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DUPONT HASKELL GLOBAL CENTERS FOR HEALTH & ENVIRONMENTAL SCIENCES
Discovery Toxicology Group

Repeated Dose Oral Toxicity 7-Day Gavage Study in Rats

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STUDY START DATE:	11-October-07
STUDY END DATE:	12-December-07
NOTEBOOK(s):	E-111389-BF
STUDY DIRECTOR:	Diane L. Nabb, Staff Toxicologist
REPORT ISSUE DATE:	February 14, 2008

OBJECTIVE

To evaluate potential subacute toxicity and kinetic behavior of the test substance when administered by oral gavage to male and female rats for 7 consecutive days.

STUDY DESIGN

Test Substance:	HFPO Dimer Acid	
Lot/Batch Number:	E112820-46MC	
Purity:	99% (doses were corrected for purity)	
Species:	Rat	
Strain:	Crl:CD(SD)	
Gender:	Male and Female	
Age at start:	~6 weeks	
Group Size:	Control	5 males, 5 females
	Low dose	8 males, 8 females (5/sex Main study, 3/sex Metabolism)
	Mid dose	5 males, 5 females (5/sex Main study)
	High dose	5 males, 5 females (5/sex Main study)
Dose Levels:	0, 30, 100, 300 mg/kg Main study 30 mg/kg for Metabolism animals	
Route:	Oral gavage	
Dosing Volume:	10 mL/kg Main study and Metabolism animals	

Dose Vehicle:	Water
Dosing Frequency:	Daily Day 0-Day 6 Main study animals Day 0-Day 7 Metabolism animals
Blood Sample Frequency:	Day 7 Metabolism animals; predose, 0.25, 0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours post dose via tail vein.

PARAMETERS

Clinical signs, body weight, clinpath (SE=D7), necropsy, organ weight, P450s, β-oxidation, AUC.

METHODS

LC/MS Sample Analyses

A. Plasma Samples

The plasma samples were received and stored frozen prior to laboratory use. The samples were prepared for analysis by pipeting 150 µL acetonitrile into a 1.7 mL microcentrifuge tube, and pipeting 50.0 µL of plasma sample. The sample tubes were then vortexed for 1 minute and centrifuged at 14,000 RCF for 30 minutes. After centrifugation, 100 µL of sample supernatant was placed into a HPLC vial and 400 µL of HPLC grade water was added and mixed. As necessary, additional sample dilutions were performed using the 15% acetonitrile in HPLC grade water solvent to ensure that the sample responses were within the calibration curve.

B. Liver and Fat Samples

The liver and fat samples were received and stored frozen prior to laboratory use. The liver tissue samples were extracted in Acetonitrile with 4% perchloric acid while the fat samples were extracted in isopropyl alcohol. The calibration standards were prepared in the appropriate matched solvents.

1. Fat and Liver Extract Preparation.

The fat and liver samples were preprocessed by chopping the tissue samples into small pieces and weighing (0.5 grams) into disposable 15-mL polypropylene centrifuge tubes. Five 5/32" ball bearings were added to each tube, and a pipet was used to add 5000 µL of the appropriate extraction solvent. The tubes were sealed with parafilm, and inserted into a SPEX Certiprep Genogrinder and homogenized for 4 minutes at 1400 strokes/minute. After homogenization, the tubes were centrifuge at 4125 rpm for 20 min at room temperature. The extract supernatant was transferred into glass vials and frozen prior to further sample preparation.

2. Fat and Liver Extract Analysis.

Approximately 100 mg of Envi-Carb graphitized carbon sorbent was placed into a 1.7-mL microcentrifuge tube. A pipet was used to add 50.0 µL of glacial acetic acid directly to the sorbent. Next, a pipet was used to add 1000 µL of sample extract into the centrifuge tube. The tubes were capped, vortexed briefly, and then centrifuged at 10,000 RCF for 10 minutes at room temperature. After centrifugation, a pipet was used to add 525 µL of the 1.7-mL microcentrifuge tube supernatant into a new 1.7 mL microcentrifuge tube and 475 µL of HPLC grade water and mixed. The samples were centrifuged at 10,000 RCF for 5 minutes at room temperature, and supernatant transferred into HPLC vials for analysis. As necessary, additional sample dilutions were performed using the matched solvent to ensure that the sample responses were within the calibration curve.

The prepared samples were analyzed by LC/MS using the following parameters:

HPLC Instrument: Agilent Model 1200
MS Instrument: Applied Biosystems API 4000

LC Parameters:
Column: Zorbax RX-C8, 150 x 2.1 mm, 5 µm particle size
Mobile Phase: A: 0.15% acetic acid and 0.15% triethyl amine in HPLC grade water
B: 0.15% acetic acid and 0.15% triethyl amine in acetonitrile

Column Temperature: 35°C
Injection Volume: 10 µL

MS Parameters:
Ion Source: Turbo Spray, Negative Ion
Temperature (TEM): 450
Dwell: 300 msec
Curtain Gas Flow (CUR): 50.0
GS1: 11
GS2: 70
IonSpray (IS) Voltage: -4500
CAD 10.0
EP -10.0
Quadrupole Resolution: Quad. 1: Unit
Quad. 3: Unit

MRM Settings

Q1 Mass	Q3 Mass	DP	CE	CXP
329.00	285.00	-20	-10	-5

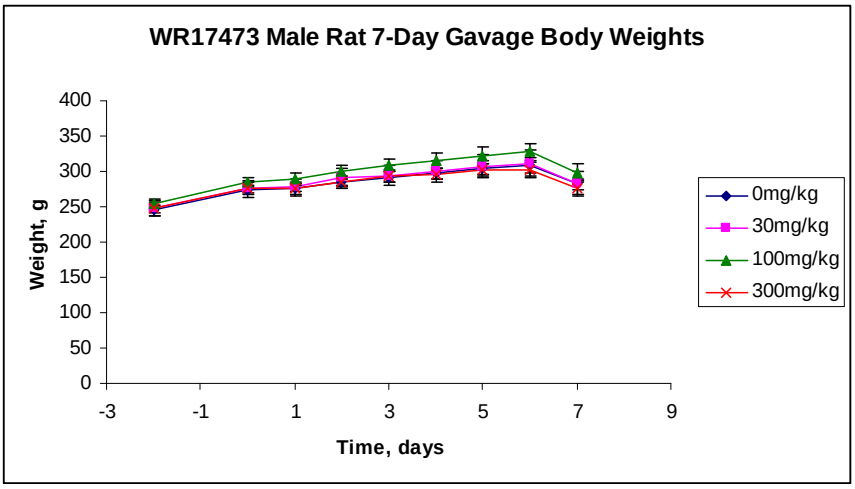
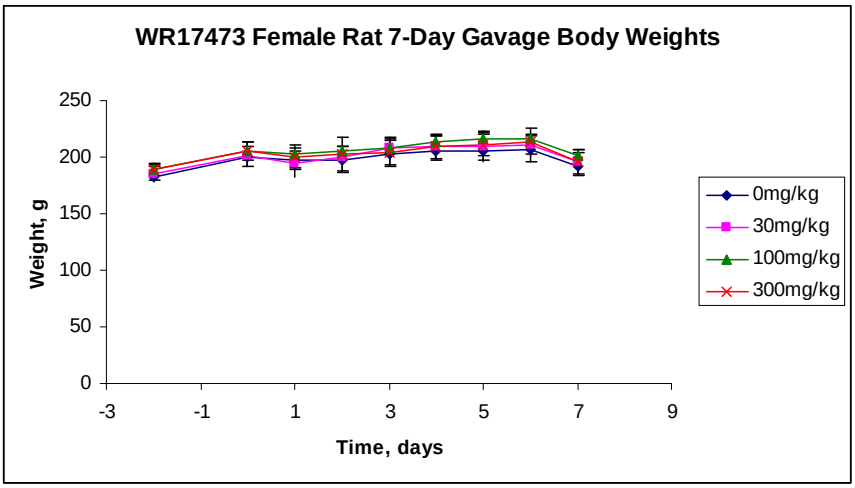
HPLC Gradient

Total Time (min)	Flow Rate (mL/min)	A(%)	B(%)
0.00	250	60.0	40.0
5.00	250	60.0	40.0
5.01	350	10.0	90.0
9.00	350	10.0	90.0
9.01	350	60.0	40.0
19.00	350	60.0	40.0
19.01	250	60.0	40.0
20.00	250	60.0	40.0

RESULTS

The individual plasma sample results are provided in Appendix A
The individual liver sample results are provided in Appendix B
The individual fat sample results are provided in Appendix C
The summary and individual clinical pathology results are provided in Appendix D
The summary and individual pathology results are provided in Appendix E
The individual mechanistic evaluation results are provided in Appendix F

Dose (mg/kg/day)	30	100	300	30	100	300
	Male			Female		
Deaths:	0/8	0/5	0/5	0/8	0/5	0/5
Comment:	No deaths.					
Clinical Signs:	0/8	0/5	0/5	0/8	0/5	0/5
Comment:	No adverse, test substance-related changes were observed for in-life parameters.					

Body Weights:	Animal body weights on test day 7 reported as percent of control: Male low dose (30 mg/kg): 98.9% of control ± 6.1% Male mid dose (100 mg/kg): 94.6% of control ± 5.4% Male high dose (300 mg/kg): 102.3% of control ± 5.2% Female low dose (30 mg/kg): 98.4% of control ± 7.9% Female mid dose (100 mg/kg): 95.7% of control ± 4.8% Female high dose (300 mg/kg): 98.4% of control ± 9.5% No significant weight effects observed at any dose level.
Graphs:	  Vales shown are mean ± standard deviation.

In the summary tables below, statistically significant values ($p \leq 0.05$) are given in bold.

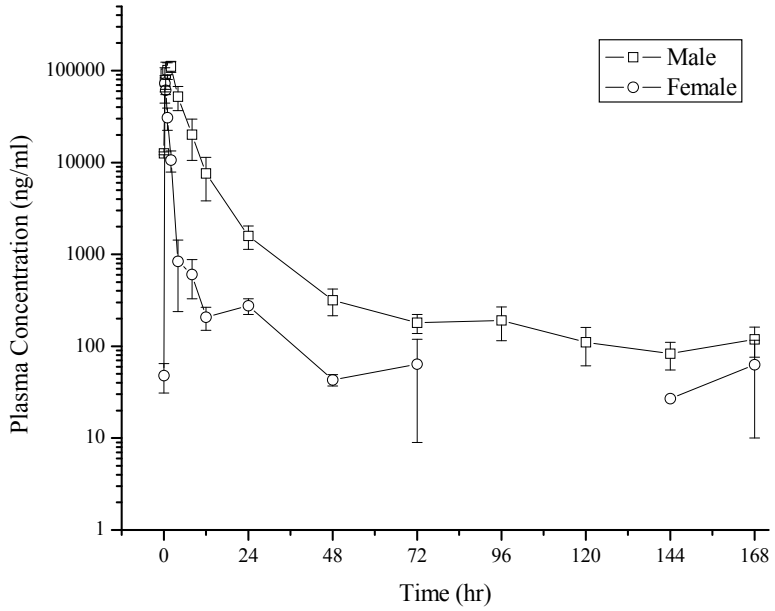
Dose (mg/kg/day)	0	30	100	300	0	30	100	300
Hematology	Male				Female			
RBC Day 7	7.46 0.24(5)	7.17 0.21(5) 96%	7.03 0.30(5) 94%	7.04 0.60(4) 94%	7.58 0.34(5)	7.87 0.32(5) 104%	7.30 0.25(5) 96%	**6.71** **0.87(4)** **89%**
HGB Day 7	14.6 0.6(5)	14.6 0.4(5) 100%	13.9 0.6(5) 95%	**13.4** **0.9(4)** **92%**	14.7 0.4(5)	15.2 0.3(5) 103%	14.4 0.3(5) 98%	13.2 1.5(4) 90%
HCT Day 7	47.3 1.7(5)	47.5 1.3(5) 100%	44.6 1.9(5) 94%	**43.7** **2.8(4)** **92%**	45.3 1.2(5)	46.9 1.2(5) 104%	44.6 0.9(5) 98%	41.3 4.1(4) 91%
MCV Day 7	63.4 1.6(5)	**66.3** **1.6(5)** **105%**	63.4 1.2(5) 100%	62.1 1.4(4) 98%	59.8 2.2(5)	59.7 2.8(5) 100%	61.2 1.1(5) 102%	61.9 3.3(4) 104%
RDW Day 7	13.0 0.5(5)	13.3 0.9(5) 102%	13.0 0.3(5) 100%	13.4 1.1(4) 103%	11.0 0.3(5)	11.2 0.6(5) 102%	11.2 0.2(5) 102%	**13.2** **2.1(4)** **120%**
ARET Day 7	286.3 61.8(5)	285.4 71.4(5) 100%	282.8 46.2(5) 99%	296.0 84.9(4) 103%	212.9 43.6(5)	210.7 21.9(5) 99%	205.1 13.5(5) 96%	524.7 214.3(4) 246%
Comment:	Bold indicates statistically significant. The percentage indicates percent of control group mean of those parameters that were statistically significant. Statistically significant decreases in some red cell mass parameters were observed in male and female rats at the highest dose tested (300 mg/kg/day). A statistically significant increase in red cell distribution width was also present in 300 mg/kg/day females.							

Dose (mg/kg/day)	0	30	100	300	0	30	100	300
Serum Chemistry	Male				Female			
ALKP Day 7	216 44(5)	**319** **32(5)** **148%**	264 71(5) 122%	**320** **64(5)** **148%**	125 33(5)	130 46(5) 104%	149 64(5) 119%	131 37(5) 105%
BILI Day 7	0.13 0.01(5)	0.11 0.02(5) 85%	0.13 0.02(5) 100%	0.15 0.05(5) 115%	0.13 0.02(5)	0.13 0.01(5) 100%	0.12 0.01(5) 92%	**0.10** **0.02(5)** **77%**
BUN Day 7	16 1(5)	15 2(5) 94%	16 3(5) 100%	**20** **2(5)** **125%**	16 2(5)	14 2(5) 88%	14 2(5) 88%	14 3(5) 88%
CREA Day 7	0.34 0.03(5)	0.33 0.02(5) 97%	0.31 0.01(5) 91%	**0.29** **0.02(5)** **85%**	0.35 0.01(5)	0.34 0.02(5) 97%	0.33 0.03(5) 94%	0.31 0.03(5) 89%
CHOL Day 7	59 9(5)	**30** **9(5)** **51%**	**39** **5(5)** **66%**	**35** **6(5)** **59%**	60 9(5)	**80** **10(5)** **133%**	64 16(5) 107%	65 9(5) 108%
TRIG Day 7	56 8(5)	46 6(5) 82%	**30** **8(5)** **54%**	**37** **8(5)** **66%**	34 5(5)	36 7(5) 106%	34 12(5) 100%	29 8(5) 85%
GLUC Day 7	95 5(5)	127 44(5) 134%	114 15(5) 120%	**120** **6(5)** **126%**	101 5(5)	102 5(5) 101%	98 5(5) 97%	99 7(5) 98%
TP Day 7	6.0 0.1(5)	6.1 0.3(5) 102%	6.1 0.3(5) 102%	**5.3** **0.4(5)** **88%**	6.2 0.3(5)	6.4 0.2(5) 103%	6.1 0.4(5) 98%	6.0 0.3(5) 97%
Albumin Day 7	3.4 0.1(5)	**3.8** **0.1(5)** **112%**	**3.8** **0.2(5)** **112%**	3.5 0.3(5) 103%	3.7 0.2(5)	3.8 0.2(5) 103%	3.7 0.2(5) 100%	3.7 0.2(5) 100%
Globulin Day 7	2.6 0.1(5)	2.4 0.2(5) 92%	**2.3** **0.2(5)** **88%**	**1.8** **0.1(5)** **69%**	2.5 0.2(5)	2.5 0.1(5) 100%	2.4 0.2(5) 96%	2.3 0.1(5) 92%
CALC Day 7	11.0 0.2(5)	10.8 0.6(5) 98%	10.8 0.3(5) 98%	**10.3** **0.2(5)** **94%**	10.8 0.3(5)	11.0 0.2(5) 102%	10.6 0.2(5) 98%	10.9 0.3(5) 101%
Comment:	Bold indicates statistically significant. The percentage indicates percent of control group mean of those parameters that were statistically significant. Decreases in serum lipids (triglycerides and/or cholesterol) were present in all dosed male groups. Other changes in clinical chemistry parameters occurred at 30 and/or 300 mg/kg/day and included increased ALKP and BUN, and decreased bilirubin, creatinine, total protein, globulin and calcium.							

Gross Path	Male	Female
Observations:	No test-substance related gross findings.	No test-substance related gross findings.

Dose (mg/kg/day)	0	30	100	300	0	30	100	300
Organ Weights	Male				Female			
Final Body Weight (g)	282.0 7.9(5)	286.2 21.0(5) 101%	298.6 11.6(5) 106%	275.7 8.1(5) 98%	192.5 8.9(5)	196.1 10.0(5) 102%	201.1 2.6(5) 104%	196.3 10.8(5) 102%
Absolute Kidneys (g)	2.359 0.118(5)	2.657 0.248(5) 113%	**2.814** **0.241(5)** **119%**	2.609 0.173(5) 111%	1.654 0.112(5)	1.801 0.171(5) 109%	1.879 0.058(5) 114%	1.782 0.189(5) 108%
Kidney/ Brain %	121.378 7.022(5)	133.832 9.325(5) 110%	136.863 11.453(5) 113%	137.517 13.301(5) 113%	90.814 5.871(5)	96.952 8.261(5) 107%	**105.078** **4.542(5)** **116%**	98.199 9.722(5) 108%
Kidneys/ Body %	0.837 0.025(5)	**0.928** **0.043(5)** **111%**	**0.941** **0.055(5)** **112%**	**0.946** **0.039(5)** **113%**	0.859 0.044(5)	0.917 0.049(5) 107%	0.934 0.031(5) 109%	0.907 0.074(5) 106%
Absolute Liver (g)	9.508 0.446(5)	**14.802** **2.146(5)** **156%**	**15.390** **1.367(5)** **162%**	**17.469** **1.557(5)** **184%**	6.211 0.403(5)	6.718 0.825(5) 108%	7.108 0.442(5) 114%	**7.480** **0.852(5)** **120%**
Liver/ Brain %	489.142 27.614(5)	**746.577** **107.789** **(5)** **153%**	**747.853** **54.465(5)** **153%**	**920.632** **103.387 (5)** **188%**	341.767 32.436 (5)	361.153 36.272(5) 106%	397.805 33.651(5) 116%	**412.703** **50.029(5)** **121%**
Liver/ Body %	3.371 0.078(5)	**5.169** **0.617(5)** **153%**	**5.156** **0.456(5)** **153%**	**6.331** **0.430(5)** **188%**	3.230 0.222(5)	3.416 0.268(5) 106%	3.536 0.255(5) 109%	**3.810** **0.378(5)** **118%**
Comment:	Increased liver weight parameters were present in males at all dose levels and in females in the 300 mg/kg/day group. Increased kidney weights were also present in all male dose groups.							

Dose (mg/kg/day)	0	30	100	300	0	30	100	300
Histopath	Male				Female			
Comment:	Microscopic findings were limited to hepatocellular hypertrophy in all treated male and female dose groups. Lesions were graded as mild in all male groups and as minimal in all female groups.							

Dose (mg/kg/day)	30	
Plasma PK	Male	Female
Clearance time (h):	24	4
Graph:		
Comment:	Based on the experimental design, the pharmacokinetic graphs resulting from this class of chemicals makes traditional methods of half-life calculation inappropriate. In order to provide a basis for comparing these chemicals to each other, the clearance time of the analyte will be calculated instead. In traditional pharmacokinetics an analyte is considered to be completely cleared after 98.4% of the analyte is cleared from the plasma. 96- and 120-hour female plasma concentrations were below LOQ. The LOQ is approximately 20 ng/mL.	

Dose (mg/kg/day)	30	100	300
Total P450:	M – 127% of control* F – No stat. sign. effect	M – 136% of control* F – No stat. sign. effect	M – 146% of control* F – No stat. sign. effect
Total P450: 7-day recovery	M – No stat. sign. effect F – No stat. sign. effect	Not analyzed	
β-oxidation:	M – 754% of control* F – No stat. sign. effect	M – 726% of control* F – No stat. sign. effect	M – 899% of control* F – 266% of control*
β-oxidation: 7-day recovery	M – 154% of control* F – No stat. sign. effect	Not analyzed	
Comment:	* Statistically significant difference from control ($p \leq 0.05$) by Dunnett's test a The % of control and statistical analysis based on comparison to the respective control group sacrificed at the end of the exposure period.		

Appendix A
Individual LC/MS Plasma Sample Results

H-28307 Plasma Concentration for the specified timepoint (ng/mL)

Rat Number	Predose	15 min	30 min	1 Hour	2 Hour	4 Hour	8 Hour	12 Hour	24 Hour	48 Hour	72 Hour	96 Hour	120 Hour	144 Hour	168 Hour	168 Hr Cardiac
Rat #206	12740	109600	128000	79600	94400	54800	19600	4380	1814	434	158	109	160	63.4	130	153
Rat #207	12080	46400	74000	102400	125200	35400	29800	11740	1876	246	154	206	61.0	69.8	156	185
Rat #208	13040	72000	76600	121200	112800	66000	10800	6620	1066	272	228	260	113	115	72.2	264
Rat #256	40.6	62400	64800	22400	13760	252	294	148	214	<LOQ	25.6	<LOQ	<LOQ	27.0	<LOQ	41.4
Rat #257	67.6	90000	54000	39200	9340	1448	816	210	298	47.0	103	<LOQ	<LOQ	<LOQ	25.2	36.8
Rat #258	35.4	67200	65000	31000	8720	812	702	266	316	38.8	<LOQ	<LOQ	<LOQ	<LOQ	99.8	<LOQ

H-28307 Plasma Concentration for the specified timepoint (ng/mL)

Rat Number	Predose	15 min	30 min	1 Hour	2 Hour	4 Hour	8 Hour	12 Hour	24 Hour	48 Hour	72 Hour	96 Hour	120 Hour	144 Hour	168 Hour	168 Hr Cardiac
Rat #206	12740	109600	128000	79600	94400	54800	19600	4380	1814	434	158	109	160	63.4	130	153
Rat #207	12080	46400	74000	102400	125200	35400	29800	11740	1876	246	154	206	61	69.8	156	185
Rat #208	13040	72000	76600	121200	112800	66000	10800	6620	1066	272	228	260	113	115	72.2	264
Rat #256	40.6	62400	64800	22400	13760	252	294	148	214	20	25.6	20	20	27	20	41.4
Rat #257	67.6	90000	54000	39200	9340	1448	816	210	298	47	103	20	20	20	25.2	36.8
Rat #258	35.4	67200	65000	31000	8720	812	702	266	316	38.8	20	20	20	20	99.8	20

Appendix B
Individual LC/MS Liver Sample Results

		H-28307 Concentration (ng/g)
Males	30 mg/kg Rat #206	218
	30 mg/kg Rat #207	362
	30 mg/kg Rat #208	178
Females	30 mg/kg Rat #256	35.8
	30 mg/kg Rat #257	24.1
	30 mg/kg Rat #258	<LOQ

Appendix C
Individual LC/MS Fat Sample Results

		H-28307 Concentration (ng/g)
Males	30 mg/kg Rat #206	<LOQ
	30 mg/kg Rat #207	<LOQ
	30 mg/kg Rat #208	<LOQ
Females	30 mg/kg Rat #256	<LOQ
	30 mg/kg Rat #257	<LOQ
	30 mg/kg Rat #258	<LOQ

Appendix D
Summary and Individual Animal Clinical Pathology Data

EXPLANATORY NOTES

ABBREVIATIONS:

General:

Adeq	-	adequate
CLOT or Clot	-	sample clotted
Incr	-	increased
Mod	-	moderate
OK	-	sample condition OK for testing
UTD	-	unable to determine
-	-	not observed, no data
.	-	not taken, not performed, not observed, or results not valid

Individual Hematology Values:

WB	-	whole blood condition
RBC	-	red blood cell count
HGB	-	hemoglobin
HCT	-	hematocrit
MCV	-	mean corpuscular (cell) volume
MCH	-	mean corpuscular (cell) hemoglobin
MCHC	-	mean corpuscular (cell) hemoglobin concentration
RDW	-	red cell distribution width
ARET	-	absolute reticulocyte count
PLT	-	platelet count
WBC	-	white blood cell count
ANEU	-	absolute neutrophil (all forms)
ALYM	-	absolute lymphocyte
AMON	-	absolute monocyte
AEOS	-	absolute eosinophil
ABAS	-	absolute basophil
ALUC	-	absolute large unstained cell
NRBC	-	nucleated red blood cell count
NC	-	not calculated or not calculable

Individual Red Blood Cell / White Blood Cell / Platelet Morphology Values:

ANIS	-	anisocytosis
MIC	-	microcytes
MAC	-	macrocytes
POLY	-	polychromasia
HYPO	-	hypochromasia
ECHI	-	echinocytes
ACAN	-	acanthocytes
TARG	-	target cells
RX	-	rouleaux
HJB	-	Howell-Jolly body
SM	-	smudge white blood cells
TOX	-	toxic granulation
DB	-	Döhle bodies
VC	-	vacuolated cytoplasm
BC	-	basophilic cytoplasm
PCE	-	platelet clumps / estimate
GP	-	giant platelets
BP	-	bizarre platelets

Individual Clinical Chemistry Values:

HEM	-	hemolysis
LIP	-	lipemia
ICT	-	icterus
AST	-	aspartate aminotransferase
ALT	-	alanine aminotransferase
SDH	-	sorbitol dehydrogenase
ALKP	-	alkaline phosphatase
BILI	-	total bilirubin
BUN	-	urea nitrogen
CREA	-	creatinine
CHOL	-	cholesterol
TRIG	-	triglycerides
GLUC	-	glucose

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  TP  -  total protein
 ALB  -  albumin
GLOB  -  globulin
CALC  -  calcium
IPHS  -  inorganic phosphorous
  NA  -  sodium
   K  -  potassium
  CL  -  chloride
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NOTES:

When individual animal data are not reported, it may be due to one of the following reasons or other reasons, all of which are explained in the study records:
the sample was clotted (CLOT)
there was insufficient sample for testing (QNS)
a valid result could not be obtained (RNV)
the sample was not suitable for testing
the animal died prior to sample collection
no sample was available for testing (NSR)

Only positive findings were recorded for special observations (e.g., additional cell types) or observations marked other.

Groups with identical values may vary in statistical significance, because tabulated statistics are rounded to fewer decimal places than the values used for statistical determination.

Summary of Hematology Values for Male Rats

	Group 1 0 mg/kg/day	Group 2 30 mg/kg/day	Group 3 100 mg/kg/day	Group 4 300 mg/kg/day
RBC ($x10^6/\mu L$)				
DAY 7	7.46	7.17	7.03	7.04
	0.24(5)	0.21(5)	0.30(5)	0.60(4)
HGB (g/dL)				
DAY 7	14.6	14.6	13.9	13.4*
	0.6(5)	0.4(5)	0.6(5)	0.9(4)
HCT (%)				
DAY 7	47.3	47.5	44.6	43.7*
	1.7(5)	1.3(5)	1.9(5)	2.8(4)
MCV (fL)				
DAY 7	63.4	66.3*	63.4	62.1
	1.6(5)	1.6(5)	1.2(5)	1.4(4)
MCH (pg)				
DAY 7	19.7	20.4*	19.8	19.1
	0.6(5)	0.2(5)	0.2(5)	0.4(4)
MCHC (g/dL)				
DAY 7	31.0	30.8	31.2	30.7
	0.3(5)	0.5(5)	0.3(5)	0.4(4)
RDW (%)				
DAY 7	13.0	13.3	13.0	13.4
	0.5(5)	0.9(5)	0.3(5)	1.1(4)
ARET ($x10^3/\mu L$)				
DAY 7	286.3	285.4	282.8	296.0
	61.8(5)	71.4(5)	46.2(5)	84.9(4)
PLT ($x10^3/\mu L$)				
DAY 7	1258	1460	1173	1343
	237(5)	79(2)	157(4)	105(3)
WBC ($x10^3/\mu L$)				
DAY 7	12.70	14.62	14.02	15.22
	1.58(5)	2.31(5)	3.09(5)	2.50(4)
ANEU ($x10^3/\mu L$)				
DAY 7	1.31	1.64	1.57	1.69
	0.56(5)	0.53(5)	0.41(5)	0.95(4)
ALYM ($x10^3/\mu L$)				
DAY 7	10.80	12.17	11.79	12.93
	1.34(5)	1.68(5)	2.63(5)	1.51(4)
AMON ($x10^3/\mu L$)				
DAY 7	0.26	0.46	0.30	0.36
	0.16(5)	0.48(5)	0.14(5)	0.20(4)
AEOS ($x10^3/\mu L$)				
DAY 7	0.10	0.19	0.10	0.09
	0.04(5)	0.19(5)	0.05(5)	0.07(4)
ABAS ($x10^3/\mu L$)				
DAY 7	0.16	0.12	0.17	0.11
	0.06(5)	0.12(5)	0.08(5)	0.13(4)
ALUC ($x10^3/\mu L$)				
DAY 7	0.08	0.04	0.09	0.05
	0.02(5)	0.04(5)	0.02(5)	0.06(4)

NRBC (/100 WBC)				
DAY 7	-	1~ 0(2)	-	-

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.
~ Due to lack of control values or variability among group means, statistical analyses were unable to be performed.

Summary of Hematology Values for Female Rats

	Group 1 0 mg/kg/day	Group 2 30 mg/kg/day	Group 3 100 mg/kg/day	Group 4 300 mg/kg/day
RBC ($x10^6/\mu L$)				
DAY 7	7.58	7.87	7.30	6.71*
	0.34(5)	0.32(5)	0.25(5)	0.87(4)
HGB (g/dL)				
DAY 7	14.7	15.2	14.4	13.2
	0.4(5)	0.3(5)	0.3(5)	1.5(4)
HCT (%)				
DAY 7	45.3	46.9	44.6	41.3
	1.2(5)	1.2(5)	0.9(5)	4.1(4)
MCV (fL)				
DAY 7	59.8	59.7	61.2	61.9
	2.2(5)	2.8(5)	1.1(5)	3.3(4)
MCH (pg)				
DAY 7	19.4	19.4	19.7	19.6
	0.7(5)	0.9(5)	0.5(5)	0.5(4)
MCHC (g/dL)				
DAY 7	32.4	32.5	32.2	31.8
	0.2(5)	0.4(5)	0.4(5)	0.9(4)
RDW (%)				
DAY 7	11.0	11.2	11.2	13.2@
	0.3(5)	0.6(5)	0.2(5)	2.1(4)
ARET ($x10^3/\mu L$)				
DAY 7	212.9	210.7	205.1	524.7
	43.6(5)	21.9(5)	13.5(5)	214.3(4)
PLT ($x10^3/\mu L$)				
DAY 7	1135	1180	1163	1354
	114(3)	109(4)	131(3)	191(3)
WBC ($x10^3/\mu L$)				
DAY 7	10.22	9.12	10.14	13.41
	2.24(5)	1.92(5)	1.23(5)	3.30(4)
ANEU ($x10^3/\mu L$)				
DAY 7	0.77	0.56	0.77	1.42
	0.29(5)	0.17(5)	0.33(5)	0.72(4)
ALYM ($x10^3/\mu L$)				
DAY 7	8.87	8.04	8.88	11.40
	1.96(5)	1.69(5)	1.20(5)	2.91(4)
AMON ($x10^3/\mu L$)				
DAY 7	0.23	0.19	0.21	0.25
	0.09(5)	0.08(5)	0.10(5)	0.11(4)
AEOS ($x10^3/\mu L$)				
DAY 7	0.13	0.12	0.12	0.11
	0.10(5)	0.06(5)	0.09(5)	0.05(4)
ABAS ($x10^3/\mu L$)				
DAY 7	0.13	0.12	0.10	0.12
	0.05(5)	0.08(5)	0.10(5)	0.04(4)
ALUC ($x10^3/\mu L$)				
DAY 7	0.09	0.08	0.06	0.11
	0.04(5)	0.05(5)	0.06(5)	0.03(4)

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    Data arranged as:  Mean
                       Standard deviation (Number of values included in calculation)

 *   Statistically significant difference from control at p < 0.05 by Dunnett/Tamhane-Dunnett
     test.
 @   Statistically significant difference from control at p < 0.05 by Dunn's test.
 ~   Due to lack of control values or variability among group means, statistical analyses were
     unable to be performed.
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Summary of Clinical Chemistry Values for Male Rats

	Group 1 0 mg/kg/day	Group 2 30 mg/kg/day	Group 3 100 mg/kg/day	Group 4 300 mg/kg/day
AST (U/L)				
DAY 7	72	77	80	85
	4(5)	11(5)	14(5)	9(5)
ALT (U/L)				
DAY 7	33	29	26	33
	6(5)	5(5)	2(5)	6(5)
SDH (U/L)				
DAY 7	11.8	12.9	5.2	5.0
	1.9(5)	5.4(5)	5.1(5)	3.7(5)
ALKP (U/L)				
DAY 7	216	319*	264	320*
	44(5)	32(5)	71(5)	64(5)
BILI (mg/dL)				
DAY 7	0.13	0.11	0.13	0.15
	0.01(5)	0.02(5)	0.02(5)	0.05(5)
BUN (mg/dL)				
DAY 7	16	15	16	20*
	1(5)	2(5)	3(5)	2(5)
CREA (mg/dL)				
DAY 7	0.34	0.33	0.31	0.29*
	0.03(5)	0.02(5)	0.01(5)	0.02(5)
CHOL (mg/dL)				
DAY 7	59	30*	39*	35*
	9(5)	9(5)	5(5)	6(5)
TRIG (mg/dL)				
DAY 7	56	46	30*	37*
	8(5)	6(5)	8(5)	8(5)
GLUC (mg/dL)				
DAY 7	95	127	114	120@
	5(5)	44(5)	15(5)	6(5)
TP (g/dL)				
DAY 7	6.0	6.1	6.1	5.3*
	0.1(5)	0.3(5)	0.3(5)	0.4(5)
ALB (g/dL)				
DAY 7	3.4	3.8*	3.8*	3.5
	0.1(5)	0.1(5)	0.2(5)	0.3(5)
GLOB (g/dL)				
DAY 7	2.6	2.4	2.3*	1.8*
	0.1(5)	0.2(5)	0.2(5)	0.1(5)
CALC (mg/dL)				
DAY 7	11.0	10.8	10.8	10.3@
	0.2(5)	0.6(5)	0.3(5)	0.2(5)
IPHS (mg/dL)				
DAY 7	8.8	9.9	10.4	9.1
	0.5(5)	1.8(5)	1.1(5)	0.8(5)
NA (mmol/L)				
DAY 7	145.9	146.6	144.6	144.9
	1.9(5)	1.6(5)	2.4(5)	0.6(5)

K (mmol/L)				
DAY 7	6.17	6.55	6.68	6.49
	0.23(5)	0.23(5)	0.25(5)	0.48(5)
CL (mmol/L)				
DAY 7	100.6	102.0	102.2	102.4
	1.1(5)	1.9(5)	1.1(5)	2.3(5)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.
~ Due to lack of control values or variability among group means, statistical analyses were unable to be performed.

Summary of Clinical Chemistry Values for Female Rats

	Group 1 0 mg/kg/day	Group 2 30 mg/kg/day	Group 3 100 mg/kg/day	Group 4 300 mg/kg/day
AST (U/L)				
DAY 7	70	71	69	75
	2(5)	14(5)	7(5)	6(5)
ALT (U/L)				
DAY 7	21	24	24	27
	2(5)	5(5)	4(5)	3(5)
SDH (U/L)				
DAY 7	12.1	10.7	11.9	11.6
	2.1(5)	4.6(5)	3.3(5)	2.9(5)
ALKP (U/L)				
DAY 7	125	130	149	131
	33(5)	46(5)	64(5)	37(5)
BILI (mg/dL)				
DAY 7	0.13	0.13	0.12	0.10*
	0.02(5)	0.01(5)	0.01(5)	0.02(5)
BUN (mg/dL)				
DAY 7	16	14	14	14
	2(5)	2(5)	2(5)	3(5)
CREA (mg/dL)				
DAY 7	0.35	0.34	0.33	0.31
	0.01(5)	0.02(5)	0.03(5)	0.03(5)
CHOL (mg/dL)				
DAY 7	60	80*	64	65
	9(5)	10(5)	16(5)	9(5)
TRIG (mg/dL)				
DAY 7	34	36	34	29
	5(5)	7(5)	12(5)	8(5)
GLUC (mg/dL)				
DAY 7	101	102	98	99
	5(5)	5(5)	5(5)	7(5)
TP (g/dL)				
DAY 7	6.2	6.4	6.1	6.0
	0.3(5)	0.2(5)	0.4(5)	0.3(5)
ALB (g/dL)				
DAY 7	3.7	3.8	3.7	3.7
	0.2(5)	0.2(5)	0.2(5)	0.2(5)
GLOB (g/dL)				
DAY 7	2.5	2.5	2.4	2.3
	0.2(5)	0.1(5)	0.2(5)	0.1(5)
CALC (mg/dL)				
DAY 7	10.8	11.0	10.6	10.9
	0.3(5)	0.2(5)	0.2(5)	0.3(5)
IPHS (mg/dL)				
DAY 7	7.7	7.7	7.6	8.1
	0.5(5)	0.3(5)	0.5(5)	0.5(5)
NA (mmol/L)				
DAY 7	144.6	145.8	145.9	145.4
	1.1(5)	1.9(5)	1.0(5)	1.7(5)

K (mmol/L)				
DAY 7	6.08	5.93	5.91	6.04
	0.07(5)	0.34(5)	0.15(5)	0.58(5)
CL (mmol/L)				
DAY 7	100.3	101.2	101.2	102.8
	1.8(5)	2.2(5)	2.3(5)	1.5(5)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.
~ Due to lack of control values or variability among group means, statistical analyses were unable to be performed.

Individual Animal Clinical Pathology Data

Group Sex	Animal Number	Day Number	WB	RBC x10^6/uL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET x10^3/uL
2m	201	7	OK	7.01	14.3	46.2	65.9	20.4	30.9	14.0	300.3
	202	7	OK	6.95	14.2	47.5	68.3	20.5	30.0	14.5	397.0
	203	7	OK	7.43	15.2	49.7	66.8	20.5	30.7	12.3	213.6
	204	7	OK	7.35	14.8	47.1	64.0	20.1	31.4	12.8	280.8
	205	7	OK	7.10	14.7	47.1	66.4	20.7	31.2	13.0	235.1
3m	301	7	OK	6.58	13.0	41.6	63.2	19.7	31.2	12.7	335.1
	302	7	OK	6.92	13.8	44.5	64.4	19.9	30.9	13.5	228.1
	303	7	OK	7.30	14.1	45.0	61.5	19.4	31.5	13.0	262.5
	304	7	OK	7.32	14.6	47.0	64.3	19.9	31.0	13.0	326.9
	305	7	OK	7.03	14.1	44.8	63.7	20.0	31.5	12.8	261.6
4m	401	7	OK	7.48	14.0	45.9	61.4	18.7	30.4	12.9	319.3
	402	7	CLOT	.	.	.	.	.	.	.	.
	403	7	OK	6.73	13.1	42.3	62.8	19.5	31.1	12.7	240.3
	404	7	OK	7.60	14.2	46.1	60.6	18.7	30.9	12.9	218.9
	405	7	OK	6.36	12.3	40.5	63.6	19.3	30.3	15.1	405.6
1f	151	7	OK	8.04	15.2	46.5	57.9	18.9	32.6	10.9	182.4
	152	7	OK	7.72	14.8	46.1	59.8	19.2	32.1	11.0	231.1
	153	7	OK	7.11	14.5	44.7	62.8	20.4	32.5	10.6	218.7
	154	7	OK	7.48	14.7	45.7	61.0	19.7	32.2	11.5	272.2
	155	7	OK	7.57	14.1	43.5	57.5	18.7	32.5	11.0	160.0
2f	251	7	OK	7.70	15.5	47.5	61.7	20.2	32.7	10.9	217.5
	252	7	OK	7.90	14.9	46.4	58.7	18.9	32.2	11.0	178.6
	253	7	OK	7.58	15.0	45.4	59.9	19.8	33.0	10.9	235.7
	254	7	OK	8.40	15.2	46.6	55.5	18.1	32.6	10.9	200.2
	255	7	OK	7.75	15.5	48.5	62.5	20.0	32.0	12.2	221.3
3f	351	7	OK	7.14	14.4	44.2	61.9	20.1	32.5	11.1	194.5
	352	7	OK	7.14	14.2	44.0	61.7	20.0	32.4	11.0	214.2
	353	7	OK	7.74	14.8	46.1	59.6	19.1	32.0	11.3	216.0
	354	7	OK	7.21	14.6	44.8	62.2	20.2	32.5	11.4	186.7
	355	7	OK	7.29	14.0	44.1	60.5	19.2	31.7	11.0	214.0
4f	451	7	OK	6.74	13.1	41.1	61.1	19.4	31.8	11.8	432.9
	452	7	OK	6.34	12.9	42.0	66.3	20.3	30.6	15.8	799.2
	453	7	OK	7.89	15.1	46.0	58.3	19.2	32.9	11.2	296.8
	454	7	CLOT	.	.	.	.	.	.	.	.
	455	7	OK	5.85	11.5	36.1	61.7	19.6	31.8	13.9	569.9

Individual Animal Clinical Pathology Data

Group Sex	Animal Number	Day Number	PLT x10^3/uL	WBC x10^3/uL	ANEU x10^3/uL	ALYM x10^3/uL	AMON x10^3/uL	AEOS x10^3/uL	ABAS x10^3/uL	ALUC x10^3/uL	NRBC /100 WBC
2m	201	7	.	14.60	2.37	11.01	0.36	0.51	0.26	0.08	.
	202	7	.	18.59	2.04	15.06	1.30	0.19	0.00	0.00	1
	203	7	1516	13.54	1.31	11.57	0.29	0.09	0.21	0.06	.
	204	7	.	12.86	1.28	11.04	0.20	0.15	0.12	0.06	.
	205	7	1404	13.51	1.22	12.15	0.14	0.00	0.00	0.00	1
3m	301	7	.	17.51	2.12	14.67	0.40	0.17	0.07	0.09	.
	302	7	1012	13.96	1.33	11.96	0.16	0.11	0.29	0.10	.
	303	7	1365	16.71	1.84	14.05	0.49	0.05	0.17	0.11	.
	304	7	1084	10.77	1.46	8.84	0.19	0.09	0.13	0.05	.
	305	7	1229	11.17	1.11	9.44	0.26	0.07	0.21	0.08	.
4m	401	7	.	14.19	0.57	13.19	0.43	0.00	0.00	0.00	1
	402	7	.	.	.	.	.	.	.	.	.
	403	7	1256	18.75	2.84	14.79	0.58	0.14	0.27	0.13	.
	404	7	1312	14.96	1.94	12.57	0.30	0.15	0.00	0.00	2
	405	7	1460	12.96	1.42	11.15	0.12	0.05	0.15	0.07	.
1f	151	7	.	14.02	0.98	12.26	0.28	0.17	0.18	0.15	.
	152	7	.	9.24	0.56	8.06	0.16	0.29	0.09	0.08	.
	153	7	1074	9.08	0.65	7.81	0.34	0.09	0.15	0.05	.
	154	7	1266	10.38	1.17	8.78	0.12	0.05	0.16	0.10	.
	155	7	1064	8.37	0.48	7.45	0.23	0.07	0.07	0.07	.
2f	251	7	.	7.60	0.41	6.72	0.13	0.22	0.08	0.04	.
	252	7	1058	9.93	0.41	8.66	0.29	0.15	0.26	0.16	.
	253	7	1294	7.91	0.66	6.95	0.11	0.08	0.05	0.05	.
	254	7	1247	12.13	0.80	10.75	0.25	0.10	0.11	0.12	.
	255	7	1120	8.02	0.52	7.13	0.15	0.07	0.10	0.05	.
3f	351	7	.	9.29	0.37	8.73	0.19	0.00	0.00	0.00	.
	352	7	.	10.94	1.10	9.13	0.13	0.24	0.20	0.13	.
	353	7	1281	9.31	1.14	7.62	0.22	0.12	0.14	0.08	.
	354	7	1022	11.92	0.61	10.77	0.14	0.14	0.18	0.09	.
	355	7	1186	9.24	0.65	8.13	0.37	0.09	0.00	0.00	.
4f	451	7	1146	16.37	1.26	14.50	0.26	0.10	0.17	0.07	.
	452	7	1523	8.86	0.58	7.80	0.17	0.08	0.11	0.10	.
	453	7	.	15.19	1.52	12.82	0.40	0.19	0.10	0.15	.
	454	7	.	.	.	.	.	.	.	.	.
	455	7	1392	13.22	2.32	10.46	0.18	0.07	0.08	0.11	.

Individual Animal Clinical Pathology Data

Group Sex	Animal Number	Day Number	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX
1m	101	7	Trace	Trace	-	-	-	-	Trace	-	-
	102	7	Trace	Trace	-	-	-	Trace	Few	-	-
	103	7	-	-	-	-	-	-	Trace	-	-
	104	7	-	-	-	Trace	-	-	Trace	-	-
	105	7	-	-	-	-	-	-	-	-	-
2m	201	7	Trace	Trace	-	-	-	-	Trace	-	-
	202	7	-	-	-	Trace	-	Trace	Mod	-	-
	203	7	-	-	-	-	-	-	Trace	-	-
	204	7	-	-	-	-	-	-	Trace	-	-
	205	7	-	-	-	-	-	-	-	-	-
3m	301	7	-	-	-	Trace	-	Many	Few	-	-
	302	7	-	-	-	-	-	Trace	Few	-	-
	303	7	-	-	-	-	-	Trace	Few	-	-
	304	7	-	-	-	-	-	Few	Trace	-	-
	305	7	-	-	-	-	-	-	Trace	-	-
4m	401	7	-	-	-	-	-	-	Trace	-	-
	402	7	CLOT	.	.	.	.	.	.	.	.
	403	7	-	-	-	-	-	-	Trace	-	-
	404	7	-	-	-	-	-	-	-	-	-
	405	7	-	-	-	Trace	-	-	Trace	-	-
1f	151	7	-	-	-	-	-	Trace	Trace	-	-
	152	7	-	-	-	-	-	-	-	-	-
	153	7	-	-	-	-	-	-	-	-	-
	154	7	-	-	-	-	-	-	-	-	-
	155	7	-	-	-	-	-	Trace	Trace	-	-
2f	251	7	-	-	-	-	-	Trace	Trace	-	-
	252	7	-	-	-	-	-	-	-	-	-
	253	7	-	-	-	-	-	Trace	Trace	-	-
	254	7	-	-	-	-	-	Few	Few	-	-
	255	7	-	-	-	-	-	-	-	-	-
3f	351	7	-	-	-	-	-	Trace	Few	-	-
	352	7	-	-	-	-	-	-	Trace	-	-
	353	7	-	-	-	-	-	Few	Few	-	-
	354	7	-	-	-	-	-	Trace	Trace	-	-
	355	7	-	-	-	-	-	Trace	Trace	-	-
4f	451	7	-	-	-	Trace	-	Few	Trace	-	-
	452	7	-	-	-	Few	-	Trace	Trace	-	-
	453	7	-	-	-	-	-	Few	Trace	-	-
	454	7	CLOT	.	.	.	.	.	.	.	.
	455	7	-	-	-	Few	-	Trace	Trace	-	-

Individual Animal Clinical Pathology Data

Group Sex	Animal Number	Day Number	HJB	SM	TOX	DB	VC	BC	PCE	GP	BP
1m	101	7	-	-	-	-	-	-	-	Trace	-
	102	7	-	-	-	-	-	-	-	Trace	-
	103	7	-	-	-	-	-	-	-	-	-
	104	7	-	-	-	-	-	-	-	Trace	-
	105	7	-	-	-	-	-	-	-	Trace	-
2m	201	7	-	-	-	-	-	-	UTD	-	-
	202	7	-	-	-	-	-	-	UTD	-	-
	203	7	-	-	-	-	-	-	-	-	-
	204	7	-	-	-	-	-	-	Adeq	-	-
	205	7	-	-	-	-	-	-	-	-	-
3m	301	7	-	-	-	-	-	-	Incr	-	-
	302	7	-	-	-	-	-	-	-	Trace	-
	303	7	-	-	-	-	-	-	-	-	-
	304	7	-	-	-	-	-	-	-	-	-
	305	7	-	-	-	-	-	-	-	-	-
4m	401	7	-	-	-	-	-	-	UTD	Trace	-
	402	7	.	.	.	.	.	.	.	.	.
	403	7	-	-	-	-	-	-	-	-	-
	404	7	-	-	-	-	-	-	-	Trace	-
	405	7	-	-	-	-	-	-	-	-	-
1f	151	7	-	-	-	-	-	-	Adeq	Trace	-
	152	7	-	-	-	-	-	-	Adeq	-	-
	153	7	-	-	-	-	-	-	-	-	-
	154	7	-	-	-	-	-	-	-	-	-
	155	7	-	-	-	-	-	-	-	-	Few
2f	251	7	-	-	-	-	-	-	Adeq	-	-
	252	7	-	-	-	-	-	-	-	Trace	-
	253	7	-	-	-	-	-	-	-	-	-
	254	7	-	-	-	-	-	-	-	-	-
	255	7	-	-	-	-	-	-	-	Trace	-
3f	351	7	-	-	-	-	-	-	UTD	Trace	-
	352	7	-	-	-	-	-	-	Incr	Trace	-
	353	7	-	-	-	-	-	-	-	-	-
	354	7	-	-	-	-	-	-	-	-	-
	355	7	-	-	-	-	-	-	-	-	-
4f	451	7	-	-	-	-	-	-	-	-	-
	452	7	-	-	-	-	-	-	-	-	-
	453	7	-	-	-	-	-	-	Adeq	-	-
	454	7	.	.	.	.	.	.	.	.	.
	455	7	-	-	-	-	-	-	-	Trace	-

Individual Animal Clinical Pathology Data

Group Sex	Animal Number	Day Number	HEM	LIP	ICT	AST U/L	ALT U/L	SDH U/L	ALKP U/L	BILI mg/dL	BUN mg/dL	CREA mg/dL	CHOL mg/dL
1m	101	7	None	None	None	75	41	12.0	289	0.14	18	0.30	49
	102	7	None	None	None	74	34	12.9	222	0.13	14	0.36	58
	103	7	None	None	None	76	28	14.0	191	0.12	16	0.33	55
	104	7	None	None	None	70	34	11.0	201	0.13	16	0.32	74
	105	7	None	None	None	67	27	9.1	175	0.13	17	0.38	59
2m	201	7	Trace	None	None	72	28	7.4	340	0.14	15	0.30	34
	202	7	None	None	None	87	36	21.4	316	0.11	14	0.35	39
	203	7	None	None	None	86	31	14.4	360	0.11	14	0.34	20
	204	7	None	None	None	77	25	9.4	279	0.10	13	0.30	21
	205	7	None	None	None	61	24	12.1	299	0.10	17	0.34	34
3m	301	7	None	None	None	105	29	4.8	373	0.12	16	0.32	32
	302	7	Trace	None	None	72	25	6.7	179	0.12	16	0.30	40
	303	7	None	None	None	71	24	13.0	240	0.11	21	0.32	45
	304	7	Trace	None	None	77	28	1.6	254	0.15	13	0.30	38
	305	7	Trace	None	None	76	26	0.0	274	0.16	13	0.31	38
4m	401	7	None	None	None	96	40	3.6	348	0.12	17	0.28	29
	402	7	None	None	None	82	31	7.0	358	0.12	21	0.31	32
	403	7	Trace	None	None	81	27	4.6	213	0.16	23	0.30	33
	404	7	Small	None	None	93	39	0.0	308	0.22	22	0.32	43
	405	7	None	None	None	73	30	9.8	372	0.11	19	0.26	38
1f	151	7	None	None	None	68	19	14.1	161	0.11	18	0.36	49
	152	7	None	None	None	73	21	12.5	109	0.13	17	0.34	71
	153	7	None	None	None	69	23	10.6	158	0.15	18	0.34	57
	154	7	None	None	None	73	22	14.0	110	0.14	14	0.35	56
	155	7	None	None	None	69	22	9.2	85	0.14	15	0.37	66
2f	251	7	None	None	None	63	22	8.9	139	0.14	14	0.30	78
	252	7	None	None	None	64	25	13.4	123	0.12	16	0.34	97
	253	7	None	None	None	96	31	3.5	90	0.11	16	0.35	75
	254	7	None	None	None	66	22	12.8	95	0.13	14	0.36	73
	255	7	None	None	None	64	19	14.9	203	0.13	12	0.34	76
3f	351	7	None	None	None	60	25	7.9	108	0.11	15	0.32	72
	352	7	None	None	None	66	18	17.1	111	0.11	17	0.38	77
	353	7	None	None	None	69	28	10.7	97	0.14	13	0.32	69
	354	7	None	None	None	69	23	11.9	187	0.11	14	0.33	63
	355	7	None	None	None	79	27	11.9	244	0.11	13	0.30	37
4f	451	7	None	None	None	76	31	7.7	193	0.08	15	0.35	62
	452	7	None	None	None	66	28	13.3	131	0.11	14	0.30	70
	453	7	None	None	None	83	23	11.3	93	0.12	19	0.32	77
	454	7	None	None	None	72	27	15.3	115	0.09	13	0.32	61
	455	7	None	None	None	76	25	10.6	124	0.10	11	0.27	55

Individual Animal Clinical Pathology Data

Group Sex	Animal Number	Day Number	TRIG mg/dL	GLUC mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	CALC mg/dL	IPHS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
1m	101	7	48	94	6.0	3.5	2.5	11.2	9.1	144.4	6.53	99.5
	102	7	58	97	6.2	3.6	2.6	11.0	8.1	147.9	5.91	99.9
	103	7	47	102	6.0	3.4	2.6	10.9	9.2	144.7	6.24	100.8
	104	7	63	93	6.1	3.3	2.8	10.8	9.1	144.5	6.06	102.3
	105	7	62	89	5.9	3.4	2.5	10.9	8.3	148.2	6.10	100.4
2m	201	7	52	125	6.3	3.9	2.4	10.4	10.0	144.4	6.93	100.8
	202	7	50	202	6.2	3.7	2.5	11.8	12.9	145.7	6.58	102.5
	203	7	40	98	6.3	3.8	2.5	10.9	8.4	148.4	6.45	103.0
	204	7	47	93	5.6	3.6	2.0	10.4	9.8	147.0	6.35	104.3
	205	7	40	115	6.3	3.9	2.4	10.6	8.5	147.5	6.43	99.6
3m	301	7	32	133	6.6	4.1	2.5	11.3	11.4	141.7	6.84	103.8
	302	7	24	110	5.9	3.7	2.2	10.6	10.5	144.1	6.93	102.0
	303	7	43	126	6.0	3.9	2.1	10.8	11.7	143.6	6.27	102.7
	304	7	25	104	6.1	3.7	2.4	10.7	9.1	145.6	6.66	101.1
	305	7	25	96	6.0	3.7	2.3	10.6	9.5	148.0	6.68	101.2
4m	401	7	39	120	5.7	3.7	2.0	10.4	9.2	144.1	6.33	103.5
	402	7	46	111	5.3	3.5	1.8	10.4	8.8	144.5	6.53	104.0
	403	7	30	124	5.0	3.3	1.7	10.3	10.3	145.6	6.49	98.7
	404	7	27	119	5.0	3.2	1.8	10.0	9.3	145.3	7.22	104.2
	405	7	43	125	5.7	3.8	1.9	10.5	8.0	144.8	5.89	101.5
1f	151	7	30	103	5.8	3.5	2.3	10.5	8.3	145.2	6.07	102.6
	152	7	40	92	6.6	3.9	2.7	10.9	7.8	143.4	6.16	99.2
	153	7	38	101	5.9	3.6	2.3	10.4	7.6	146.3	6.13	101.6
	154	7	32	106	6.4	3.8	2.6	10.9	7.0	144.3	6.07	99.9
	155	7	28	102	6.4	3.8	2.6	11.1	7.7	143.9	5.99	98.2
2f	251	7	43	102	6.6	4.0	2.6	11.4	7.4	145.9	5.83	98.4
	252	7	32	104	6.3	3.9	2.4	11.0	7.3	146.5	5.85	100.3
	253	7	33	106	6.5	3.8	2.7	10.8	7.9	144.3	6.51	104.1
	254	7	28	94	6.3	3.9	2.4	11.0	7.6	143.7	5.61	102.7
	255	7	45	105	6.1	3.6	2.5	10.9	8.1	148.5	5.83	100.5
3f	351	7	52	95	5.8	3.5	2.3	10.5	8.1	144.8	5.72	100.2
	352	7	38	93	6.7	4.0	2.7	10.9	7.9	146.5	6.09	104.7
	353	7	33	97	6.4	3.8	2.6	10.7	8.0	144.8	5.93	98.3
	354	7	31	100	6.0	3.6	2.4	10.6	7.2	147.1	5.99	101.5
	355	7	18	106	5.7	3.5	2.2	10.3	6.9	146.1	5.80	101.1
4f	451	7	27	96	5.7	3.4	2.3	10.8	8.2	144.3	6.57	102.4
	452	7	33	93	6.2	3.8	2.4	11.3	8.2	147.8	6.56	101.0
	453	7	42	96	6.2	3.8	2.4	10.7	8.2	143.6	6.00	105.2
	454	7	23	110	5.7	3.6	2.1	11.1	8.5	146.2	5.16	102.2
	455	7	22	98	6.0	3.8	2.2	10.5	7.3	145.0	5.92	103.1

Appendix E
Summary and Individual Animal Pathology Data

Mean Final Body and Organ Weights from Male Rats

	Group 1 0 mg/kg/day	Group 2 30 mg/kg/day	Group 3 100 mg/kg/day	Group 4 300 mg/kg/day
MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)				
BRAIN	1.945	1.984	2.056	1.902
	0.049(5)	0.092(5)	0.051(5)	0.076(5)
HEART	1.189	1.176	1.246	1.093
	0.170(5)	0.130(5)	0.073(5)	0.066(5)
KIDNEYS	2.359	2.657	2.814*	2.609
	0.118(5)	0.248(5)	0.241(5)	0.173(5)
LIVER	9.508	14.802*	15.390*	17.469*
	0.446(5)	2.146(5)	1.367(5)	1.557(5)
SPLEEN	0.617	0.614	0.679	0.589
	0.069(5)	0.109(5)	0.091(5)	0.038(5)
TESTES	2.918	2.952	2.982	2.985
	0.146(5)	0.176(5)	0.165(5)	0.152(5)
THYMUS	0.539	0.498	0.547	0.501
	0.162(5)	0.118(5)	0.112(5)	0.066(5)
FINAL BODY WEIGHT (grams)				
	282.0	286.2	298.6	275.7
	7.9(5)	21.0(5)	11.6(5)	8.1(5)
MEAN RELATIVE ORGAN WEIGHTS (% of body weight)				
BRAIN/	0.690	0.695	0.690	0.691
FINAL BODY * 100	0.030(5)	0.035(5)	0.036(5)	0.046(5)
HEART/	0.421	0.410	0.417	0.397
FINAL BODY * 100	0.052(5)	0.019(5)	0.017(5)	0.021(5)
KIDNEYS/	0.837	0.928*	0.941*	0.946*
FINAL BODY * 100	0.025(5)	0.043(5)	0.055(5)	0.039(5)
LIVER/	3.371	5.169*	5.156*	6.331*
FINAL BODY * 100	0.078(5)	0.617(5)	0.456(5)	0.430(5)
SPLEEN/	0.219	0.214	0.227	0.214
FINAL BODY * 100	0.027(5)	0.022(5)	0.028(5)	0.015(5)
TESTES/	1.035	1.034	1.000	1.084
FINAL BODY * 100	0.048(5)	0.063(5)	0.060(5)	0.074(5)
THYMUS/	0.191	0.174	0.184	0.182
FINAL BODY * 100	0.057(5)	0.038(5)	0.039(5)	0.025(5)

MEAN RELATIVE ORGAN WEIGHTS (% of brain weight)

HEART/	61.243	59.148	60.653	57.529
BRAIN * 100	9.596(5)	4.144(5)	3.926(5)	3.851(5)
KIDNEYS/	121.378	133.832	136.863	137.517
BRAIN * 100	7.022(5)	9.325(5)	11.453(5)	13.301(5)
LIVER/	489.142	746.577*	747.853*	920.632*
BRAIN * 100	27.614(5)	107.789(5)	54.465(5)	103.387(5)
SPLEEN/	31.667	30.871	33.051	31.012
BRAIN * 100	2.886(5)	4.356(5)	4.427(5)	2.809(5)
TESTES/	150.077	148.864	145.146	157.088
BRAIN * 100	8.221(5)	8.609(5)	9.482(5)	9.813(5)
THYMUS/	27.884	25.056	26.631	26.337
BRAIN * 100	8.970(5)	5.618(5)	5.756(5)	3.225(5)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.

Mean Final Body and Organ Weights from Female Rats

	Group 1 0 mg/kg/day	Group 2 30 mg/kg/day	Group 3 100 mg/kg/day	Group 4 300 mg/kg/day
MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (grams)				
BRAIN	1.822	1.859	1.791	1.815
	0.082(5)	0.118(5)	0.102(5)	0.067(5)
HEART	0.847	0.854	0.910	0.854
	0.092(5)	0.060(5)	0.086(5)	0.056(5)
KIDNEYS	1.654	1.801	1.879	1.782
	0.112(5)	0.171(5)	0.058(5)	0.189(5)
LIVER	6.211	6.718	7.108	7.480*
	0.403(5)	0.825(5)	0.442(5)	0.852(5)
SPLEEN	0.478	0.462	0.415	0.483
	0.098(5)	0.048(5)	0.039(5)	0.057(5)
THYMUS	0.455	0.512	0.499	0.451
	0.063(5)	0.097(5)	0.106(5)	0.105(5)
FINAL BODY WEIGHT (grams)				
	192.5	196.1	201.1	196.3
	8.9(5)	10.0(5)	2.6(5)	10.8(5)
MEAN RELATIVE ORGAN WEIGHTS (% of body weight)				
BRAIN/	0.948	0.948	0.891	0.926
FINAL BODY * 100	0.053(5)	0.036(5)	0.049(5)	0.055(5)
HEART/	0.440	0.435	0.453	0.435
FINAL BODY * 100	0.049(5)	0.013(5)	0.045(5)	0.023(5)
KIDNEYS/	0.859	0.917	0.934	0.907
FINAL BODY * 100	0.044(5)	0.049(5)	0.031(5)	0.074(5)
LIVER/	3.230	3.416	3.536	3.810*
FINAL BODY * 100	0.222(5)	0.268(5)	0.255(5)	0.378(5)
SPLEEN/	0.247	0.236	0.206	0.246
FINAL BODY * 100	0.042(5)	0.025(5)	0.019(5)	0.024(5)
THYMUS/	0.236	0.260	0.248	0.230
FINAL BODY * 100	0.024(5)	0.039(5)	0.051(5)	0.053(5)
MEAN RELATIVE ORGAN WEIGHTS (% of brain weight)				
HEART/	46.690	45.952	50.961	47.101
BRAIN * 100	7.071(5)	2.172(5)	6.038(5)	3.192(5)

KIDNEYS/	90.814	96.952	105.078*	98.199
BRAIN * 100	5.871(5)	8.261(5)	4.542(5)	9.722(5)
LIVER/	341.767	361.153	397.805	412.703*
BRAIN * 100	32.436(5)	36.272(5)	33.651(5)	50.029(5)
SPLEEN/	26.126	24.894	23.116	26.656
BRAIN * 100	4.628(5)	2.772(5)	0.883(5)	3.470(5)
THYMUS/	25.008	27.514	27.905	24.980
BRAIN * 100	3.424(5)	4.596(5)	5.867(5)	6.437(5)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.

Individual Animal Final Body and Organ Weights

Group Sex	Animal Number	Bodywt g	Brain g	Heart g	Kidneys g	Liver g	Spleen g	Testes g	Thymus g
1m	101	275.6	1.987	0.969	2.359	9.244	0.719	3.056	0.320
	102	288.2	1.870	1.360	2.386	9.770	0.531	2.932	0.723
	103	279.4	1.985	1.275	2.260	9.583	0.616	2.733	0.499
	104	292.3	1.956	1.294	2.542	10.041	0.631	3.058	0.482
	105	274.3	1.927	1.047	2.250	8.901	0.587	2.809	0.672
	Mean	281.96	1.9450	1.1890	2.3594	9.5078	0.6168	2.9176	0.5392
	S.D.	7.93	0.0486	0.1705	0.1182	0.4462	0.0687	0.1457	0.1615
	N	5	5	5	5	5	5	5	5
2m	201	280.3	1.925	1.097	2.740	17.181	0.589	2.739	0.580
	202	318.7	2.112	1.376	3.053	16.926	0.803	3.042	0.635
	203	260.7	1.917	1.036	2.438	13.063	0.527	2.790	0.516
	204	289.1	1.915	1.159	2.525	14.263	0.594	3.134	0.355
	205	282.0	2.053	1.212	2.530	12.579	0.559	3.055	0.403
	Mean	286.16	1.9844	1.1760	2.6572	14.8024	0.6144	2.9520	0.4978
	S.D.	21.02	0.0920	0.1298	0.2476	2.1464	0.1088	0.1757	0.1176
	N	5	5	5	5	5	5	5	5
3m	301	306.0	2.022	1.256	2.860	15.929	0.642	2.803	0.670
	302	287.7	2.014	1.224	2.471	13.569	0.698	2.976	0.645
	303	286.2	2.105	1.135	2.677	15.564	0.547	3.028	0.479
	304	300.1	2.118	1.325	3.031	17.214	0.789	2.872	0.535
	305	313.1	2.022	1.292	3.031	14.672	0.720	3.233	0.404
	Mean	298.62	2.0562	1.2464	2.8140	15.3896	0.6792	2.9824	0.5466
	S.D.	11.62	0.0508	0.0729	0.2412	1.3674	0.0907	0.1653	0.1117
	N	5	5	5	5	5	5	5	5
4m	401	278.6	1.928	1.181	2.649	17.582	0.543	3.106	0.523
	402	262.2	2.014	1.035	2.376	16.090	0.595	3.039	0.497
	403	275.5	1.822	1.036	2.582	16.379	0.623	3.127	0.457
	404	278.5	1.902	1.145	2.578	17.265	0.557	2.782	0.600
	405	283.6	1.845	1.069	2.859	20.030	0.625	2.870	0.429
	Mean	275.68	1.9022	1.0932	2.6088	17.4692	0.5886	2.9848	0.5012
	S.D.	8.08	0.0756	0.0664	0.1733	1.5575	0.0375	0.1518	0.0660
	N	5	5	5	5	5	5	5	5

Nominal Dose: Group 1 - 0 mg/kg/ day Group 2 - 30 mg/kg/day Group 3 - 100 mg/kg/day Group 4 - 300 mg/kg/day

Individual Animal Final Body and Organ Weights

Group Sex	Animal Number	Brain %FBW	Heart %FBW	Kidney %FBW	Liver %FBW	Spleen %FBW	Testes %FBW	Thymus %FBW
1m	101	0.7210	0.3516	0.8560	3.3541	0.2609	1.1089	0.1161
	102	0.6489	0.4719	0.8279	3.3900	0.1842	1.0173	0.2509
	103	0.7105	0.4563	0.8089	3.4298	0.2205	0.9782	0.1786
	104	0.6692	0.4427	0.8697	3.4352	0.2159	1.0462	0.1649
	105	0.7025	0.3817	0.8203	3.2450	0.2140	1.0241	0.2450
	Mean	0.69042	0.42084	0.83656	3.37082	0.21910	1.03494	0.19110
	S.D.	0.03024	0.05164	0.02540	0.07762	0.02740	0.04808	0.05690
	N	5	5	5	5	5	5	5
2m	201	0.6868	0.3914	0.9775	6.1295	0.2101	0.9772	0.2069
	202	0.6627	0.4318	0.9580	5.3110	0.2520	0.9545	0.1992
	203	0.7353	0.3974	0.9352	5.0107	0.2021	1.0702	0.1979
	204	0.6624	0.4009	0.8734	4.9336	0.2055	1.0841	0.1228
	205	0.7280	0.4298	0.8972	4.4606	0.1982	1.0833	0.1429
	Mean	0.69504	0.41026	0.92826	5.16908	0.21358	1.03386	0.17394
	S.D.	0.03495	0.01907	0.04281	0.61746	0.02192	0.06284	0.03833
	N	5	5	5	5	5	5	5
3m	301	0.6608	0.4105	0.9346	5.2056	0.2098	0.9160	0.2190
	302	0.7000	0.4254	0.8589	4.7164	0.2426	1.0344	0.2242
	303	0.7355	0.3966	0.9354	5.4382	0.1911	1.0580	0.1674
	304	0.7058	0.4415	1.0100	5.7361	0.2629	0.9570	0.1783
	305	0.6458	0.4126	0.9681	4.6860	0.2300	1.0326	0.1290
	Mean	0.68958	0.41732	0.94140	5.15646	0.22728	0.99960	0.18358
	S.D.	0.03614	0.01694	0.05547	0.45628	0.02795	0.06024	0.03928
	N	5	5	5	5	5	5	5
4m	401	0.6920	0.4239	0.9508	6.3108	0.1949	1.1149	0.1877
	402	0.7681	0.3947	0.9062	6.1365	0.2269	1.1590	0.1895
	403	0.6613	0.3760	0.9372	5.9452	0.2261	1.1350	0.1659
	404	0.6829	0.4111	0.9257	6.1993	0.2000	0.9989	0.2154
	405	0.6506	0.3769	1.0081	7.0628	0.2204	1.0120	0.1513
	Mean	0.69098	0.39652	0.94560	6.33092	0.21366	1.08396	0.18196
	S.D.	0.04617	0.02104	0.03858	0.43010	0.01512	0.07350	0.02453
	N	5	5	5	5	5	5	5

Nominal Dose: Group 1 - 0 mg/kg/ day Group 2 - 30 mg/kg/day Group 3 - 100 mg/kg/day Group 4 - 300 mg/kg/day

Individual Animal Final Body and Organ Weights

Group Sex	Animal Number	Heart %Brain	Kidney %Brain	Liver %Brain	Spleen %Brain	Testes %Brain	Thymus %Brain
1m	101	48.7670	118.7217	465.2240	36.1852	153.7997	16.1047
	102	72.7273	127.5936	522.4599	28.3957	156.7914	38.6631
	103	64.2317	113.8539	482.7708	31.0327	137.6826	25.1385
	104	66.1554	129.9591	513.3436	32.2597	156.3395	24.6421
	105	54.3332	116.7618	461.9097	30.4619	145.7706	34.8729
	Mean	61.24292	121.37802	489.14160	31.66704	150.07676	27.88426
	S.D.	9.59621	7.02222	27.61368	2.88624	8.22081	8.96986
	N	5	5	5	5	5	5
2m	201	56.9870	142.3377	892.5195	30.5974	142.2857	30.1299
	202	65.1515	144.5549	801.4205	38.0208	144.0341	30.0663
	203	54.0428	127.1779	681.4293	27.4909	145.5399	26.9171
	204	60.5222	131.8538	744.8042	31.0183	163.6554	18.5379
	205	59.0356	123.2343	612.7131	27.2284	148.8066	19.6298
	Mean	59.14782	133.83172	746.57732	30.87116	148.86434	25.05620
	S.D.	4.14355	9.32509	107.78907	4.35631	8.60872	5.61784
	N	5	5	5	5	5	5
3m	301	62.1167	141.4441	787.7844	31.7507	138.6251	33.1355
	302	60.7746	122.6912	673.7339	34.6574	147.7656	32.0258
	303	53.9192	127.1734	739.3824	25.9857	143.8480	22.7553
	304	62.5590	143.1067	812.7479	37.2521	135.5996	25.2597
	305	63.8971	149.9011	725.6182	35.6083	159.8912	19.9802
	Mean	60.65332	136.86330	747.85336	33.05084	145.14590	26.63130
	S.D.	3.92614	11.45306	54.46477	4.42659	9.48188	5.75645
	N	5	5	5	5	5	5
4m	401	61.2552	137.3963	911.9295	28.1639	161.0996	27.1266
	402	51.3903	117.9742	798.9076	29.5432	150.8937	24.6773
	403	56.8606	141.7124	898.9572	34.1932	171.6246	25.0823
	404	60.1998	135.5415	907.7287	29.2850	146.2671	31.5457
	405	57.9404	154.9593	1085.6369	33.8753	155.5556	23.2520
	Mean	57.52926	137.51674	920.63198	31.01212	157.08812	26.33678
	S.D.	3.85089	13.30107	103.38698	2.80936	9.81345	3.22491
	N	5	5	5	5	5	5

Nominal Dose: Group 1 - 0 mg/kg/ day Group 2 - 30 mg/kg/day Group 3 - 100 mg/kg/day Group 4 - 300 mg/kg/day

Individual Animal Final Body and Organ Weights

Group Sex	Animal Number	Bodywt g	Brain g	Heart g	Kidneys g	Liver g	Spleen g	Thymus g
1f	151	195.9	1.871	0.819	1.749	6.701	0.559	0.457
	152	186.9	1.676	0.967	1.572	6.531	0.348	0.440
	153	199.7	1.846	0.914	1.800	5.946	0.564	0.466
	154	200.2	1.858	0.788	1.585	6.148	0.517	0.544
	155	179.7	1.860	0.745	1.562	5.729	0.402	0.369
	Mean	192.48	1.8222	0.8466	1.6536	6.2110	0.4780	0.4552
	S.D.	8.91	0.0822	0.0916	0.1121	0.4028	0.0977	0.0626
	N	5	5	5	5	5	5	5
2f	251	194.3	1.720	0.840	1.862	6.906	0.444	0.546
	252	192.8	1.878	0.869	1.687	6.515	0.395	0.431
	253	207.5	2.000	0.900	1.915	7.417	0.461	0.662
	254	182.0	1.760	0.756	1.563	5.395	0.485	0.427
	255	203.9	1.936	0.904	1.977	7.356	0.523	0.494
	Mean	196.10	1.8588	0.8538	1.8008	6.7178	0.4616	0.5120
	S.D.	10.05	0.1176	0.0605	0.1713	0.8250	0.0476	0.0972
	N	5	5	5	5	5	5	5
3f	351	201.6	1.800	0.758	1.823	6.952	0.419	0.481
	352	198.7	1.899	0.961	1.956	7.667	0.459	0.453
	353	203.9	1.835	0.928	1.875	7.111	0.431	0.677
	354	198.3	1.625	0.959	1.826	7.332	0.354	0.488
	355	203.2	1.798	0.944	1.916	6.479	0.411	0.396
	Mean	201.14	1.7914	0.9100	1.8792	7.1082	0.4148	0.4990
	S.D.	2.55	0.1016	0.0860	0.0576	0.4423	0.0386	0.1059
	N	5	5	5	5	5	5	5
4f	451	201.1	1.784	0.796	1.583	6.590	0.516	0.451
	452	207.4	1.886	0.917	1.972	8.131	0.542	0.365
	453	182.8	1.869	0.800	1.636	6.539	0.399	0.330
	454	187.0	1.719	0.854	1.730	7.841	0.505	0.531
	455	203.4	1.816	0.904	1.989	8.299	0.452	0.576
	Mean	196.34	1.8148	0.8542	1.7820	7.4800	0.4828	0.4506
	S.D.	10.79	0.0673	0.0565	0.1888	0.8518	0.0572	0.1050
	N	5	5	5	5	5	5	5

Nominal Dose: Group 1 - 0 mg/kg/ day Group 2 - 30 mg/kg/day Group 3 - 100 mg/kg/day Group 4 - 300 mg/kg/day

Individual Animal Final Body and Organ Weights

Group Sex	Animal Number	Brain %FBW	Heart %FBW	Kidney %FBW	Liver %FBW	Spleen %FBW	Thymus %FBW
1f	151	0.9551	0.4181	0.8928	3.4206	0.2853	0.2333
	152	0.8967	0.5174	0.8411	3.4944	0.1862	0.2354
	153	0.9244	0.4577	0.9014	2.9775	0.2824	0.2334
	154	0.9281	0.3936	0.7917	3.0709	0.2582	0.2717
	155	1.0351	0.4146	0.8692	3.1881	0.2237	0.2053
	Mean	0.94788	0.44028	0.85924	3.23030	0.24716	0.23582
	S.D.	0.05297	0.04894	0.04442	0.22196	0.04209	0.02362
	N	5	5	5	5	5	5
2f	251	0.8852	0.4323	0.9583	3.5543	0.2285	0.2810
	252	0.9741	0.4507	0.8750	3.3791	0.2049	0.2235
	253	0.9639	0.4337	0.9229	3.5745	0.2222	0.3190
	254	0.9670	0.4154	0.8588	2.9643	0.2665	0.2346
	255	0.9495	0.4434	0.9696	3.6077	0.2565	0.2423
	Mean	0.94794	0.43510	0.91692	3.41598	0.23572	0.26008
	S.D.	0.03620	0.01332	0.04914	0.26758	0.02532	0.03941
	N	5	5	5	5	5	5
3f	351	0.8929	0.3760	0.9043	3.4484	0.2078	0.2386
	352	0.9557	0.4836	0.9844	3.8586	0.2310	0.2280
	353	0.9000	0.4551	0.9196	3.4875	0.2114	0.3320
	354	0.8195	0.4836	0.9208	3.6974	0.1785	0.2461
	355	0.8848	0.4646	0.9429	3.1885	0.2023	0.1949
	Mean	0.89058	0.45258	0.93440	3.53608	0.20620	0.24792
	S.D.	0.04853	0.04455	0.03115	0.25539	0.01889	0.05091
	N	5	5	5	5	5	5
4f	451	0.8871	0.3958	0.7872	3.2770	0.2566	0.2243
	452	0.9094	0.4421	0.9508	3.9204	0.2613	0.1760
	453	1.0224	0.4376	0.8950	3.5771	0.2183	0.1805
	454	0.9193	0.4567	0.9251	4.1930	0.2701	0.2840
	455	0.8928	0.4444	0.9779	4.0801	0.2222	0.2832
	Mean	0.92620	0.43532	0.90720	3.80952	0.24570	0.22960
	S.D.	0.05529	0.02320	0.07377	0.37755	0.02377	0.05278
	N	5	5	5	5	5	5

Nominal Dose: Group 1 - 0 mg/kg/ day Group 2 - 30 mg/kg/day Group 3 - 100 mg/kg/day Group 4 - 300 mg/kg/day

Individual Animal Final Body and Organ Weights

Group Sex	Animal Number	Heart %Brain	Kidney %Brain	Liver %Brain	Spleen %Brain	Thymus %Brain
1f	151	43.7734	93.4794	358.1507	29.8771	24.4254
	152	57.6969	93.7947	389.6778	20.7637	26.2530
	153	49.5125	97.5081	322.1018	30.5525	25.2438
	154	42.4112	85.3068	330.8934	27.8256	29.2788
	155	40.0538	83.9785	308.0108	21.6129	19.8387
	Mean	46.68956	90.81350	341.76690	26.12636	25.00794
	S.D.	7.07058	5.87055	32.43573	4.62806	3.42441
	N	5	5	5	5	5
2f	251	48.8372	108.2558	401.5116	25.8140	31.7442
	252	46.2726	89.8296	346.9116	21.0330	22.9499
	253	45.0000	95.7500	370.8500	23.0500	33.1000
	254	42.9545	88.8068	306.5341	27.5568	24.2614
	255	46.6942	102.1178	379.9587	27.0145	25.5165
	Mean	45.95170	96.95200	361.15320	24.89366	27.51440
	S.D.	2.17194	8.26104	36.27170	2.77223	4.59615
	N	5	5	5	5	5
3f	351	42.1111	101.2778	386.2222	23.2778	26.7222
	352	50.6056	103.0016	403.7388	24.1706	23.8547
	353	50.5722	102.1798	387.5204	23.4877	36.8937
	354	59.0154	112.3692	451.2000	21.7846	30.0308
	355	52.5028	106.5628	360.3448	22.8587	22.0245
	Mean	50.96142	105.07824	397.80524	23.11588	27.90518
	S.D.	6.03839	4.54199	33.65055	0.88252	5.86728
	N	5	5	5	5	5
4f	451	44.6188	88.7332	369.3946	28.9238	25.2803
	452	48.6214	104.5599	431.1241	28.7381	19.3531
	453	42.8036	87.5334	349.8662	21.3483	17.6565
	454	49.6800	100.6399	456.1373	29.3775	30.8901
	455	49.7797	109.5264	456.9934	24.8899	31.7181
	Mean	47.10070	98.19856	412.70312	26.65552	24.97962
	S.D.	3.19246	9.72221	50.02898	3.47043	6.43656
	N	5	5	5	5	5

Nominal Dose: Group 1 - 0 mg/kg/ day Group 2 - 30 mg/kg/day Group 3 - 100 mg/kg/day Group 4 - 300 mg/kg/day

Appendix F
Individual Mechanistic Evaluation Data

Peroxisomal Beta-Oxidation Activity in Male Rats

Animal Number	Timepoint	Group	Dosage (mg/kg)	Rate (nmol/mg-min)	Group Average	Standard Deviation	
101	7-Day	1	0	9.4	7.2	1.5	
102	7-Day	1	0	7.5			
103	7-Day	1	0	5.4			
104	7-Day	1	0	6.3			
105	7-Day	1	0	7.6			
201	7-Day	2	30	72.5	54.3	13.3	*
202	7-Day	2	30	52.2			
203	7-Day	2	30	61.0			
204	7-Day	2	30	48.9			
205	7-Day	2	30	37.1			
301	7-Day	3	100	66.3	52.3	12.5	*
302	7-Day	3	100	49.8			
303	7-Day	3	100	63.6			
304	7-Day	3	100	45.7			
305	7-Day	3	100	36.3			
401	7-Day	4	300	56.8	64.7	5.2	*
402	7-Day	4	300	70.7			
403	7-Day	4	300	66.8			
404	7-Day	4	300	63.1			
405	7-Day	4	300	66.1			
206	7-Day Recovery	2	30	11.6	11.1	0.5	*[a]
207	7-Day Recovery	2	30	10.8			
208	7-Day Recovery	2	30	10.8			

* Statistically significant difference from control ($p \leq 0.05$) by Dunnett's test.
[a] Statistical analysis based on comparison to the control group sacrificed at the end of the exposure period.

Peroxisomal Beta-Oxidation Activity in Female Rats

Animal Number	Timepoint	Group	Dosage (mg/kg)	Rate (nmol/mg-min)	Group Average	Standard Deviation	
151	7-Day	1	0	9.9	7.9	1.9	
152	7-Day	1	0	4.8			
153	7-Day	1	0	8.2			
154	7-Day	1	0	7.7			
155	7-Day	1	0	8.7			
251	7-Day	2	30	10.9	9.7	2.8	
252	7-Day	2	30	14.0			
253	7-Day	2	30	7.5			
254	7-Day	2	30	7.7			
255	7-Day	2	30	8.2			
351	7-Day	3	100	7.7	10.7	2.2	
352	7-Day	3	100	12.9			
353	7-Day	3	100	9.5			
354	7-Day	3	100	12.7			
355	7-Day	3	100	10.5			
451	7-Day	4	300	19.9	21.0	2.7	*
452	7-Day	4	300	17.1			
453	7-Day	4	300	22.5			
454	7-Day	4	300	24.4			
455	7-Day	4	300	21.0			
256	7-Day Recovery	2	30	9.5	8.8	1.1	[a]
257	7-Day Recovery	2	30	9.4			
258	7-Day Recovery	2	30	7.6			

* Statistically significant difference from control ($p \leq 0.05$) by Dunnett's test.
[a] Statistical analysis based on comparison to the control group sacrificed at the end of the exposure period.

Microsomal Cytochrome P-450 Content in Male Rats

Animal Number	Timepoint	Group	Dosage (mg/kg)	nmol/mg protein	Group Average	Standard Deviation	
101	7-Day	1	0	0.647	0.658	0.056	
102	7-Day	1	0	0.581			
103	7-Day	1	0	0.639			
104	7-Day	1	0	0.693			
105	7-Day	1	0	0.729			
201	7-Day	2	30	0.677	0.837	0.124	*
202	7-Day	2	30	0.755			
203	7-Day	2	30	0.890			
204	7-Day	2	30	0.997			
205	7-Day	2	30	0.867			
301	7-Day	3	100	0.792	0.896	0.133	*
302	7-Day	3	100	0.781			
303	7-Day	3	100	0.888			
304	7-Day	3	100	0.907			
305	7-Day	3	100	1.111			
401	7-Day	4	300	1.028	0.961	0.097	*
402	7-Day	4	300	1.054			
403	7-Day	4	300	0.921			
404	7-Day	4	300	0.813			
405	7-Day	4	300	0.991			
206	7-Day Recovery	2	30	0.632	0.656	0.022	[a]
207	7-Day Recovery	2	30	0.660			
208	7-Day Recovery	2	30	0.676			

* Statistically significant difference from control ($p \leq 0.05$) by Dunnett's test.
[a] Statistical analysis based on comparison to the control group sacrificed at the end of the exposure period.

Microsomal Cytochrome P-450 Content in Female Rats

Animal Number	Timepoint	Group	Dosage (mg/kg)	nmol/mg protein	Group Average	Standard Deviation	
151	7-Day	1	0	0.412	0.389	0.055	
152	7-Day	1	0	0.300			
153	7-Day	1	0	0.372			
154	7-Day	1	0	0.429			
155	7-Day	1	0	0.430			
251	7-Day	2	30	0.467	0.428	0.036	
252	7-Day	2	30	0.404			
253	7-Day	2	30	0.397			
254	7-Day	2	30	0.468			
255	7-Day	2	30	0.403			
351	7-Day	3	100	0.417	0.329	0.088	
352	7-Day	3	100	0.225			
353	7-Day	3	100	0.423			
354	7-Day	3	100	0.299			
355	7-Day	3	100	0.280			
451	7-Day	4	300	0.399	0.477	0.068	
452	7-Day	4	300	0.431			
453	7-Day	4	300	0.549			
454	7-Day	4	300	0.546			
455	7-Day	4	300	0.462			
256	7-Day Rec	2	30	0.525	0.424	0.088	[a]
257	7-Day Rec	2	30	0.384			
258	7-Day Rec	2	30	0.362			

There were no statistically significant differences from control ($p \leq 0.05$) by Dunnett's test.
[a] Statistical analysis based on comparison to the control group sacrificed at the end of the exposure period.