4.38 mg/kg-d	**Mean**	0.03079	1.4418	0.3379	0.7906	0.1605	7.5507	1.4995	0.6082	0.9147	0.7160	N/A	N/A
	SD	0.002681	0.17664	0.04465	0.09158	0.03050	0.93589	0.12604	0.04821	0.14130	0.16380	N/A	N/A
	N	10	10	10	10	10	10	10	10	10	10		
17.5 mg/kg-d	**Mean**	0.03104	1.5431	0.4114	0.8641	0.2025	7.6829	1.5654	0.6268	0.8615	0.8170	0.0157	N/A
	SD	0.004670	0.18524	0.04692	0.09069	0.06042	1.40078	0.15451	0.06026	0.15475	0.27185	0.00824	N/A
	N	10	10	10	10	10	10	10	10	10	10	10	
70 mg/kg-d	**Mean**	0.02888	1.3224*	0.4971*	0.6967*	0.1305*	6.1344*	0.9848*	0.3975*	0.7935	0.6628	0.0267*	0.0054*
	SD	0.001384	0.16763	0.09915	0.09466	0.02578	1.26687	0.45430	0.06992	0.17333	0.21703	0.00407	0.00092
	N	8	9	9	9	9	9	9	9	9	9	9	9

* $p<0.05$ compared to controls

Table U-10
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Organ Mass Summary
Female Rats

Group	Animal ID	Body Weight[1]	Body Weight[2]	Brain	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Uterus	Ovaries	Thyroid	Pituitary
Corn Oil Control	**Mean**	312.6	296.9	2.051	0.07434	1.969	0.508	1.194	0.236	9.223	0.633	0.128	0.027	0.019
	SD	23.70	22.83	0.0730	0.007306	0.1307	0.0581	0.0942	0.0406	0.9797	0.2064	0.0257	0.0076	0.0055
	N	10	10	10	10	10	10	10	10	10	10	10	10	9
1.09 mg/kg-d	**Mean**	295.3	282.5	2.007	0.07457	1.934	0.540	1.129	0.239	9.041	0.655	0.138	N/A	N/A
	SD	20.42	18.57	0.0448	0.009121	0.1285	0.0873	0.0845	0.0487	0.9623	0.1858	0.0228	N/A	N/A
	N	10	10	10	10	10	10	10	10	10	10	10		
4.38 mg/kg-d	**Mean**	305.2	292.9	2.056	0.06845	1.897	0.520	1.175	0.250	9.252	0.627	0.138	N/A	N/A
	SD	24.64	24.64	0.0575	0.006882	0.2207	0.0802	0.1076	0.0409	1.1346	0.2083	0.0197	N/A	N/A
	N	10	10	10	10	10	10	10	10	10	10	10		
17.5 mg/kg-d	**Mean**	305.1	291.4	1.996	0.06472*	1.870	0.594*	1.168	0.278	8.372*	0.572	0.130	0.023	N/A
	SD	16.68	14.98	0.0714	0.007343	0.1436	0.0902	0.0784	0.0537	0.6372	0.2067	0.0220	0.0044	N/A
	N	9	9	9	9	9	9	9	9	9	9	9	9	
70 mg/kg-d	**Mean**	261.1*	248.8*	2.064	0.06045	1.794	0.586*	1.080	0.250	7.923	0.534	0.123	0.041*	0.014
	SD	25.96	24.32	0.0755	0.004081	0.1374	0.0814	0.1195	0.0571	0.7973	0.1833	0.0250	0.0118	0.0053
	N	9	9	9	9	9	9	9	9	9	9	9	9	9

[1] Non-fasted Day 90 Body Weight

[2] Fasted Day 91 Body Weight

* $p<0.05$ compared to controls

Table U-11
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Organ to Body Mass Ratio Summary
Female Rats

Group	Animal ID	Brain	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Uterus	Ovaries	Thyroid	Pituitary
Corn Oil Control	**Mean**	0.0066	0.00024	0.0063	0.0016	0.0038	0.0008	0.0295	0.0020	0.0004	0.00009	0.000062
	SD	0.00054	0.000010	0.00039	0.00015	0.00016	0.00013	0.00265	0.00068	0.00007	0.000022	0.0000185
		10	10	10	10	10	10	10	10	10	10	9
1.09 mg/kg-d	**Mean**	0.0068	0.00025	0.0066	0.0018	0.0038	0.0008	0.0306	0.0022	0.0005	N/A	N/A
	SD	0.00048	0.000032	0.00029	0.00022	0.00031	0.00019	0.00208	0.00066	0.00008	N/A	N/A
		10	10	10	10	10	10	10	10	10		
4.38 mg/kg-d	**Mean**	0.0068	0.00023	0.0062	0.0017	0.0039	0.0008	0.0303	0.0020	0.0005	N/A	N/A
	SD	0.00056	0.000026	0.00060	0.00028	0.00032	0.00017	0.00271	0.00063	0.00008	N/A	N/A
		10	10	10	10	10	10	10	10	10		
17.5 mg/kg-d	**Mean**	0.0066	0.00021	0.0061	0.0019	0.0038	0.0009	0.0274	0.0019	0.0004	0.00008	N/A
	SD	0.00026	0.000015	0.00031	0.00027	0.00027	0.00020	0.00150	0.00070	0.00006	0.000014	N/A
		9	9	9	9	9	9	9	9	9	9	
70 mg/kg-d	**Mean**	0.0080*	0.00023	0.0069*	0.0023*	0.0041	0.0010	0.0304	0.0021	0.0005	0.00016*	0.000055
	SD	0.00072	0.000029	0.00046	0.00032	0.00020	0.00024	0.00117	0.00084	0.00009	0.000043	0.0000215
		9	9	9	9	9	9	9	9	9	9	9

* $p<0.05$ compared to controls

Table U-12
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Organ to Brain Mass Ratio Summary
Female Rats

Group	Animal ID	Adrenals	Kidneys	Spleen	Heart	Thymus	Liver	Uterus	Ovaries	Thyroid	Pituitary
Corn Oil Control	**Mean**	0.03629	0.9613	0.2479	0.5828	0.1150	4.5023	0.3105	0.0623	0.01308	0.009390
	SD	0.003745	0.07314	0.02840	0.04559	0.01779	0.49667	0.10328	0.01219	0.003550	0.0026983
	N	10	10	10	10	10	10	10	10	10	9
1.09 mg/kg-d	**Mean**	0.03714	0.9641	0.2691	0.5622	0.1194	4.5095	0.3279	0.0688	N/A	N/A
	SD	0.004263	0.06897	0.04315	0.03341	0.02523	0.49914	0.09988	0.01070	N/A	N/A
	N	10	10	10	10	10	10	10	10		
4.38 mg/kg-d	**Mean**	0.03330	0.9240	0.2532	0.5716	0.1217	4.5016	0.3059	0.0672	N/A	N/A
	SD	0.003309	0.11527	0.04026	0.04963	0.02195	0.54544	0.10605	0.00999	N/A	N/A
	N	10	10	10	10	10	10	10	10		
17.5 mg/kg-d	**Mean**	0.03239	0.9368	0.2978	0.5857	0.1398	4.1949	0.2868	0.0650	0.01170	N/A
	SD	0.002967	0.05725	0.04257	0.03987	0.02820	0.27860	0.10492	0.01077	0.002235	N/A
	N	9	9	9	9	9	9	9	9	9	
70 mg/kg-d	**Mean**	0.02905*	0.8702	0.2841	0.5231*	0.1208	3.8397*	0.2602	0.0593	0.01966*	0.006905
	SD	0.001861	0.07077	0.03949	0.05372	0.02496	0.36384	0.09606	0.01128	0.005608	0.0026855
	N	9	9	9	9	9	9	9	9	9	9

* $p<0.05$ compared to controls

Appendix V

Subchronic Sperm Analysis

Abbreviations:

mg/kg-d: milligrams per kilogram per day
(f): animal died on study
%: percent
SD: standard deviation

Table V-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Sperm Analysis
Male Rats

Group	Animal ID	Cauda Wt. (grams)	Sample (Millions)	Motile Cells (Millions)	Progressive Cells (Millions)	Motile Cells (%)	Progressive Cells (%)	Sperm/Gram Cauda (Millions)
	21-1281	0.332	82.7	15.8	0.5	19.0	1.0	249.0
Corn Oil	21-1282	0.320	75.8	9.2	0.1	12.0	0.0	236.9
Control	21-1295	0.293	36.7	0.8	0.0	2.0	0.0	125.3
	21-1296	0.307	43.6	4.5	0.2	10.0	0.0	142.1
	21-1297	0.271	21.1	5.6	0.3	27.0	1.0	77.7
	21-1298	0.263	37.2	9.6	0.8	26.0	2.0	141.5
	21-1299	0.242	31.1	9.3	0.6	30.0	2.0	128.4
	21-1300	0.341	32.7	7.8	0.6	24.0	2.0	96.0
	21-1309	0.372	16.3	4.6	0.3	28.0	2.0	43.9
	21-1310	0.309	37.7	13.1	0.7	35.0	2.0	121.9
	Mean	**0.305**	**41.5**	**8.0**	**0.4**	**21.3**	**1.2**	**136.3**
	SD	**0.0391**	**21.53**	**4.40**	**0.27**	**10.34**	**0.92**	**64.00**
	21-1293	0.300	29.4	9.8	0.4	33.0	1.0	98.0
1.09 mg/kg-d	21-1294	0.363	25.9	3.9	0.2	15.0	1.0	71.3
	21-1315	0.288	42.2	6.0	0.3	14.0	1.0	146.5
	21-1316	0.254	49.0	11.2	1.1	23.0	2.0	192.8
	21-1317	0.301	48.7	10.5	0.5	22.0	1.0	161.8
	21-1318	0.244	36.4	1.6	0.1	4.0	0.0	149.2
	21-1321	0.296	36.1	12.1	0.6	33.0	2.0	122.0
	21-1322	0.318	52.7	8.5	0.4	16.0	1.0	165.7
	21-1323	0.315	41.1	13.0	0.5	32.0	1.0	130.6
	21-1324	0.314	56.9	14.2	1.0	25.0	2.0	181.4
	Mean	**0.30**	**41.84**	**9.1**	**0.5**	**21.7**	**1.2**	**141.9**
	SD	**0.03**	**10.08**	**4.1**	**0.3**	**9.57**	**0.63**	**37.45**
	21-1275	0.275	72.4	12.4	0.3	17.0	0.0	263.3
4.38 mg/kg-d	21-1276	0.381	80.9	11.7	0.6	15.0	1.0	212.5
	21-1277	0.273	57.9	11.0	0.3	19.0	0.0	212.0
	21-1278	0.274	72.1	10.7	0.4	15.0	1.0	263.1
	21-1279	0.286	28.0	3.3	0.3	12.0	1.0	97.8
	21-1280	0.247	38.8	6.2	0.5	16.0	1.0	157.3
	21-1291	0.298	36.9	7.3	0.5	20.0	1.0	123.9
	21-1292	0.276	31.6	3.8	0.1	12.0	0.0	114.4
	21-1313	0.254	18.1	1.6	0.1	9.0	0.0	71.3
	21-1314	0.327	37.7	8.9	0.5	24.0	1.0	115.4
	Mean	**0.29**	**47.44**	**7.7**	**0.4**	**15.9**	**0.6**	**163.1**
	SD	**0.04**	**21.68**	**3.9**	**0.2**	**4.38**	**0.52**	**69.75**
	21-1283	0.342	60.9	6.1	0.1	10.0	0.0	178.0
17.5 mg/kg-d	21-1284	0.315	74.4	9.5	0.4	13.0	0.0	236.2
	21-1289	0.269	72.0	5.6	0.2	8.0	0.0	267.7
	21-1290	0.269	39.2	11.0	0.6	28.0	2.0	145.5
	21-1301	0.240	34.4	2.0	0.1	6.0	0.0	143.2
	21-1302	0.289	34.5	5.8	0.5	17.0	1.0	119.3
	21-1305	0.318	28.5	3.1	0.3	11.0	1.0	89.7
	21-1306	0.257	37.9	5.9	0.2	16.0	1.0	147.4
	21-1311	0.317	24.9	6.7	0.5	27.0	2.0	78.6
	21-1312	0.270	21.1	5.1	0.2	24.0	1.0	78.0
	Mean	**0.29**	**42.78**	**6.1**	**0.3**	**16.0**	**0.8**	**148.4**
	SD	**0.03**	**19.30**	**2.6**	**0.2**	**7.92**	**0.79**	**64.10**
	21-1285	0.117	2.1	0.0	0.0	0.0	0.0	17.8
70 mg/kg-d	21-1286	0.139	1.0	0.1	0.0	11.0	0.0	7.0
	21-1287	0.136	4.4	0.5	0.1	10.0	2.0	32.2
	21-1288	0.195	9.9	0.7	0.1	7.0	1.0	50.8
	21-1303	0.179	7.5	0.0	0.0	0.0	0.0	42.0
	21-1304	0.258	11.1	0.9	0.1	8.0	1.0	43.0
	21-1307	0.193	3.8	0.0	0.0	0.0	0.0	19.8
	21-1308	0.172	17.3	0.8	0.1	5.0	1.0	100.5
	21-1319	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1320	0.237	13.3	2.9	0.2	22.0	1.0	56.2
	Mean	**0.18**	**7.82**	**0.7**	**0.1**	**7.0**	**0.7**	**41.0**
	SD	**0.05**	**5.50**	**0.9**	**0.1**	**7.09**	**0.71**	**27.60**

Table V-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Sperm Analysis Summary
Male Rats

Group	Animal ID	Cauda Wt. (grams)	Sample (Millions)	Motile Cells (Millions)	Progressive Cells (Millions)	Motile Cells (%)	Progressive Cells (%)	Sperm/Gram Cauda (Millions)
Corn Oil Control	**Mean**	0.305	41.5	8.0	0.4	21.3	1.2	136.3
	SD	0.0391	21.53	4.40	0.27	10.34	0.92	64.00
	N	10	10	10	10	10	10	10
1.09 mg/kg-d	**Mean**	0.30	41.84	9.1	0.5	21.7	1.2	141.9
	SD	0.03	10.08	4.1	0.3	9.57	0.63	37.45
	N	10	10	10	10	10	10	10
4.38 mg/kg-d	**Mean**	0.29	47.44	7.7	0.4	15.9	0.6	163.1
	SD	0.04	21.68	3.9	0.2	4.38	0.52	69.75
	N	10	10	10	10	10	10	10
17.5 mg/kg-d	**Mean**	0.29	42.78	6.1	0.3	16.0	0.8	148.4
	SD	0.03	19.30	2.6	0.2	7.92	0.79	64.10
	N	10	10	10	10	10	10	10
70 mg/kg-d	**Mean**	0.18*	7.82	0.7*	0.1*	7.0*	0.7	41.0*
	SD	0.05	5.50	0.9	0.1	7.09	0.71	27.60
	N	9	9	9	9	9	9	9

* $p<0.05$ compared to controls

Appendix W

Subchronic Clinical and Gross Pathological Observations

Abbreviations:

mg/kg-d: milligrams per kilogram per day

Table W-1
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Clinical Signs

Male Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
Corn Oil Control	21-1281	Normal	0	90
		Dried red material - nose	56	56
	21-1282	Normal	0	90
		Dried red material - nose	63	80
	21-1295	Normal	0	90
		Dried red material - nose	12	72
		Chromodaccoryhea - right eye	67	84
	21-1296	Normal	0	90
	21-1297	Normal	0	90
		Dried red material - nose	57	57
		Part of dose around mouth	85	85
	21-1298	Normal	0	90
		Dried red material - nose	35	35
	21-1299	Normal	0	54
		Red staining - right front paw	26	26
		Dried red material - nose	55	66
		Barbering - both front limbs	64	90
	21-1300	Normal	0	90
		Dried red material - nose	43	85
	21-1309	Normal	0	57
		Barbering - both front limbs	58	90
	21-1310	Normal	0	46
		Barbering - both front limbs	47	90

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.
Clinical signs may be observed intermittently between the first and last day observed.

Table W-1 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Clinical Signs

Male Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
1.09 mg/kg-d	21-1293	Normal	0	90
		Part of dose around mouth	32	32
	21-1294	Normal	0	90
		Part of dose around mouth	12	13
		Scab - back of neck	28	32
	21-1315	Normal	0	90
		Dried red material - nose	3	81
	21-1316	Normal	0	90
		Dried red material - nose	28	63
		Slight congested breathing	34	34
	21-1317	Normal	0	90
		Dried red material - nose	51	72
		Excitable	67	67
	21-1318	Normal	0	90
		Dried red material - nose	2	2
		Slight congested breathing	35	35
		Excitable	69	69
	21-1321	Normal	0	90
	21-1322	Normal	0	90
		Dried red material - nose	3	86
		Irritable	66	74
	21-1323	Normal	0	90
		Dried red material - nose	5	86
		Irritable	7	52
		Small amount of dose on chin	9	79
		Excitable	37	37
	21-1324	Normal	0	90
		Irritable	25	25
		Barbering - both front limbs	50	85
		Part of dose around mouth	52	65
		Dried red material - nose	64	64

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.
Clinical signs may be observed intermittently between the first and last day observed.

Table W-1 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Clinical Signs

Male Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
4.38 mg/kg-d	21-1275	Normal	0	90
		Scab - right shoulder	8	13
		Dried red material - nose	23	86
		Sore - right side of face	76	85
		Hair loss - right side of face	86	86
	21-1276	Normal	0	90
		Part of dose around mouth	32	32
		Dried red material - nose	60	89
	21-1277	Normal	0	90
		Scab - right shoulder	8	18
		Sore - right shoulder	17	17
		Dried red material - nose	83	83
	21-1278	Normal	0	90
		Dried red material - nose	52	73
	21-1279	Normal	0	90
		Dried red material - nose	71	71
	21-1280	Normal	0	90
		Dried red material - nose	14	80
		Irritable	70	70
		Excitable	83	83
	21-1291	Normal	0	90
		Dried red material - nose	1	71
		Scab - left side of face	62	67
		Sore - left side of face	65	79
		Sore - right side of face	75	78
		Sore - both sides of face	77	77
		Hair loss - right side of face	79	79
		Hair loss - both sides of face	81	81
		Hair loss - left side of face	84	87
	21-1292	Normal	0	90
		Dried red material - nose	1	83
		Barbering - right front limb	59	89
	21-1313	Normal	0	88
		Dried red material - nose	3	90
		Scab - behind right ear	47	62
		Scab - under left ear	63	66
		Scab - behind both ears	64	64
	21-1314	Normal	0	90
		Dried red material - nose	3	3

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.
Clinical signs may be observed intermittently between the first and last day observed.

Table W-1 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Clinical Signs

Male Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
17.5 mg/kg-d	21-1283	Normal	0	90
		Dried red material - nose	2	89
		Part of dose around mouth	15	15
	21-1284	Normal	0	90
		Dried red material - nose	2	85
		Irritable	10	10
	21-1289	Normal	0	90
	21-1290	Normal	0	90
		Dried red material - nose	21	74
	21-1301	Normal	0	90
		Dried red material - nose	65	65
	21-1302	Normal	0	90
	21-1305	Normal	0	88
		Small amount of dose on chin	1	1
		Dried red material - nose	58	90
		Dried red material - front paws	72	72
	21-1306	Normal	0	90
		Irritable	48	74
		Dried red material - nose	58	65
		Part of dose around mouth	63	63
	21-1311	Normal	0	90
		Scab - right shoulder	12	15
		Dried red material - nose	43	85
		Barbering - right front limb	62	89
		Barbering - both front limbs	75	75
	21-1312	Normal	0	47
		Dried red material - nose	6	8
		Scab - right shoulder	11	21
		Hair loss - right side of face	48	89
		Sore - right side of face	50	78
		Hair loss - left side of face	50	77
		Sore - both sides of face	51	75
		Scab - left side of face	62	65
		Hair loss - both sides of face	64	81
		Scabs - both sides of face	66	68
		Hair loss - left abdominal area	70	90
		Sore - left abdominal area	71	76
		Hair loss - left shoulder	75	75

[a] Represents the first day the clinical sign was observed.

[b] Represents the last day the clinical sign was observed.

Clinical signs may be observed intermittently between the first and last day observed.

Table W-1 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Clinical Signs

Male Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
70 mg/kg-d	21-1285	Normal	0	90
		Dried red material - nose	2	89
		Barbering - both front limbs	64	74
		Excitable	64	64
		Dried red material - both front limbs	71	71
		Slightly lethargic	78	78
	21-1286	Normal	0	90
		Dried red material - nose	55	87
		Excitable	83	83
	21-1287	Normal	0	90
		Dried red material - nose	51	60
		Excitable	66	66
		Dried red material - both front paws	77	77
	21-1288	Normal	0	88
		Dried red material - nose	12	90
		Rough haircoat	73	73
		Irritable	76	76
		Part of dose around mouth	77	77
		Slight congested breathing	77	77
	21-1303	Normal	0	85
		Irritable	7	7
		Dried red material - nose	43	90
		Dried red material - front paws	53	53
		Rough haircoat	75	90
		Seizure activity	86	86
	21-1304	Normal	0	1
		Dried red material - nose	52	85
		Swollen back left paw	63	70
	21-1307	Normal	0	84
		Part of dose around mouth	10	10
		Dried red material - nose	15	90
		Irritable	46	46
		Seizure activity	70	70
		Dried red material - front paws	72	72
		Rough haircoat	79	81
	21-1308	Normal	0	90
		Irritable	5	74
		Dried red material - nose	15	88
		Rough haircoat	35	81
		Part of dose around mouth	63	73
		Salivation	66	66
		Disoriented	70	70
	21-1319	Normal	0	71
		Dried red material - nose	10	73
		Squinting	72	73
		Shaking	72	72
		Dried red mateirial - front paws	73	73
		Lethargic	73	73
		Rough haircoat	73	73
		Hunched posture	74	74
		Squinting	74	74
		Twitching	74	74
		Euthanized	74	74
	21-1320	Normal	0	90
		Irritable	5	87
		Dried red material - nose	8	88
		Scab between shoulder blades	13	14
		Rough haircoat	84	84

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.
Clinical signs may be observed intermittently between the first and last day observed.

Table W-2
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Clinical Signs

Female Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
Corn Oil Control	21-1325	Normal	0	90
		Dried red material - nose	40	80
	21-1326	Normal	0	42
		Hair loss- back of neck	40	47
		Hair loss - head and back of neck	48	90
		Hair loss - side of face	53	54
		Hair loss - both sides of face	55	55
		Hair loss - head	66	82
	21-1331	Normal	0	47
		Excitable	44	44
		Barbering - both front limbs	48	90
	21-1332	Normal	0	90
		Dried red material - nose	77	77
	21-1345	Normal	0	90
	21-1346	Normal	0	90
		Dried red material - nose	76	76
	21-1347	Normal	0	90
		Dried red material - nose	16	83
	21-1348	Normal	0	90
	21-1363	Normal	0	90
	21-1364	Normal	0	90

[a] Represents the first day the clinical sign was observed.

[b] Represents the last day the clinical sign was observed.

Clinical signs may be observed intermittently between the first and last day observed.

Table W-2 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Clinical Signs

Female Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
1.09 mg/kg-d	21-1333	Normal	0	90
		Small amount of dose around mouth	20	21
		Sores - back of neck	20	45
		Scab - back of neck	21	25
		Barbering - right front limb	86	86
		Dried red material - nose	86	86
	21-1334	Normal	0	90
		Irritable	7	7
		Dried red material - nose	51	51
	21-1335	Normal	0	90
	21-1336	Normal	0	90
	21-1341	Normal	0	90
		Dried red material - nose	74	89
	21-1342	Normal	0	90
		Irritable	4	4
	21-1371	Normal	0	86
		Excitable	26	26
		Barbering - right front limb	53	67
		Hair loss - left side of face	58	88
		Barbering - left front limb	62	62
		Hair loss - both sides of neck	67	90
		Hair loss - abdomen	67	76
		Barbering - both front limbs	74	74
	21-1372	Normal	0	55
		Irritable	2	62
		Excitable	26	29
		Barbering - left front limb	49	57
		Barbering - both front limbs	58	90
	21-1373	Normal	0	90
	21-1374	Normal	1	90
		Scab - right corner of mouth	0	0
		Irritable	3	63
		Excitable	26	60
		Bright yellow urine staining	47	47

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.
Clinical signs may be observed intermittently between the first and last day observed.

Table W-2 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Clinical Signs

Female Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
4.38 mg/kg-d	21-1339	Normal	0	90
	21-1340	Normal	0	90
	21-1351	Normal	0	51
		Barbering - both front limbs	44	90
		Hair loss - right side of neck	52	65
		Barbering - right front limb	60	60
		Hair loss - head and neck	61	61
		Hair loss - right shoulder	62	80
		Hair loss - both shoulders	66	90
		Hair loss - head	73	73
		Barbering - left front limb	79	82
	21-1352	Normal	0	61
		Sore - right corner of mouth	5	5
		Barbering - both front limbs	42	90
		Barbering - left front limb	55	55
		Hair loss - right abdomen	67	90
	21-1355	Normal	0	90
	21-1356	Normal	0	90
	21-1357	Normal	0	90
		Dried red material - nose	39	77
	21-1358	Normal	0	90
		Dried red material - nose	81	81
	21-1359	Normal	0	84
		Barbering - left front limb	70	90
		Barbering - both front limbs	77	77
	21-1360	Normal	0	90
		Excitable	7	7
		Dried red material - nose	51	52

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.
Clinical signs may be observed intermittently between the first and last day observed.

Table W-2 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Clinical Signs

Female Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
17.5 mg/kg-d	21-1327	Normal	0	90
		Dried red material - nose	38	69
		Excitable	40	40
		Irritable	46	76
	21-1328	Normal	0	90
	21-1329	Normal	0	90
		Small amount of dose around mouth	29	29
		Dried red material - nose	42	43
	21-1330	Normal	0	90
		Dried red material - nose	3	81
		Irritable	4	4
	21-1343	Normal	0	44
		Dried red material - nose	18	50
		Small mass - left side	42	50
		Mass - left side	47	76
		Mass - left side with minor bleeding	77	77
		Mass - left side with open wound	78	78
		Euthanized due to mass with wound	78	78
	21-1344	Normal	0	90
		Irritable	3	78
	21-1353	Normal	0	90
		Dried red material - nose	52	80
	21-1354	Normal	0	90
	21-1367	Normal	0	90
		Dried red material - nose	57	57
	21-1368	Normal	0	84
		Irritable	7	7
		Excitable	11	42
		Hair loss - right side of face	51	90
		Sore - right side of face	53	55

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.
Clinical signs may be observed intermittently between the first and last day observed.

Table W-2 (con't)
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Clinical Signs

Female Rats

Group	Animal ID	Observation	First Day[a]	Last Day[b]
70 mg/kg-d	21-1337	Normal	0	89
		Dried red material - nose	9	90
		Small amount of dose around mouth	19	19
		Excitable	29	39
		Irritable	71	71
	21-1338	Normal	0	89
		Irritable	5	5
		Dried red material - nose	7	90
		Small amount of dose around mouth	80	80
	21-1349	Normal	0	89
		Irritable	3	72
		Dried red material - nose	16	90
	21-1350	Normal	0	90
		Dried red material - nose	49	82
		Excitable	75	75
		Irritable	78	78
	21-1361	Normal	0	89
		Barbering - both front limbs	40	90
		Dried red material - nose	40	62
		Irritable	56	56
		Seizure activity	89	89
	21-1362	Normal	0	90
		Dried red material - nose	10	89
		Barbering - both front limbs	51	82
		Chromodaccoryhea- left eye	52	55
		Barbering - right front limb	63	81
	21-1365	Normal	0	87
		Dried red material - nose	1	90
		Excitable	28	28
		Irritable	75	75
		Seizure activity	88	90
	21-1366	Normal	0	90
		Dried red material - nose	40	87
		Small amount of dose around mouth	46	46
	21-1369	Normal	0	57
		Excitable	35	35
		Dried red material - nose	41	61
		Mass - anterior neck	58	60
		Mass - anterior neck with scab	59	62
		Euthanized due to mass under neck	62	62
	21-1370	Normal	0	87
		Seizure activity	35	81
		Dried red material - nose	36	90
		Slightly lethargic	88	88

[a] Represents the first day the clinical sign was observed.
[b] Represents the last day the clinical sign was observed.
Clinical signs may be observed intermittently between the first and last day observed.

Table W-3
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Gross Necropsy Observations
Male Rats

Group	Animal ID	Gross Observations
	21-1281	No gross lesions recognized
Corn Oil	21-1282	No gross lesions recognized
Control	21-1295	No gross lesions recognized
	21-1296	No gross lesions recognized
	21-1297	No gross lesions recognized
	21-1298	No gross lesions recognized
	21-1299	No gross lesions recognized
	21-1300	No gross lesions recognized
	21-1309	No gross lesions recognized
	21-1310	No gross lesions recognized
	21-1293	No gross lesions recognized
1.09 mg/kg-d	21-1294	No gross lesions recognized
	21-1315	No gross lesions recognized
	21-1316	No gross lesions recognized
	21-1317	No gross lesions recognized
	21-1318	Numerous 1 mm red dots on thymus surface
	21-1321	No gross lesions recognized
	21-1322	No gross lesions recognized
	21-1323	No gross lesions recognized
	21-1324	No gross lesions recognized
	21-1275	No gross lesions recognized
4.38 mg/kg-d	21-1276	No gross lesions recognized
	21-1277	No gross lesions recognized
	21-1278	No gross lesions recognized
	21-1279	No gross lesions recognized
	21-1280	No gross lesions recognized
	21-1291	No gross lesions recognized
	21-1292	No gross lesions recognized
	21-1313	No gross lesions recognized
	21-1314	2-3 mm yellow/white mass on tip of liver next to a ligament
	21-1283	No gross lesions recognized
17.5 mg/kg-d	21-1284	No gross lesions recognized
	21-1289	No gross lesions recognized
	21-1290	No gross lesions recognized
	21-1301	No gross lesions recognized
	21-1302	No gross lesions recognized
	21-1305	No gross lesions recognized
	21-1306	Pancreas appears slightly swollen and mottled brown and yellow
	21-1311	2-3 mm yellow/white mass on edge of liver
	21-1312	Patches of groomed hair on left side of abdomen, thorax, and face
	21-1285	Numerous 1-2 mm red spots of hemorrhage on thymus
70 mg/kg-d	21-1286	No gross lesions recognized
	21-1287	No gross lesions recognized
	21-1288	No gross lesions recognized
	21-1303	Unkempt haircoat; Porphyrin staining around nose; Mottled brown mesenteric lymph nodes; Slight gas in large intestine; Flaccid testis
	21-1304	Unkempt haircoat; No digesta in small intestine (only fluid); Pancreas is slightly swollen, mottled brown/yellow; Rectum is slightly swollen with 4 small red dots on mucosal surface
	21-1307	Numerous red 1 mm dots on thymus surface; Testis flaccid bilaterally
	21-1308	Numerous red 1 mm dots on thymus surface
	21-1319	Early euthanasia; Dried red material on front paws and nose; Rough exterior spleen surface; Liver mottled throughout; Stomach has dark red areas on interior surface; Large intestine has dark red matter; Cecum has pink content that lacks consistency; Pancreas and mesenteric lymph nodes were bright white
	21-1320	No gross lesions recognized

Table W-4
Protocol No. 38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Gross Necropsy Observations
Female Rats

Group	Animal ID	Gross Observations
	21-1325	Gas filled cecum; Small intestines appear flaccid and slightly reddened
Corn Oil	21-1326	Liver yellow in color
Control	21-1331	Hair loss (grooming) on both front legs
	21-1332	No gross lesions recognized
	21-1345	No gross lesions recognized
	21-1346	No gross lesions recognized
	21-1347	No gross lesions recognized
	21-1348	No gross lesions recognized
	21-1363	No gross lesions recognized
	21-1364	No gross lesions recognized
	21-1333	No gross lesions recognized
1.09 mg/kg-d	21-1334	No gross lesions recognized
	21-1335	No gross lesions recognized
	21-1336	Slightly dilated and reddened small intestines
	21-1341	No gross lesions recognized
	21-1342	No gross lesions recognized
	21-1371	Less overall body fat than usual
	21-1372	Slightly yellowish liver; 2 mm white mass on medial edge of liver lobe
	21-1373	No gross lesions recognized
	21-1374	No gross lesions recognized
	21-1339	No gross lesions recognized
4.38 mg/kg-d	21-1340	No gross lesions recognized
	21-1351	No gross lesions recognized
	21-1352	Slight grooming on right abdomen
	21-1355	No gross lesions recognized
	21-1356	No gross lesions recognized
	21-1357	No gross lesions recognized
	21-1358	No gross lesions recognized
	21-1359	No gross lesions recognized
	21-1360	No gross lesions recognized
	21-1327	No gross lesions recognized
17.5 mg/kg-d	21-1328	No gross lesions recognized
	21-1329	Yellowish liver
	21-1330	Slightly yellow liver
	21-1343	Early euthanasia; 3 x 2.5 x 2 cm multilobed dermal/subdermal freely moveable mass on left chest wall below elbow; 1 cm area of ulceration with minimal hemorrhage on mass (mammary fibroadenoma); Jejunum pale with light yellow, normal contents; 7 mm dark red/orange mass adjacent to terminal esophagus (possibly lymph node); Brain/cerebrum slightly yellow in color
	21-1344	No gross lesions recognized
	21-1353	No gross lesions recognized
	21-1354	No gross lesions recognized
	21-1367	Small intestines flaccid and slightly reddened
	21-1368	No gross lesions recognized
	21-1337	Slightly yellowish liver; Both kidneys are brown to gray in color; Flaccid intestines;
70 mg/kg-d		Noticeably less fat than other animals on study
	21-1338	Slightly yellow liver; Both kidneys are brown to gray in color; Flaccid intestines
	21-1349	Less fat than usual; Brownish-yellow liver
	21-1350	No gross lesions recognized
	21-1361	Thymus has one discolored side that is pink/red
	21-1362	No gross lesions recognized
	21-1365	Thymus is half normal size and both lobes discolored dark red
	21-1366	No gross lesions recognized
	21-1369	Early euthanasia; 2x2x1 cm bilobed firm mass on right ventral neck; 7 mm diameter ulceration of mass through skin with scab; Mass was subcutaneous on dissection and not attached or affecting adjacent tissues; Right side of mass contained bloody fluid; Right cervical lymph node enlarged 2-3x normal
	21-1370	Less body fat than usual

Appendix X

Subchronic Urinalysis

Abbreviations:

mg/kg-d: milligrams per kilogram per day
ml: milliliter
mg/dL: milligrams per deciliter
(f): animal died on study
sl.: slightly
neg.: negative
mod.: moderate
pos.: positive
hem.: hemolyzed
non-hem.: non-hemolyzed

Table X-1
Protocol No.38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Urinalysis
Male Rats

Group	Animal ID	Volume (ml)	Color	Appearance	Water Consumed (ml)	Glucose	Bilirubin	Ketone	Specific Gravity	Blood	pH	Protein (mg/dL)	Urobilinogen (mg/dL)	Nitrite	Leukocytes
	21-1281	5	yellow	clear	10.0	neg.	neg.	neg.	1.035	hem. trace	6.5	30	0.2	neg.	neg.
Corn Oil	21-1282	3	dark yellow	clear	5.0	neg.	mod.	mod. >	1.035	neg.	7.0	30	0.2	neg.	neg.
Control	21-1295	4.75	dark yellow	clear	5.0	neg.	neg.	neg.	1.033	mod.	6.5	30	0.2	neg.	neg.
	21-1296	5.25	dark yellow	clear	10.0	neg.	neg.	small	1.035	neg.	7.0	30	0.2	neg.	neg.
	21-1297	2	yellow	clear	5.0	neg.	neg.	neg.	1.030	neg.	6.5	30	0.2	neg.	neg.
	21-1298	3.5	dark yellow	sl. cloudy	3.0	neg.	small	trace >	1.035	neg.	6.5	30	0.2	neg.	neg.
	21-1299	3	yellow	clear	10.0	neg.	neg.	neg. >	1.035	neg.	6.0	30	0.2	neg.	neg.
	21-1300	12	light yellow	clear	12.0	neg.	neg.	neg.	1.015	neg.	7.0	trace	0.2	neg.	neg.
	21-1309	8	yellow	clear	15.0	neg.	small	small	1.025	neg.	7.0	30	0.2	neg.	trace
	21-1310	1.75	gold	sl. cloudy	5.0	neg.	mod.	trace >	1.035	neg.	6.0	100	0.2	neg.	neg.
	Mean	**4.8**			**8.0**				**1.0313**		**6.60**		**0.20**		
	SD	**3.12**			**3.92**				**0.00660**		**0.394**		**0.000**		
	21-1293	3.75	dark yellow	clear	10.0	neg.	small	trace >	1.035	neg.	6.5	30	0.2	neg.	neg.
1.09 mg/kg-d	21-1294	13.5	light yellow	clear	20.0	neg.	neg.	trace	1.019	neg.	6.0	trace	0.2	neg.	neg.
	21-1315	4	dark yellow	clear	2.5	neg.	neg.	small	1.026	neg.	7.5	30	0.2	neg.	neg.
	21-1316	13	straw	clear	15.0	neg.	neg.	trace	1.017	neg.	6.5	trace	0.2	neg.	neg.
	21-1317	11	light yellow	clear	12.0	neg.	neg.	neg.	1.022	neg.	7.0	trace	0.2	neg.	neg.
	21-1318	10	light yellow	clear	12.0	neg.	neg.	neg.	1.018	neg.	7.0	trace	0.2	neg.	neg.
	21-1321	3.5	yellow	clear	10.0	neg.	neg.	neg.	1.033	non-hem. trace	6.5	30	0.2	neg.	neg.
	21-1322	8	yellow	sl. cloudy	2.0	neg.	neg.	small	1.026	neg.	7.0	30	0.2	neg.	neg.
	21-1323	8.5	yellow	sl. cloudy	7.0	neg.	neg.	neg.	1.029	neg.	7.0	100	0.2	neg.	trace
	21-1324	6	yellow	clear	2.0	neg.	neg.	neg. >	1.035	hem. trace	6.5	30	0.2	neg.	neg.
	Mean	**8.1**			**9.3**				**1.0260**		**6.75**		**0.20**		
	SD	**3.75**			**5.97**				**0.00691**		**0.425**		**0.000**		
	21-1275	13	light yellow	clear	20.0	neg.	neg.	trace	1.018	small	6.5	trace	0.2	neg.	neg.
4.38 mg/kg-d	21-1276	11.5	light yellow	clear	10.0	neg.	neg.	trace	1.018	small	6.5	trace	0.2	neg.	neg.
	21-1277	5.5	yellow	clear	5.0	neg.	neg.	neg.	1.028	neg.	6.5	trace	0.2	neg.	neg.
	21-1278	7.5	light yellow	clear	10.0	neg.	neg.	trace	1.020	neg.	6.5	30	0.2	neg.	neg.
	21-1279	6	yellow	sl. cloudy	10.0	neg.	neg.	trace	1.027	neg.	7.5	30	0.2	neg.	neg.
	21-1280	4.5	yellow	clear	10.0	neg.	neg.	neg.	1.030	neg.	6.5	trace	0.2	neg.	neg.
	21-1291	7	yellow	clear	10.0	neg.	neg.	neg.	1.027	neg.	6.5	trace	0.2	neg.	neg.
	21-1292	5	dark yellow	clear	10.0	neg.	neg.	trace >	1.035	neg.	6.0	30	0.2	neg.	neg.
	21-1313	3.5	dark yellow	clear	5.0	neg.	neg.	trace >	1.035	neg.	6.5	30	0.2	neg.	neg.
	21-1314	8	yellow	clear	10.0	neg.	neg.	neg.	1.026	neg.	6.5	trace	0.2	neg.	neg.
	Mean	**7.2**			**10.0**				**1.0264**		**6.55**		**0.20**		
	SD	**3.04**			**4.08**				**0.00620**		**0.369**		**0.000**		
	21-1283	9	yellow	clear	15.0	neg.	neg.	trace	1.022	neg.	6.5	trace	0.2	neg.	neg.
17.5 mg/kg-d	21-1284	1.75	gold	clear	10.0	neg.	mod.	mod. >	1.035	neg.	7.0	30	0.2	pos.	neg.
	21-1289	5.5	light yellow	clear	15.0	neg.	neg.	neg.	1.019	neg.	7.0	trace	0.2	pos.	neg.
	21-1290	7.75	yellow	clear	10.0	neg.	small	small	1.033	neg.	6.0	trace	0.2	neg.	neg.
	21-1301	9.75	straw	clear	15.0	neg.	neg.	neg.	1.011	hem. trace	8.0	trace	0.2	pos.	neg.
	21-1302	8.75	light yellow	clear	10.0	neg.	neg.	neg.	1.019	neg.	7.5	trace	0.2	pos.	neg.
	21-1305	10	light yellow	clear	15.0	neg.	neg.	neg.	1.018	neg.	7.0	trace	0.2	pos.	neg.
	21-1306	9	light yellow	clear	10.0	neg.	neg.	neg.	1.026	neg.	7.0	30	0.2	pos.	trace
	21-1311	9.5	yellow	clear	15.0	neg.	neg.	neg.	1.019	neg.	6.5	trace	0.2	neg.	neg.
	21-1312	5	yellow	clear	5.0	neg.	neg.	neg.	1.033	neg.	6.5	30	0.2	neg.	neg.
	Mean	**7.6**			**12.0**				**1.0235**		**6.90**		**0.20**		
	SD	**2.68**			**3.50**				**0.00795**		**0.568**		**0.000**		
	21-1285	22	straw	clear	20.0	neg.	neg.	neg.	1.010	neg.	7.5	trace	0.2	pos.	neg.
70 mg/kg-d	21-1286	31	straw	clear	30.0	neg.	neg.	neg.	1.007	neg.	7.0	neg.	0.2	pos.	neg.
	21-1287	6	gold	clear	5.0	neg.	small	neg.	1.033	neg.	6.0	100	0.2	pos.	trace
	21-1288	11.5	yellow	sl. cloudy	5.0	neg.	neg.	trace	1.023	neg.	6.5	30	0.2	pos.	neg.
	21-1303	13.5	yellow	clear	10.0	neg.	neg.	neg.	1.022	neg.	7.0	trace	0.2	pos.	trace
	21-1304	28	straw	clear	30.0	neg.	neg.	trace	1.011	neg.	7.5	trace	0.2	pos.	trace
	21-1307	18	straw	clear	10.0	neg.	neg.	neg.	1.014	neg.	7.5	trace	0.2	pos.	neg.
	21-1308	6	dark yellow	sl. cloudy	2.5	neg.	neg.	neg.	1.025	neg.	7.5	30	0.2	pos.	trace
	21-1319	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1320	16	yellow	clear	15.0	neg.	neg.	neg.	1.019	neg.	6.5	trace	0.2	pos.	neg.
	Mean	**16.9***			**14.2**				**1.0182***		**7.00**		**0.20**	*	*
	SD	**8.86**			**10.46**				**0.00841**		**0.559**		**0.000**		

* p<0.05 compared to controls

Table X-2
Protocol No.38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Urinalysis
Female Rats

Group	Animal ID	Volume (ml)	Color	Appearance	Water Consumed (ml)	Glucose	Bilirubin	Ketone	Specific Gravity	Blood	pH	Protein (mg/dL)	Urobilinogen (mg/dL)	Nitrite	Leukocytes
	21-1325	3.5	light yellow	clear	15.0	neg.	neg.	neg.	1.026	neg.	6.0	trace	0.2	neg.	neg.
Corn Oil	21-1326	9	light yellow	clear	10.0	neg.	neg.	neg.	1.020	neg.	7.0	trace	0.2	neg.	neg.
Control	21-1331	4.5	bright yellow	clear	10.0	neg.	neg.	neg.	1.034	neg.	6.0	trace	0.2	neg.	neg.
	21-1332	4.5	yellow	clear	10.0	neg.	neg.	neg.	1.025	neg.	6.0	trace	0.2	neg.	neg.
	21-1345	3.75	bright yellow	clear	8.0	neg.	neg.	neg. >	1.035	neg.	6.0	trace	0.2	neg.	neg.
	21-1346	3	yellow	clear	8.0	neg.	neg.	neg. >	1.035	neg.	6.0	trace	0.2	neg.	neg.
	21-1347	7	light yellow	clear	10.0	neg.	neg.	neg.	1.019	neg.	6.5	neg.	0.2	neg.	neg.
	21-1348	1.5	dark yellow	clear	5.0	neg.	small	neg. >	1.035	neg.	6.0	30	0.2	neg.	neg.
	21-1363	10.25	straw	clear	5.0	neg.	neg.	neg.	1.017	neg.	7.0	neg.	0.2	neg.	neg.
	21-1364	2	bright yellow	clear	10.0	neg.	small	neg. >	1.035	neg.	6.0	trace	0.2	neg.	neg.
	Mean	**4.9**			**9.1**				**1.0281**		**6.25**		**0.20**		
	SD	**2.93**			**2.88**				**0.00753**		**0.425**		**0.000**		
	21-1333	4	yellow	clear	5.0	neg.	neg.	neg.	1.032	neg.	6.0	trace	0.2	neg.	neg.
1.09 mg/kg-d	21-1334	4.25	yellow	clear	5.0	neg.	neg.	neg.	1.031	neg.	6.0	trace	0.2	neg.	neg.
	21-1335	1.5	dark yellow	clear	10.0	neg.	small	neg. >	1.035	neg.	6.0	30	0.2	neg.	neg.
	21-1336	4.5	light yellow	clear	10.0	neg.	neg.	neg.	1.024	neg.	6.5	trace	0.2	neg.	neg.
	21-1341	12.25	straw	clear	15.0	neg.	neg.	neg.	1.011	neg.	7.5	neg.	0.2	neg.	neg.
	21-1342	7	yellow	clear	10.0	neg.	neg.	neg.	1.027	neg.	6.5	trace	0.2	neg.	neg.
	21-1371	10.25	straw	clear	10.0	neg.	neg.	neg.	1.013	neg.	7.0	neg.	0.2	neg.	neg.
	21-1372	7	light yellow	clear	10.0	neg.	neg.	neg.	1.023	neg.	6.5	neg.	0.2	neg.	neg.
	21-1373	3.25	bright yellow	clear	5.0	neg.	neg.	neg. >	1.035	neg.	6.5	trace	0.2	neg.	neg.
	21-1374	3.25	bright yellow	sl. cloudy	5.0	neg.	neg.	neg. >	1.035	neg.	6.5	30	0.2	neg.	neg.
	Mean	**5.7**			**8.5**				**1.0266**		**6.50**		**0.20**		
	SD	**3.38**			**3.37**				**0.00887**		**0.471**		**0.000**		
	21-1339	2	dark yellow	clear	5.0	neg.	small	neg. >	1.035	neg.	6.0	30	0.2	neg.	neg.
4.38 mg/kg-d	21-1340	2.25	dark yellow	clear	5.0	neg.	neg.	neg. >	1.035	neg.	6.0	30	0.2	neg.	neg.
	21-1351	1.5	straw	clear	5.0	neg.	neg.	neg.	1.034	neg.	6.5	neg.	0.2	neg.	neg.
	21-1352	3.5	yellow	clear	5.0	neg.	neg.	neg.	1.027	neg.	6.5	trace	0.2	neg.	neg.
	21-1355	5.5	yellow	clear	10.0	neg.	neg.	neg.	1.023	neg.	6.5	trace	0.2	neg.	neg.
	21-1356	1.25	bright yellow	clear	2.0	neg.	neg.	neg. >	1.035	neg.	6.0	30	0.2	neg.	neg.
	21-1357	1.25	bright yellow	clear	8.0	neg.	small	neg. >	1.035	neg.	6.0	100	0.2	neg.	neg.
	21-1358	1.5	bright yellow	clear	2.0	neg.	small	neg. >	1.035	neg.	6.0	30	0.2	neg.	neg.
	21-1359	3.5	yellow	clear	2.0	neg.	neg.	neg.	1.028	neg.	6.5	trace	0.2	neg.	neg.
	21-1360	2.75	bright yellow	clear	2.0	neg.	neg.	neg. >	1.035	neg.	6.5	trace	0.2	neg.	neg.
	Mean	**2.5**			**4.6***				**1.0322**		**6.25**		**0.20**		
	SD	**1.35**			**2.76**				**0.00447**		**0.264**		**0.000**		
	21-1327	1.5	dark yellow	sl. cloudy	10.0	neg.	small	neg. >	1.035	neg.	6.0	30	0.2	neg.	neg.
17.5 mg/kg-d	21-1328	4	light yellow	clear	10.0	neg.	neg.	neg.	1.032	neg.	6.0	trace	0.2	neg.	neg.
	21-1329	8	light yellow	clear	10.0	neg.	neg.	neg.	1.022	neg.	7.0	trace	0.2	neg.	neg.
	21-1330	5.25	yellow	clear	8.0	neg.	neg.	neg.	1.028	neg.	6.5	trace	0.2	neg.	neg.
	21-1343	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1344	6	yellow	clear	10.0	neg.	neg.	neg.	1.022	neg.	6.5	trace	0.2	neg.	neg.
	21-1353	4.25	bright yellow	clear	2.0	neg.	neg.	neg.	1.032	neg.	6.5	trace	0.2	neg.	neg.
	21-1354	20	light yellow	clear	20.0	neg.	neg.	neg.	1.011	neg.	7.5	neg.	0.2	neg.	neg.
	21-1367	11	straw	clear	12.0	neg.	neg.	neg.	1.014	neg.	6.5	neg.	0.2	neg.	neg.
	21-1368	5.5	yellow	clear	10.0	neg.	neg.	neg.	1.026	neg.	6.5	trace	0.2	neg.	neg.
	Mean	**7.3**			**10.2**				**1.0247**		**6.56**		**0.20**		
	SD	**5.46**			**4.63**				**0.00823**		**0.464**		**0.000**		
	21-1337	16	straw	clear	30.0	neg.	neg.	neg.	1.007	neg.	7.0	neg.	0.2	pos.	neg.
70 mg/kg-d	21-1338	8	bright yellow	clear	15.0	neg.	neg.	neg.	1.018	neg.	6.5	trace	0.2	pos.	neg.
	21-1349	4.75	dark yellow	clear	5.0	neg.	neg.	neg.	1.030	neg.	7.0	30	0.2	pos.	neg.
	21-1350	10.5	yellow	clear	10.0	neg.	neg.	neg.	1.015	neg.	7.5	trace	0.2	pos.	neg.
	21-1361	8	yellow	clear	5.0	neg.	neg.	neg.	1.017	neg.	7.5	trace	0.2	pos.	trace
	21-1362	17	straw	clear	15.0	neg.	neg.	neg.	1.009	neg.	8.0	trace	0.2	pos.	trace
	21-1365	21	straw	clear	27.0	neg.	neg.	neg.	1.008	neg.	7.0	neg.	0.2	pos.	neg.
	21-1366	22	straw	clear	20.0	neg.	neg.	neg.	1.007	neg.	7.5	neg.	0.2	pos.	neg.
	21-1369	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)	(f)
	21-1370	7	bright yellow	clear	8.0	neg.	neg.	neg.	1.022	neg.	7.0	trace	0.2	pos.	neg.
	Mean	**12.7***			**15.0**				**1.0148***		**7.22***		**0.20**	*	
	SD	**6.42**			**9.14**				**0.00790**		**0.441**		**0.000**		

* p<0.05 compared to controls

Appendix Y

Subchronic Thyroid Hormone Analysis

Abbreviations:

mg/kg-d: milligrams per kilogram per day
ND: values were outside of the calibration curve
(f): animal died on study
picograms/ml: picograms per milliliter

Table Y-1
Protocol No.38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Thyroid Hormone Data
Male Rats

Group	Animal ID	Plate Number	T_3 (picograms/ml)	T_4 (picograms/ml)	TSH (picograms/ml)
	21-1281	1	15574.33	724865.73	2303.25
Corn Oil	21-1282	1	24801.39	730216.27	2058.93
Control	21-1295	2	24432.84	837316.04	1120.14
	21-1296	1	21494.28	711214.54	6393.77
	21-1297	3	18163.46	668734.05	634.96
	21-1298	1	25646.21	692026.15	3038.22
	21-1299	1	22108.57	751676.92	2471.11
	21-1300	1	23301.34	866756.87	3017.69
	21-1309	1	25107.06	770087.73	1935.80
	21-1310	3	18019.77	782501.15	2693.93
		Mean	**21864.93**	**753539.55**	**2566.78**
		SD	**3501.496**	**62437.692**	**1550.876**
	21-1293	3	17696.40	670303.89	2423.25
1.09 mg/kg-d	21-1294	1	19963.70	754577.10	1794.01
	21-1315	3	22570.53	781355.49	1329.33
	21-1316	2	27010.78	903810.42	997.97
	21-1317	2	21545.73	870033.17	ND
	21-1318	2	21464.13	979567.01	1139.07
	21-1321	1	25637.89	802907.26	1498.82
	21-1322	1	23300.01	802122.36	3483.49
	21-1323	1	23258.61	703125.90	2021.63
	21-1324	2	28722.04	878407.19	2146.71
		Mean	**23116.98**	**814620.98**	**1870.48**
		SD	**3296.667**	**94613.249**	**769.705**
	21-1275	1	15607.92	701304.63	1680.13
4.38 mg/kg-d	21-1276	1	17127.77	698775.23	6983.80
	21-1277	1	25993.01	735241.00	1816.40
	21-1278	1	14137.97	687720.89	1971.29
	21-1279	2	20393.08	773082.42	3920.37
	21-1280	1	19203.14	752685.53	2279.00
	21-1291	1	12314.06	653849.72	595.00
	21-1292	3	20499.84	761689.02	2986.32
	21-1313	2	22235.50	846695.08	6288.21
	21-1314	2	22740.31	872176.80	2703.26
		Mean	**19025.26**	**748322.03**	**3122.38**
		SD	**4228.714**	**69331.895**	**2054.091**
	21-1283	1	15498.64	671384.98	4011.27
17.5 mg/kg-d	21-1284	3	18853.26	689160.78	668.10
	21-1289	2	20817.64	728662.88	1884.72
	21-1290	1	30075.61	820379.59	ND
	21-1301	1	18841.27	783512.35	1853.75
	21-1302	2	20908.26	682735.23	2171.57
	21-1305	2	21434.62	787735.85	968.84
	21-1306	2	29473.83	838042.35	1500.79
	21-1311	1	23033.26	732146.72	1638.97
	21-1312	2	47572.93	743371.62	1912.93
		Mean	**24650.93**	**747713.24**	**1845.66**
		SD	**9255.019**	**58141.351**	**943.353**
	21-1285	3	28234.72	624620.18	3138.66
70 mg/kg-d	21-1286	1	19451.32	624876.15	14060.72
	21-1287	2	20797.90	763309.15	4098.23
	21-1288	2	20853.87	796803.62	5461.34
	21-1303	1	33758.00	464977.94	17719.42
	21-1304	1	18033.31	656552.56	6991.72
	21-1307	2	31252.31	408544.92	11799.44
	21-1308	1	27044.38	720691.25	10235.73
	21-1319	(f)	(f)	(f)	(f)
	21-1320	3	24035.49	725302.08	2489.39
		Mean	**24829.03**	**642853.09**	**8443.85***
		SD	**5537.088**	**131553.324**	**5309.724**

* $p<0.05$ compared to controls

Table Y-2
Protocol No.38-18-12-01
Subchronic Oral Toxicity of FOX-7 in Rats

90-Day Individual Thyroid Hormone Data
Female Rats

Group	Animal ID	Plate Number	T_3 (picograms/ml)	T_4 (picograms/ml)	TSH (picograms/ml)
	21-1325	2	18680.93	484027.18	ND
Corn Oil	21-1326	2	34890.29	452702.63	ND
Control	21-1331	2	17567.58	499465.15	956.37
	21-1332	2	19855.74	505010.09	728.64
	21-1345	3	15682.05	536607.31	555.93
	21-1346	3	21730.63	574287.97	786.11
	21-1347	1	ND	724141.22	ND
	21-1348	1	15592.56	543707.29	2321.89
	21-1363	1	25355.66	603657.32	1022.57
	21-1364	3	17604.77	583770.19	926.45
		Mean	**20773.36**	**550737.64**	**1042.57**
		SD	**6118.629**	**77132.770**	**585.821**
	21-1333	3	15969.01	446789.37	ND
1.09 mg/kg-d	21-1334	2	20743.95	524326.20	410.57
	21-1335	2	17614.92	498480.75	ND
	21-1336	2	19804.92	522299.34	2340.49
	21-1341	3	19249.69	586354.22	1089.56
	21-1342	2	19207.72	785218.29	733.27
	21-1371	2	27257.25	663162.42	243.05
	21-1372	2	20883.64	564681.68	504.24
	21-1373	1	24057.56	682925.28	1123.99
	21-1374	1	18007.61	534179.88	1154.15
		Mean	**20279.63**	**580841.74**	**949.92**
		SD	**3279.900**	**101549.644**	**661.311**
	21-1339	1	18170.31	480659.45	465.11
4.38 mg/kg-d	21-1340	2	29025.47	738266.27	634.32
	21-1351	1	17139.34	536071.58	1187.92
	21-1352	3	25762.39	515875.24	484.42
	21-1355	2	20176.37	568474.90	551.66
	21-1356	3	19319.29	437570.41	436.81
	21-1357	3	22006.41	490560.55	513.76
	21-1358	1	15985.87	538026.86	958.52
	21-1359	2	20061.25	610567.33	720.56
	21-1360	3	13378.21	496542.65	1186.09
		Mean	**20102.49**	**541261.52**	**713.92**
		SD	**4601.636**	**84348.100**	**292.801**
	21-1327	2	22403.04	548712.08	587.20
17.5 mg/kg-d	21-1328	2	22327.90	539576.95	1117.28
	21-1329	3	14607.69	460346.05	1182.51
	21-1330	3	19238.40	528128.75	ND
	21-1343	(f)	(f)	(f)	(f)
	21-1344	3	18019.09	545816.17	845.12
	21-1353	1	20865.01	439586.87	710.97
	21-1354	2	20495.90	646084.49	1896.92
	21-1367	3	13836.06	453672.25	1063.54
	21-1368	2	21113.62	622918.60	579.91
		Mean	**19211.86**	**531649.13**	**997.93**
		SD	**3150.649**	**72139.313**	**432.589**
	21-1337	3	12638.76	281948.51	9148.11
70 mg/kg-d	21-1338	2	22552.01	592361.69	5519.03
	21-1349	1	41565.33	378704.75	2840.38
	21-1350	2	16763.20	352816.78	9611.82
	21-1361	1	21695.35	355795.84	15480.97
	21-1362	1	22680.01	378543.20	14129.30
	21-1365	3	30189.99	343015.59	ND
	21-1366	1	26128.45	552098.13	7413.04
	21-1369	(f)	(f)	(f)	(f)
	21-1370	2	29432.75	474095.83	8638.65
		Mean	**24849.54**	**412153.37***	**9097.66***
		SD	**8403.911**	**104028.386**	**4163.442**

* $p<0.05$ compared to controls

Appendix Z

Subchronic Histopathology Report

PATHOLOGY REPORT
FOR

Protocol No. 38-18-12-01

Study Title

The Subchronic Oral Toxicity of 1,1-diamino-2,2-dinitroethene (FOX-7) in Rats (Rattus norvegicus)

Study Director

Lee Crouse

Prepared by:

MAJ Robert Kim, DVM, PhD, DACVPM, DACVP

Performing Laboratory

Defense Centers for Public Health-Aberdeen
Toxicology (DCPH-ATOX-TEV)
8300 Ricketts Point Road
Building E-2850
Aberdeen Proving Ground, MD 21010-5403

Table of Contents

1 Objective

The purpose of this study is to determine the potential adverse effects from a subchronic (90-day) repetitive oral exposure to FOX-7, an insensitive energetic compound.

2 Materials and Methods

2.1 Animals

This study was conducted using male and female Sprague-Dawley rats from Charles River Laboratories.

2.2 Exposure Methods

The test article was administered via oral gavage for the entire length of the study. The following table provides a summary of the animal exposures by group.

Table 1. Animal Exposure Summary

Group #	Chemical	Route	Targeted Exposure Length (days)	Target Concentration (mg/kg-d)	# of male rats	# of female rats
0	Vehicle Control	Oral gavage	90	0	10	10
1	FOX7	Oral gavage	90	1.09	10	10
2	FOX7	Oral gavage	90	4.38	10	10
3	FOX7	Oral gavage	90	17.5	10	10
4	FOX7	Oral gavage	90	70	10	10

2.3 Necropsy Procedures and Sample Processing

Rats were euthanized with carbon dioxide followed by gross examination and tissue collection for preservation and fixation.

The following tissues were collected and preserved/fixed: mammary gland; heart; lung; thymus; thyroid with parathyroid glands; trachea; adrenal glands; kidneys; liver; lymph nodes (mandibular and mesenteric); spleen; urinary bladder; cecum; colon; duodenum; ileum; jejunum; stomach (forestomach, glandular stomach); prostate ; seminal vesicles with coagulating glands and their fluids (as one unit); ovaries; testes; epididymides; uterus (with oviducts and cervix); vagina; peripheral nerve; fresh bone marrow aspirate; skeletal muscle; skin; spinal cord (at three levels: cervical, mid-thoracic, and lumbar); brain; pituitary gland; eye.

2.4 Histopathology

Tissues were fixed in formalin, trimmed into cassettes, processed, embedded in paraffin, sectioned via a microtome to a thickness of 4-5 um, and stained with hematoxylin and eosin using a routine automatic stainer. Additionally, the testis and epididymis were initially fixed in modified Davidson's solution and additionally stained with the Periodic Acid Schiff (PAS) stain.

The tissues from the high dose group (70 mg/kg-d), and vehicle control were processed and analyzed. Tissues from lower dose groups were evaluated when a significant difference was observed in lesion incidence between the high-dose group compared to the control group, see Table 2 regarding tissues examined. The general criteria for establishing a histologic score included the following: Score: '0' = the tissue is essentially normal or observed in <1% of the sampled tissue; '1' means minimum (1-5% of tissue affected); '2' means mild (6-20% of tissue affected); '3' = moderate (21-40%); '4' = marked (41%-60% of tissue affected); '5' = severe (>60% of tissue affected).
Absent= not present for microscopic examination due to sampling error, out of the plane of section, or other similar reason.

3 Results

3.1 Gross Findings

Minimal gross findings were annotated at the time of necropsy. Liver palor was variable and inconsistent amongst all dose groups when compared to control animals.

3.2 Histopathology

Test article-related microscopic findings were most notably observed in the thyroid gland and male reproductive organs to include testes, epididymides, and seminal vesicles. See Table 2 for the individual histopathologic findings from the 0 and 70 mg/kg-d dose groups.

The thyroid glands of male and female rats of the highest 70 mg/kg-d dose group demonstrated multifocal to mostly diffuse hypertrophy of follicular epithelial cells. The cytoplasm of follicular epithelial cells contained a material resembling the same homogenous acidophilic properties of colloid. Intracellular colloid displaced the normal more granular and slightly vacuolated cytoplasm located generally around the nucleus towards the apical surface. Pronounced hypertrophy of follicular epithelial cells resulted in compression of the interstitial space and overall, less colloid in follicles of high dose animals compared to controls. Thyroid mass and mass ratios were significantly elevated in the 70 mg/kg-d males and females relative to concurrent controls.

Bilateral seminiferous tubule atrophy was observed in 6 out of 10 male rats in the high dose 70 mg/kg-d group with near complete loss of germ cells and tubules exhibiting few remaining Sertoli cells. The seminiferous tubules lumen contained minimal numbers of degenerate cells and cellular debris. Overall, tubules were shrunken in diameter, and the interstitial space was variably expanded by pale, pink vacuolated fluid interpreted as edema. Seminiferous tubules of the 17.5 mg/kg-d medium dose group were similar to controls (Table 3).

The epididymides of 8 of the 70 mg/kg-d high dose males were devoid of spermatozoa while the remaining 2 in the group had spermatozoa within lumen visually similar to controls. The second highest dose group 17.5 mg/kg-d were similar to controls (Table 3).

Epithelial cells lining the coagulating glands exhibited hypertrophy in the high dose 70 mg/kg-d group, with individual cells enlarged by an accumulation of secretory material resulting in distension of the cytoplasm and basilar displacement of the nucleus. This increase in size resulted in crowding of the cells and the epithelium with subsequent folding and protrusion into glandular acini. An overall decrease in the amount of secretory content of acini and slight collapse of the glands were also observed resulting epithelial cell hyperplasia. The second highest dose group 17.5 mg/kg-d were normal compared to controls (Table 4).

4 Discussion

Gross lesions in this study were overall minimal with variability in liver palor that did not demonstrate a consistent pattern with dose groups. Liver palor in this study was most likely attributed to the dosing vehicle (corn oil) resulting in fat accumulation in the liver.

Histopathologic changes due to test article administration compared to controls were observed in the highest dose group, 70 mg/kg-d. Subsequent evaluation of these tissues at the second highest dose, 17.5 mg/kg-d, yielded results that were most similar to controls. These differences strongly suggest that a dose greater than 17.5 mg/kg-d may be warranted to further delineate where observable histopathologic changes could be detected. Additional studies are required to clarify the dose relationship if necessary.

The thyroid gland exhibited follicular cell hypertrophy with cellular distension; most likely a result of accumulation of material resembling colloid. Rats in the 70 mg/kg-d dose group demonstrated an increase in overall weight of the thyroid glands compared to controls (0.062 vs 0.029 grams in males, 0.041 vs 0.027 grams in females). Serum T4 levels were lower, although not significantly compared to controls (643 vs 754 ng/ml) in males and were significantly lower (412 vs 551 ng/ml) in females. TSH levels in the 70 mg/kg-d group were significantly and remarkably elevated in both sexes relative to controls (3 vs 8 ng/ml in males and 1 vs 9 ng/ml in females). The second highest dose group, 17 mg/kg-d, were normal compared to controls. The appearance of epithelial cells suggest colloid production was active, however the retention within cells resulted in cellular hypertrophy. The retained colloid and potential absence of release in the bloodstream are likely the cause of colloid depletion reflected in the lower serum T4 levels. These findings strongly suggest the test article is a goitrogenic agent. Thyroid hormones may decrease due to hepatic enzyme stimulation by the test article causing increased hormone metabolism and subsequent increase in TSH to counter the effect. As thyroid hormone levels normalize, TSH would typically normalize also, but may not have occurred by 90 days.

The mechanism or cause of testicular and coagulating gland lesions following test article administration warrants further investigation. The mechanism(s) leading to these histopathologic changes are largely unknown. The tubular atrophy noted in this study is

considered a non-specific end-stage lesion which may be caused by Sertoli cell injury, direct cytotoxicity, hypoxia or other mechanism. The observed decrease in spermatozoa in the epididymis strongly suggest the presence of long-standing atrophy that may have occurred over the course of days or weeks.

Histopathologic changes in the liver were minimal with vacuolar change as the most common. This finding is most likely due to ingestion of the test article vehicle, corn oil, resulting in intracellular lipid accumulation. Distribution of vacuolar change predominated in the periportal regions of hepatic lobules and noted through all dose groups to include controls. An increased severity of vacuolar change was observed in the high dose group compared to the controls. This lipid-type vacuolar degeneration was variably accompanied by rare necrosis of individual hepatocytes.

In summary, FOX-7 administration at 70 mg/kg-d results in histopathologic changes most notably in the thyroid gland and male reproductive organs (testes, epididymis, seminal vesicles). The goitrogen-like properties of FOX-7 strongly suggest disruption of thyroid gland production within rats and warrants further investigation to understand the mechanism of action. Histopathologic changes of the male reproductive tract following FOX-7 administration are unknown but confirmed by the differences in 70 mg/kg-d dosed animals versus controls. Altogether, these histopathologic findings in rats should be considered when utilizing this test article in future studies.

5 Point of Contact

Questions pertaining to this report should be referred to MAJ Robert Kim at 410-436-7014, or by e-mail: robert.k.kim2.mil@health.mil.

Prepared By:

KIM.ROBERT.K.1407357937 Digitally signed by KIM.ROBERT.K.1407357937
Date: 2024.01.18 11:08:36 -05'00'

ROBERT KIM Date
Chief, Office of Toxicologic Pathology

References

1. Everds, N.E., et al., Interpreting stress responses during routine toxicity studies: a review of the biology, impact, and assessment. Toxicol Pathol, 2013. 41(4): p. 560-614.

2. Hailey JR, Walker NJ, Sells DM, Brix AE, Jokinen MP, Nyska A. Classification of proliferative hepatocellular lesions in harlan sprague-dawley rats chronically exposed to dioxin-like compounds. *Toxicol Pathol,* 2005, 33: 165–174

3. Karbe E, Kerlin RL Cystic degeneration/Spongiosis hepatis in rats. *Toxicol Pathol*, 2002, 30: 216–227

4. Kittel B, Ruehl-Fehlert C, Morawietz G, Klapwijk J, Elwell MR, Lenz B, et al.: Revised guides for organ sampling and trimming in rats and mice--Part 2. A joint publication of the RITA and NACAD groups. *Exp Toxicol Pathol* 2004:55(6):413-431.

5. Morawietz G, Ruehl-Fehlert C, Kittel B, Bube A, Keane K, Halm S, et al.: Revised guides for organ sampling and trimming in rats and mice--Part 3. A joint publication of the RITA and NACAD groups. *Exp Toxicol Pathol* 2004:55(6):433-449.

6. QSARC SOP 800, *Animal Euthanasia*, 2017, Army Public Health Center, Aberdeen Proving Ground, MD.

7. Swenberg JM, Short B, Strasser J, Charbonneau M. 1989. The comparative pathobiology of α2u- globulin nephropathy. Toxicol Appl Pharmacol 97:35-46.

Table 2. Incidence of Histopathologic Findings, 0 and 70 mg/kg-day

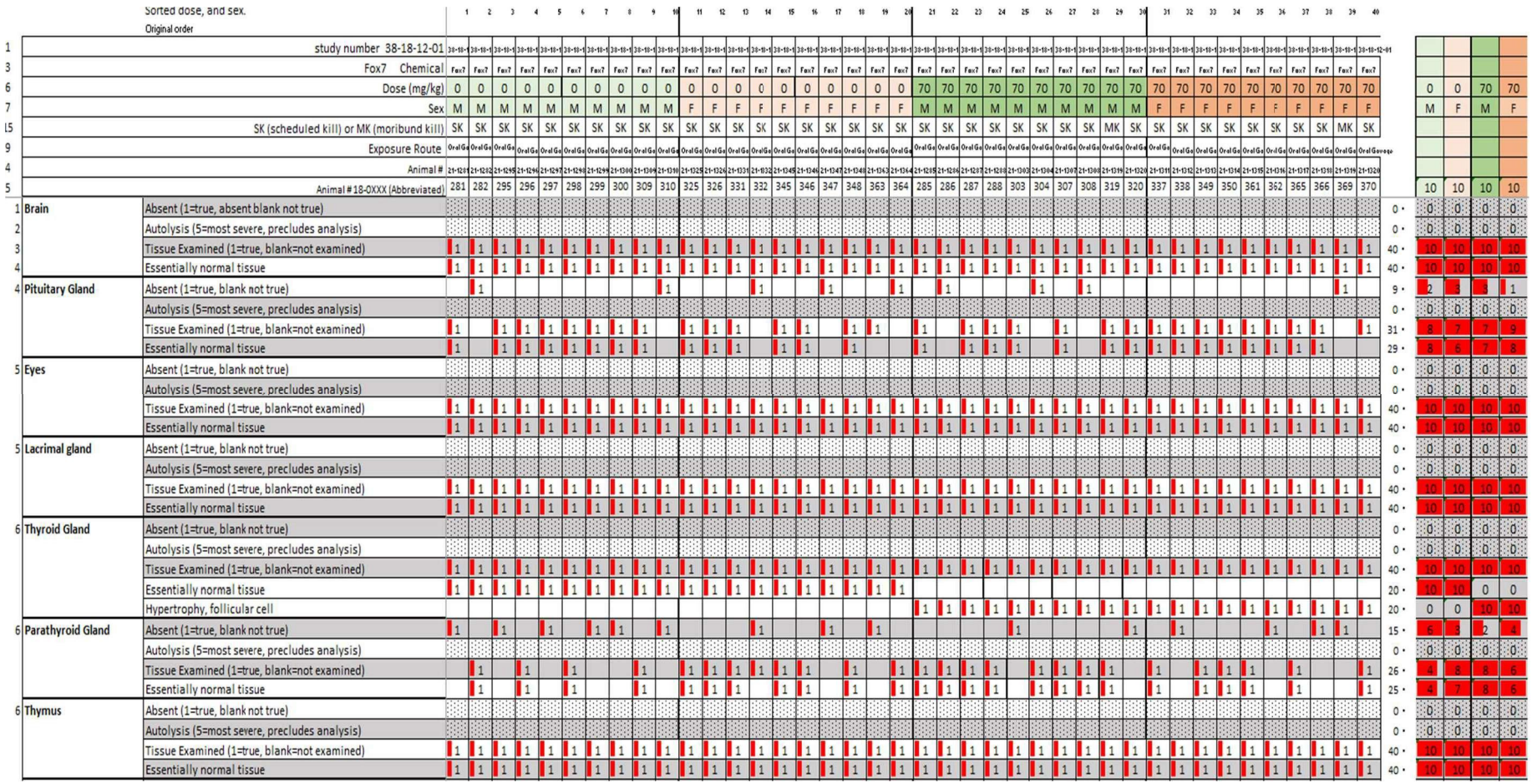


Table 2. Incidence of Histopathologic Findings, 0 and 70 mg/kg-day (cont.)

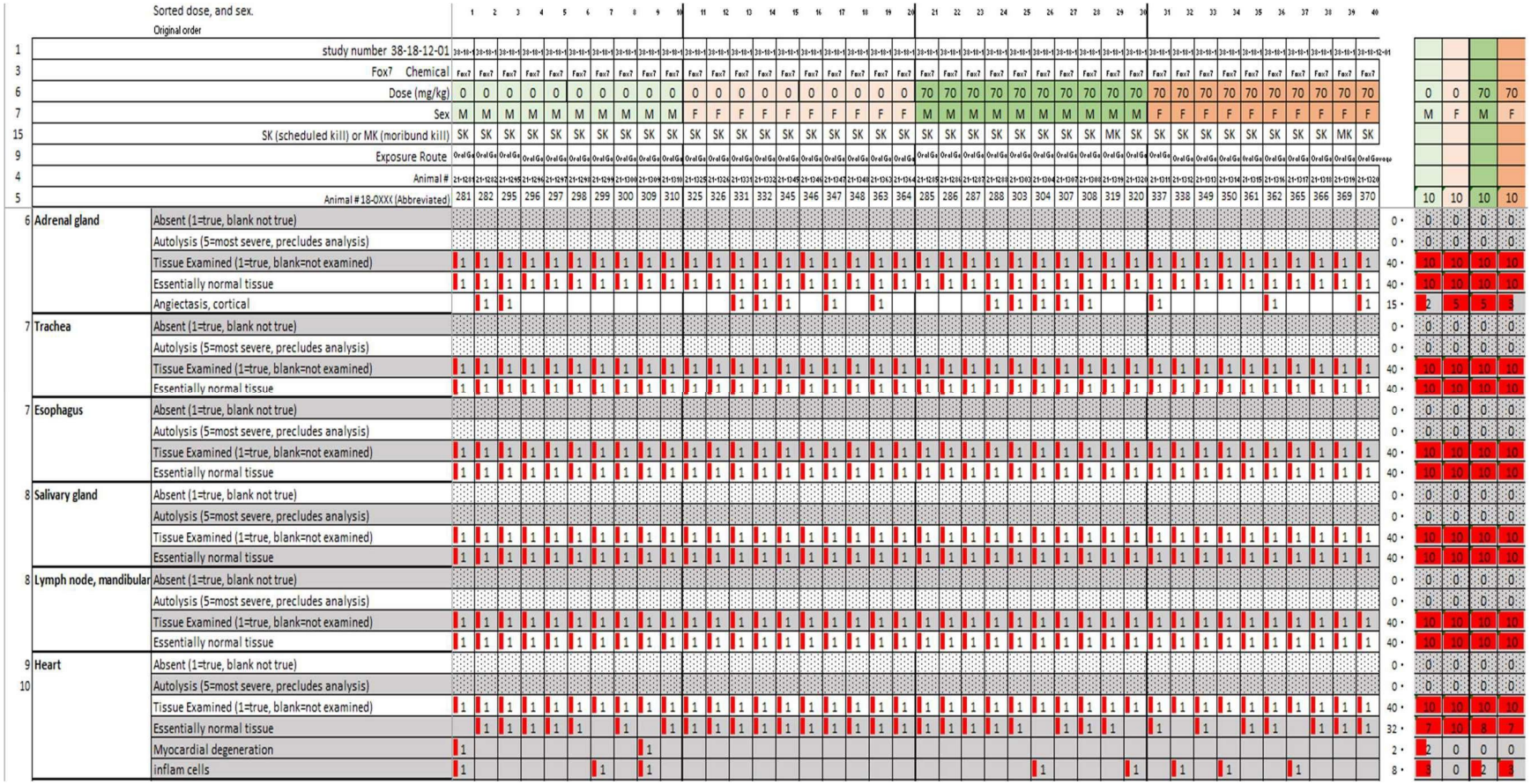


Table 2. Incidence of Histopathologic Findings, 0 and 70 mg/kg-day (cont.)

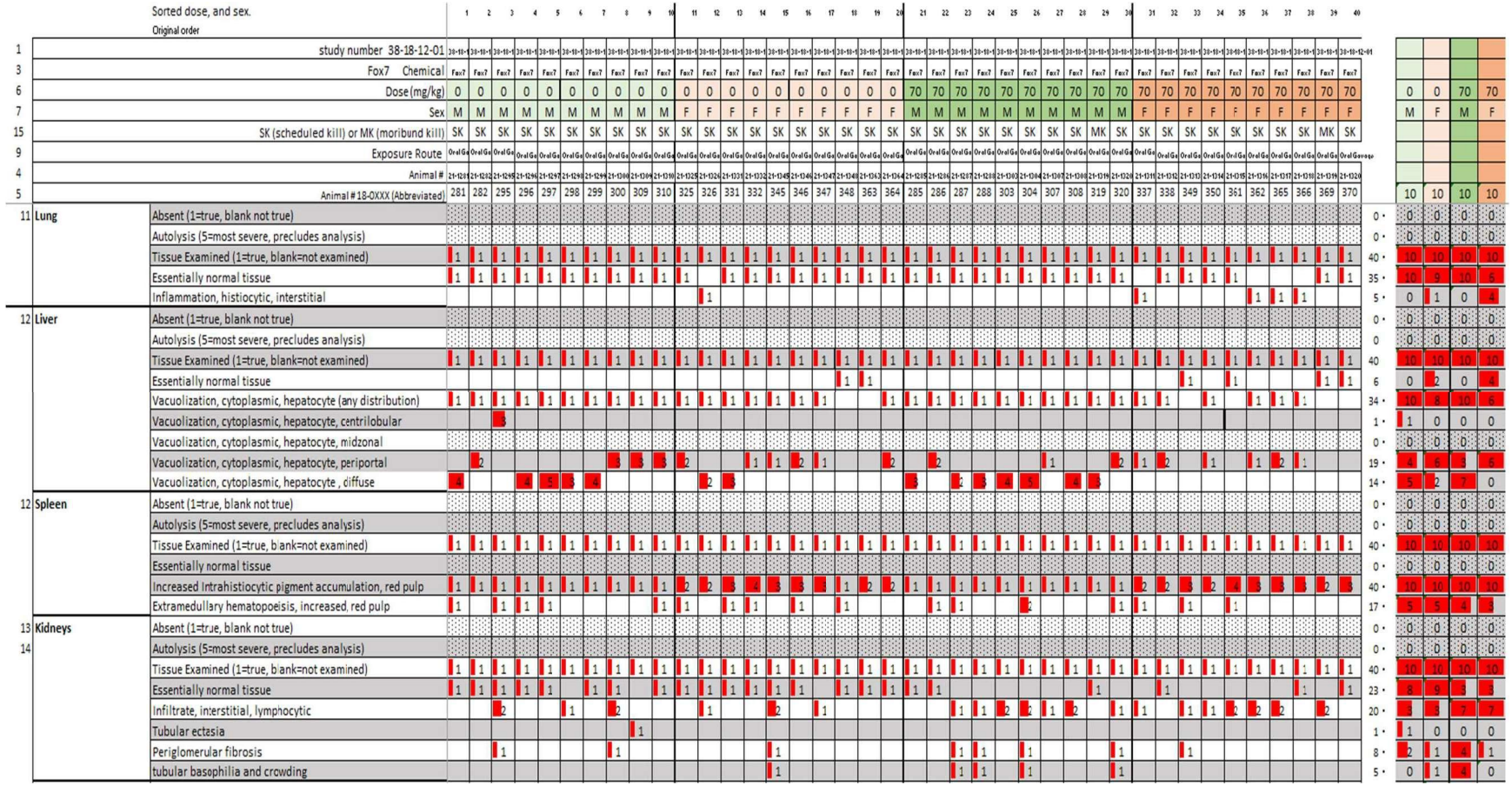


Table 2. Incidence of Histopathologic Findings, 0 and 70 mg/kg-day (cont.)

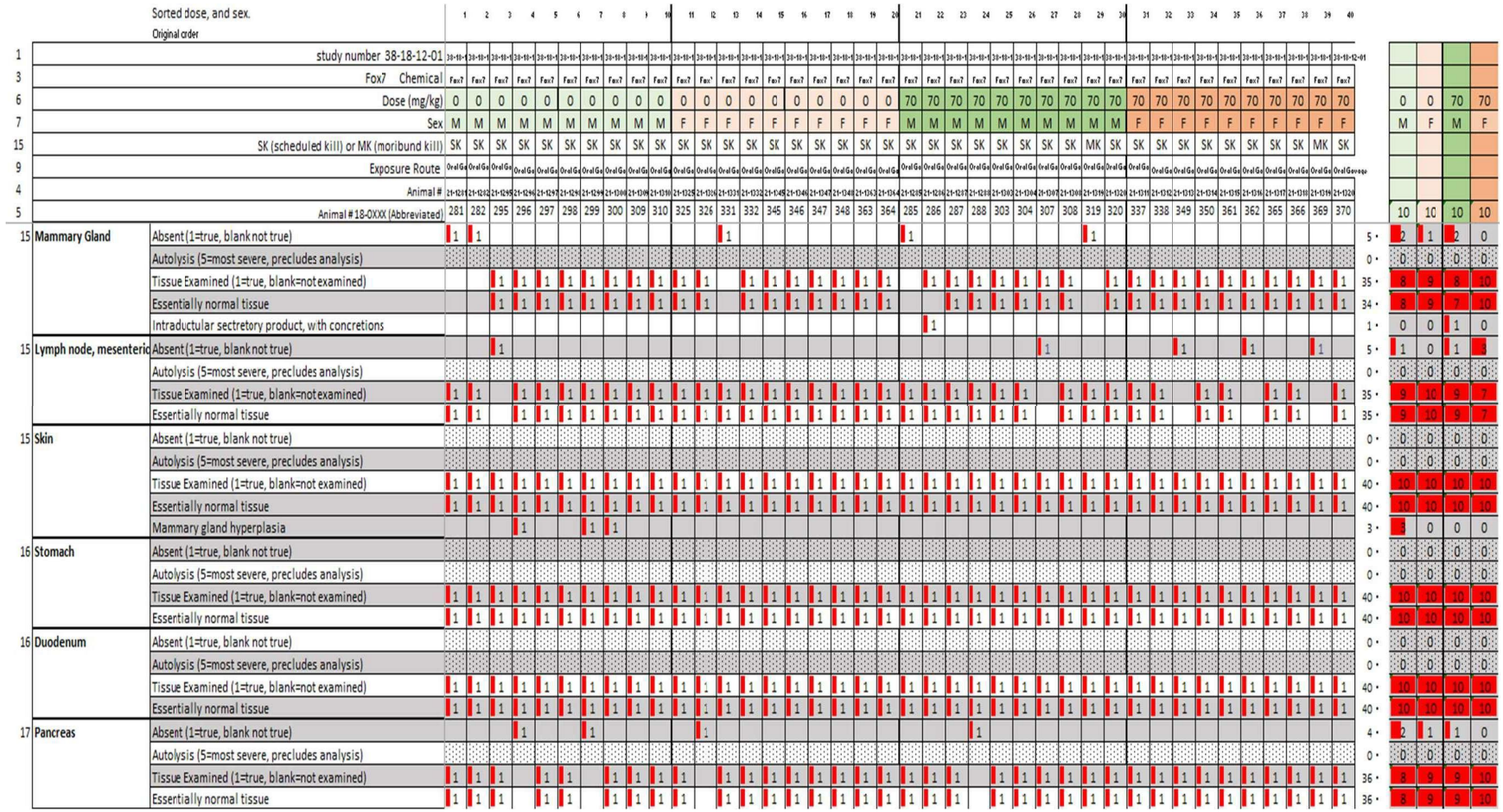


Table 2. Incidence of Histopathologic Findings, 0 and 70 mg/kg-day (cont.)

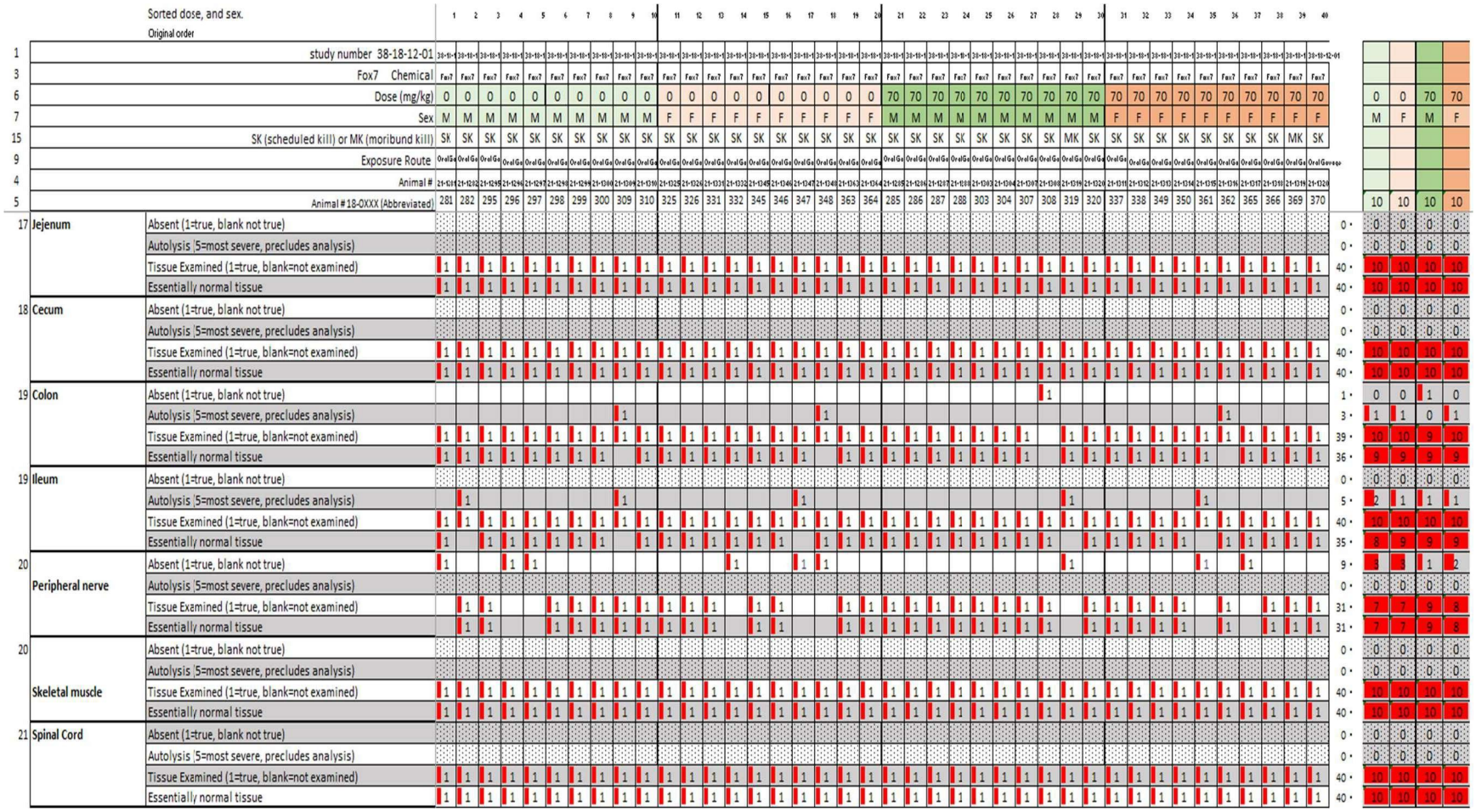


Table 2. Incidence of Histopathologic Findings, 0 and 70 mg/kg-day (cont.)

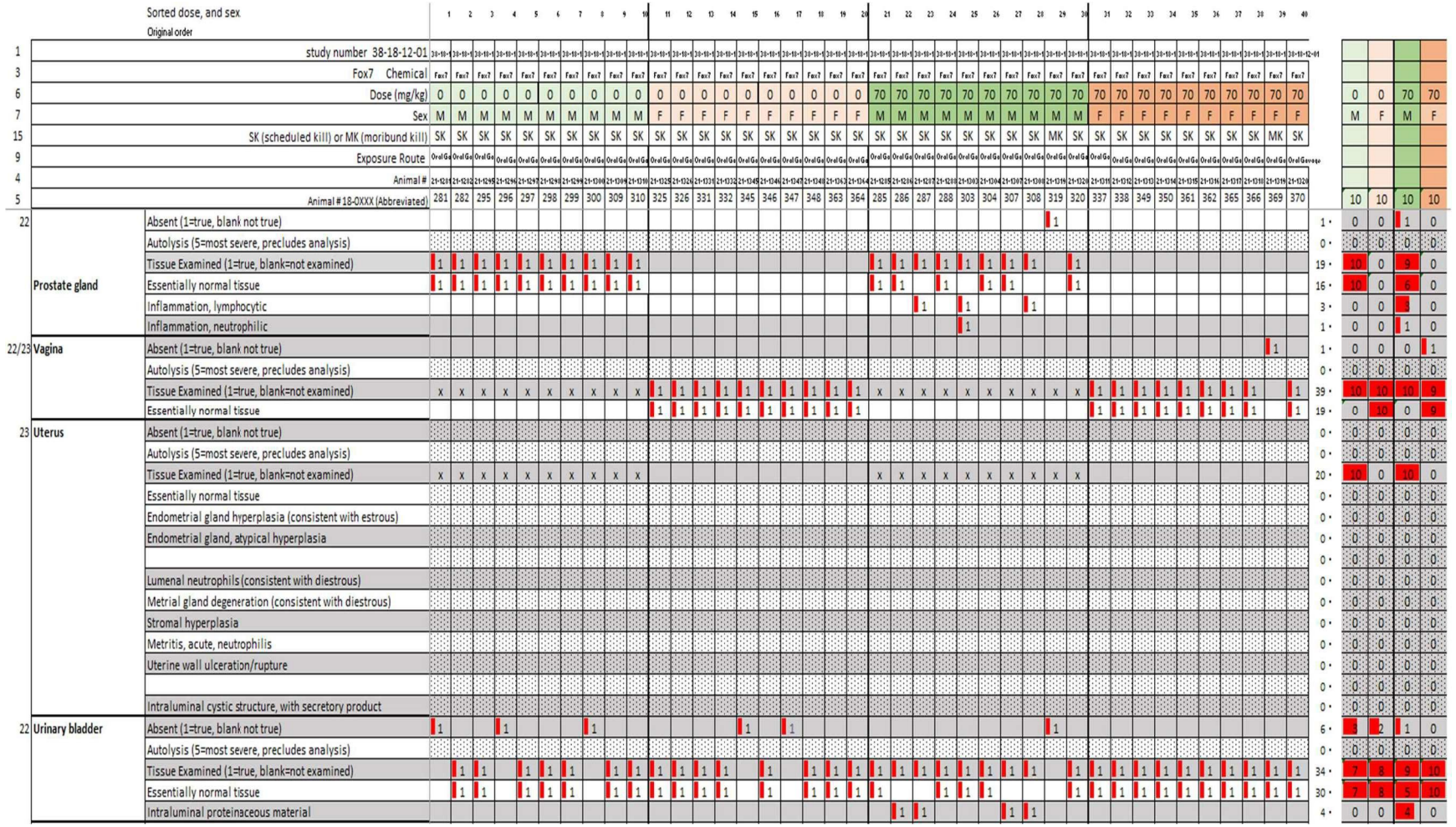


Table 2. Incidence of Histopathologic Findings, 0 and 70 mg/kg-day (cont.)

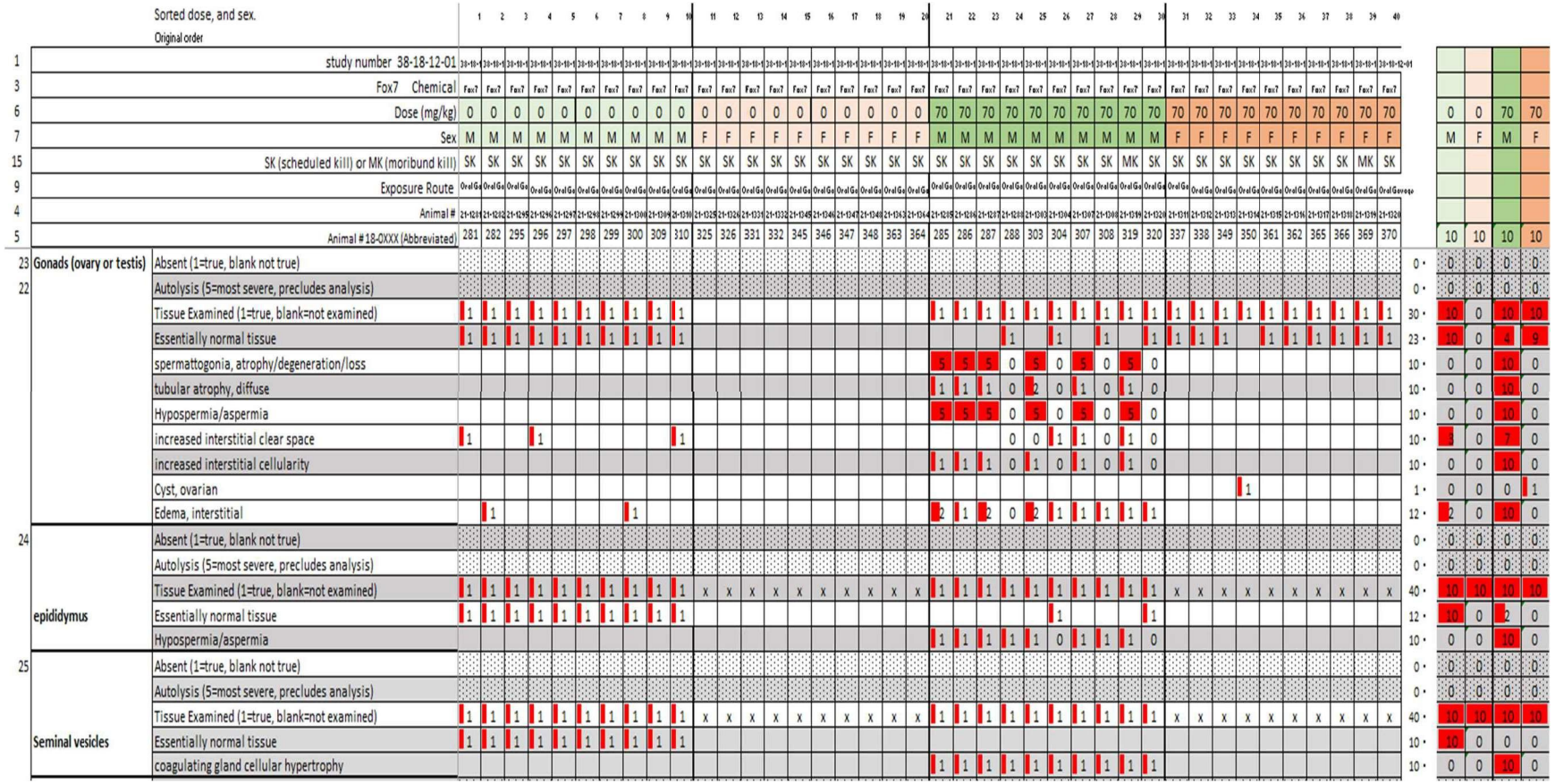
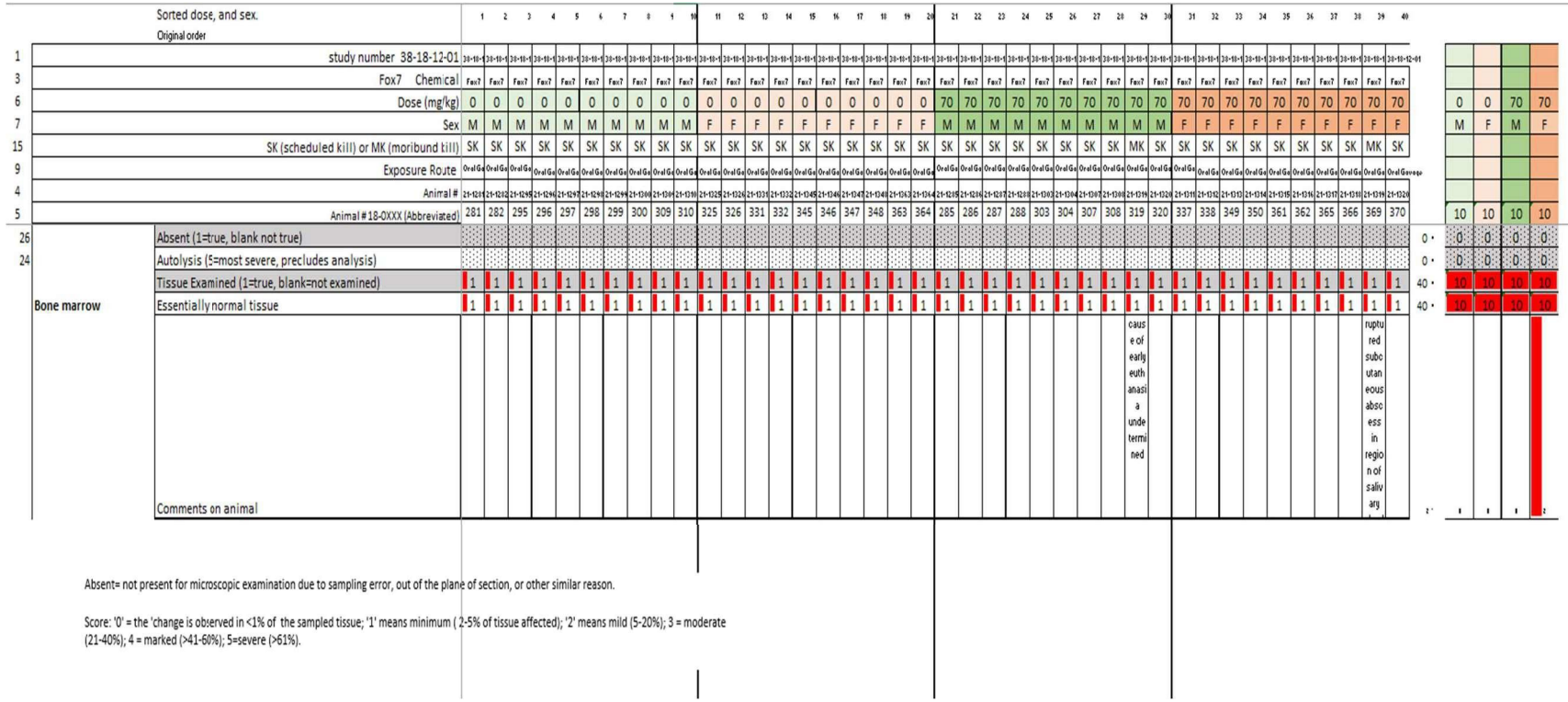


Table 2. Incidence of Histopathologic Findings, 0 and 70 mg/kg-day (cont.)



Absent= not present for microscopic examination due to sampling error, out of the plane of section, or other similar reason.

Score: '0' = the 'change is observed in <1% of the sampled tissue; '1' means minimum (2-5% of tissue affected); '2' means mild (5-20%); 3 = moderate (21-40%); 4 = marked (>41-60%); 5=severe (>61%).

Table 3. Incidence of Male Reproductive Histopathologic Findings, 17.5 mg/kg-day

		study number 38-18-12-01											
		Fox7 Chemical											
		sex	male	male	male	male	male	male	male	male	male	male		male
		dose	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5		17.5
		SK (scheduled kill) or MK (moribund kill)	SK	SK	SK	SK	SK	SK	SK	SK	SK	SK		
			1283	1284	1289	1290	1301	1302	1305	1306	1311	1312		
23	**Gonads (testis)**	Absent (1=true, blank not true)											0	0
		Autolysis (5=most severe, precludes analysis)											0	0
		Tissue Examined (1=true, blank=not examined)	1	1	1	1	1	1	1	1	1	1	10	10
		Essentially normal tissue	1	1	1	1	1	1	1	1	1	1	10	10
	Epididymis	Absent (1=true, blank not true)											0	0
		Autolysis (5=most severe, precludes analysis)											0	0
		Tissue Examined (1=true, blank=not examined)	1	1	1	1	1	1	1	1	1	1	10	10
		Essentially normal tissue	1	1	1	1	1	1	1	1	1	1	10	10

Table 4. Incidence of Thyroid Histopathologic Findings, 17.5 mg/kg-day

study number 38-18-12-01																								
Fox7 Chemical																								
sex	male	male	male	male	male	male	male	male	male	male	female	female	female	female	female	female	female	female	female	female		male	female
dose	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5	17.5		17.5	17.5
SK (scheduled kill) or MK (moribund kill)	SK	SK	SK	SK	SK	SK	SK	SK	SK	SK	SK	SK	SK	SK	MK	SK	SK	SK	SK	SK			
	1283	1284	1289	1290	1301	1302	1305	1306	1311	1312	1327	1328	1329	1330	1343	1344	1353	1354	1367	1368			
Absent (1=true, blank not true)																					0	0	0
Autolysis (5=most severe, precludes analysis)																					0	0	0
Tissue Examined (1=true, blank=not examined)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	20	10	10
Essentially normal tissue	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	20	10	10
Infiltrates, histiocytic				1									1								2	1	1
comments															MK-mammary fibroadenoma of thoracic mammary gland								

Appendix AA

Subchronic Benchmark Dose Analysis

Subchronic Benchmark Dose Information

Table 1. Female Hemoglobin Concentration Dataset

Dose	N	Mean	Std. Dev.
[Custom]	[Custom]	[Custom]	[Custom]
0	10	15.8	0.71
1.09	10	15.9	0.5
4.38	10	15.5	0.5
17.5	9	15.3	0.59
70	9	12.3	0.83

Table 2. Model Output for Benchmark Dose Analysis

Model	Analysis Type	Restriction	RiskType	BMRF	BMD	BMDL	BMDU	Test 4 P-Value	AIC	Unnormalized Log Posterior Probability	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group	BMDS Recommendation
Exponential 3 (CV - normal)	frequentist	Restricted	Std. Dev.	1	19.32495	10.7364	36.132313	0.4303055	97.01207894	-	0.271014148	0.119445619	Viable - Alternate
Exponential 5 (CV - normal)	frequentist	Restricted	Std. Dev.	1	19.32495	10.7366	36.132313	0.1940604	99.01207894	-	0.271013963	0.11944572	Viable - Alternate
Hill (CV - normal)	frequentist	Restricted	Std. Dev.	1	19.3727	10.8985	36.254575	0.1956963	98.99976406	-	0.263277893	0.118702885	Viable - Alternate
Polynomial Degree 3 (CV - normal)	frequentist	Restricted	Std. Dev.	1	25.79941	10.8513	39.016256	0.1900791	99.04256371	-	-0.302684785	0.261861595	Viable - Alternate
Polynomial Degree 2 (CV - normal)	frequentist	Restricted	Std. Dev.	1	21.02997	10.9905	31.98898	0.476861	96.80661966	-	0.035052989	0.131340874	Viable - Alternate
Power (CV - normal)	frequentist	Restricted	Std. Dev.	1	19.20352	10.9021	36.391467	0.4434639	96.95183689	-	0.28364937	0.094941235	Viable - Alternate
Linear (CV - normal)	**frequentist**	**Unrestricted**	**Std. Dev.**	**1**	**12.31734**	**10.212**	**15.375174**	**0.355799**	**96.56754547**	**-**	**1.396590423**	**-0.476872752**	**Viable - Recommended**

Figure 1. Selected Linear Model Graph