

# **Toxicological Evaluation of a Novel Umami Flavour Compound: 2-(((3-(2,3-dimethoxyphenyl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)pyridine**

Donald S. Karanewsky<sup>a</sup>, Amy J. Arthur<sup>a,1</sup>, Hanghui Liu<sup>a</sup>, Bert Chi<sup>a</sup>, Lily Ida<sup>a</sup>, and Stacy Markison<sup>a,b</sup>

<sup>a</sup>Senomyx, Inc., 4767 Nexus Centre Drive, San Diego, CA 92121

<sup>b</sup>Current address: Crinetics Pharmaceuticals, Inc., 6197 Cornerstone Ct, San Diego, CA 92121

## **Supplemental Material**

## Supplemental Material

### Table of Contents

#### **Qualitative Metabolic Profiling of S3643 Using Human and Rat Mixed Gender Pooled Hepatic Microsomes**

Incubation of S3643 with rat and human liver microsomes.....	5
Control Microsome Incubations for Testosterone.....	5
Analytical Methods.....	5
Figure 1. +ESI Extracted Ion Chromatogram of Four Synthetic Standards and m/z 345.1016 Metabolites M344A (RT = 5.35 min) and M344 B (RT = 4.27 min) in RLM Incubations (60 min).....	8
Table 1. Major Metabolites of S3643 in Rat and Human Microsomal Incubations.....	9
Figure 2a. Proposed Fragmentation of S3643.....	9
Figure 2b. Proposed Fragmentation of M344A.....	10
Figure 2c. Proposed Fragmentation of M344B.....	10
Figure 2d. Proposed Fragmentation of M314A.....	11
Figure 2e. Proposed Fragmentation of M314B.....	11
Figure 2f. Proposed Fragmentation of M330A.....	12
Figure 2g. Proposed Fragmentation of M330B.....	12
Figure 2h. Proposed Fragmentation of M330C.....	12
Figure 2i. Proposed Fragmentation of M330D.....	13
Figure 2j. Proposed Fragmentation of M300.....	13

#### **Pharmacokinetics and Bioavailability of S3643 in Sprague-Dawley Rats**

Experimental Study Design.....	14
Sample Collection, Handling, Storage, and Transfer.....	14
Plasma Sample Preparation.....	15
LC-MS/MS Analysis.....	15
Figure 3. Structures of S3643 and Internal Standard S9767.....	16
Table 2. Concentrations and Pharmacokinetic Parameters of S3643 in Plasma Following Single Intravenous Administration to SD Rats.....	17
Table 3. Concentrations and Pharmacokinetic Parameters of S3643 in Plasma Following Single Oral Administration to SD Rats.....	18
Table 4. Comparison of S3643 Exposure ( $AUC_{last}$ and $C_{max}$ ) in Plasma Between Female and Male Following Single IV and Oral Administration to SD Rats.....	19
Table 5. Absolute Bioavailability of S3643 in Plasma Following Single IV and Oral Administration to SD Rats.....	19

#### ***In Vivo* Metabolism of S3643 in Rats**

Experimental Study Design.....	20
Sample Collection, Handling, Storage, and Transfer.....	20
Plasma Sample Preparation.....	20
LC-QTOF/MS Analysis.....	20
Table 6. Phase II Metabolites of S3643 Observed in Rat Plasma.....	21
Figure 4a. Proposed Fragmentation of M394.....	22

Figure 4b. Proposed Fragmentation of M520.....	22
--	----

**Reverse Bacterial Mutation Assay: S3643**

Table 7. Plate Incorporation Assay.....	23
Table 8. Preincubation Assay.....	26

***In Vitro* Chromosome Aberration Test of S3643 in Human Lymphocytes**

Table 9. Relative Growth Rate.....	29
Table 10. Relative Mitotic Index.....	30
Table 11-1. Structural Chromosome Aberrations, 3 Hours, -S9.....	31
Table 11-2. Structural Chromosome Aberrations, 3 Hours, +S9.....	32
Table 11-3. Structural Chromosome Aberrations, 20 Hours, -S9.....	33
Table 11-4. Numerical Chromosome Aberrations.....	34

***In Vitro* Micronucleus Test of S3643 in Chinese Hamster Ovary Cells**

Table 12-1. Cytostasis.....	35
Table 12-2. Micronuclei Incidence.....	36

**28-Day Toxicology Study of S3643 in Sprague-Dawley Rats**

Study Design.....	37
Table 13. Pathology Procedures.....	37
Table 14-1. Summary of Body Weights – Male.....	39
Table 14-2. Summary of Body Weights – Female.....	39
Table 15-1. Summary of Food Consumption Values – Male.....	40
Table 15-2. Summary of Food Consumption Values – Female.....	40
Table 16-1. Summary of Hematology Values – Male.....	41
Table 16-2. Summary of Hematology Values – Female.....	43
Table 17-1. Summary of Coagulation Values – Male.....	45
Table 17-2. Summary of Coagulation Values – Female.....	45
Table 18-1. Summary of Clinical Chemistry Values – Male.....	46
Table 18-2. Summary of Clinical Chemistry Values – Female.....	49
Table 19-1. Summary of Urinalysis Values – Male.....	52
Table 19-2. Summary of Urinalysis Values – Female.....	52
Table 20-1. Summary of Macroscopic Observations – Male.....	53
Table 20-2. Summary of Macroscopic Observations – Female.....	53
Table 21-1. Summary of Organ Weight Values – Male.....	54
Table 21-2. Summary of Organ Weight Values – Female.....	61
Table 22-1. Summary of Microscopic Observations – Male.....	68
Table 22-2. Summary of Microscopic Observations – Female.....	68

**90-Day Toxicology Study of S3643 in Sprague-Dawley Rats**

Study Design.....	69
Sample Collection for Toxicokinetic Analysis.....	69
Sample Preparation for Toxicokinetic Analysis.....	69

Analytical Method.....	69
Table 23-1. Concentration Analysis of S3643 in Plasma on Day 7.....	70
Table 23-2. Concentration Analysis of S3643 in Plasma on Day 90.....	71
Table 24. Pathology Procedures.....	72
Table 25-1. Summary of Body Weights – Male.....	74
Table 25-2. Summary of Body Weights – Female.....	75
Table 25-3. Summary of Toxicokinetic Body Weights – Male.....	76
Table 25-4. Summary of Toxicokinetic Body Weights – Female.....	77
Table 26-1. Summary of Food Consumption Values – Male.....	78
Table 26-2. Summary of Food Consumption Values – Female.....	79
Table 27-1. Summary of Hematology Values – Male.....	80
Table 27-2. Summary of Hematology Values – Female.....	83
Table 28-1. Summary of Coagulation Values – Male.....	86
Table 28-2. Summary of Coagulation Values – Female.....	86
Table 29-1. Summary of Clinical Chemistry Values – Male.....	87
Table 29-2. Summary of Clinical Chemistry Values – Female.....	92
Table 30-1. Summary of Urinalysis Values – Male.....	97
Table 30-2. Summary of Urinalysis Values – Female.....	97
Table 31-1. Summary of Macroscopic Observations – Male.....	98
Table 31-2. Summary of Macroscopic Observations – Female.....	99
Table 32-1. Summary of Organ Weight Values – Male.....	100
Table 32-2. Summary of Organ Weight Values – Female.....	107
Table 33-1. Summary of Microscopic Observations – Male.....	113
Table 33-2. Summary of Microscopic Observations – Female.....	121

## Qualitative Metabolic Profiling of S3643 Using Human and Rat Mixed Gender Pooled Hepatic Microsomes

PharmOptima Study No. 2011-156  
Senomyx Study No. S3643-PK2

### Incubation of S3643 with rat and human liver microsomes

A stock solution of S3643 was prepared at 2.0 mM in methanol. Exactly 13.9  $\mu\text{L}$  of 2.0 mM S3643 was added to 2.5 mL of human and rat microsomes (0.556 mg/mL in potassium phosphate buffer). Two hundred and twenty-five  $\mu\text{L}$  of microsomes containing S3643 were aliquoted to 1.5 mL microcentrifuge tubes. At this point, 0 minute incubation samples received 500  $\mu\text{L}$  of acetonitrile. Samples then received 25  $\mu\text{L}$  of either potassium phosphate buffer (minus NADPH control) or potassium phosphate buffer containing 14.4 mM NADPH. Samples were then incubated at 37°C for 60 minutes. (The final microsome concentration for each species was 0.50 mg/mL; the final concentration of S3643 was 10  $\mu\text{M}$ ). After 60 minutes, 500  $\mu\text{L}$  of acetonitrile was added to samples to quench all microsomal activity. Samples were then centrifuged at 14,000 rpm for 10 minutes at 4°C to separate the precipitated microsomes from the supernatant containing S3643 and its potential metabolites. The samples were stored at -80°C until analysis, when they were thawed at room temperature, and analyzed in a chilled autosampler at 10°C.

### Control Microsome Incubations for Testosterone

A stock solution of testosterone was prepared at 20 mM in methanol. Exactly 8.3  $\mu\text{L}$  of testosterone 20 mM stock was added to 1.50 mL of pooled mixed gender human and rat microsomes at 0.556 mg/mL. Two hundred and twenty-five  $\mu\text{L}$  of microsomes containing testosterone were aliquoted to 1.5 mL microcentrifuge tubes. At this point, samples received 25  $\mu\text{L}$  of either potassium phosphate buffer (minus NADPH control) or 14.4 mM NADPH in potassium phosphate buffer. Samples were incubated at 37°C for 60 minutes. (The final microsome concentration for each species was 0.50 mg/mL; the final concentration of testosterone was 99.1  $\mu\text{M}$ ). After 60 minutes, 500  $\mu\text{L}$  of acetonitrile was added to samples to quench all microsomal activity. Samples were centrifuged at 14,000 rpm for 10 minutes at 4°C to separate the precipitated microsomes from the supernatant containing testosterone and metabolites. The samples were stored at -80°C until analysis, when they were thawed at room temperature, and analyzed in a chilled autosampler at 10°C.

## Analytical Methods

### HPLC Conditions

HPLC pump:	Thermo Electron Accela Pump
Autosampler:	LEAP Technologies HTC PAL
Injection volume:	10 $\mu\text{L}$
Flow rate:	0.300 mL/min
Mobile Phase:	A: 1 mM ammonium acetate in water B: 1 mM ammonium acetate in methanol
Gradient:	0.0 – 1.0 min isocratic 5% B 1.0 – 5.5 min linear gradient 5 – 100% B

Column: 5.5 – 6.5 min isocratic at 100% B  
6.6 – 10.0 min re-equilibrate at 5% B  
Phenomenex Kinetex C18, 2.6  $\mu\text{m}$ , 50  $\times$  2.1 mm, 100 Å pore size,  
with guard column.

### **ESI + MS Conditions**

Instrument: Thermo Electron Quantum Access  
Ionization: Heated Electrospray (HESI)  
Resolution: 0.7 Thompsons (Th) at half peak height  
Spray Voltage: 5000 V  
Vaporizer Temperature: 325°C  
Sheath Gas Pressure: 30 psi  
Auxiliary Gas Pressure: 25 (arbitrary Thermo units)  
Sweep Gas pressure: 5 (arbitrary Thermo units)  
Capillary Temperature: 350°C  
Tube Lens Offset: 77  
Skimmer Offset: 6

### **ESI - MS Conditions**

Instrument: Thermo Electron Quantum Access  
Ionization: Heated Electrospray (HESI)  
Resolution: 0.7 Thompsons (Th) at half peak height  
Spray Voltage: 2500 V  
Vaporizer Temperature: 200°C  
Sheath Gas Pressure: 30 psi  
Auxiliary Gas Pressure: 25 (arbitrary Thermo units)  
Sweep Gas pressure: 5 (arbitrary Thermo units)  
Capillary Temperature: 250°C  
Tube Lens Offset: -77  
Skimmer Offset: 2

### **LC-QTOF/MS Analysis**

Samples from duplicate incubations with rat microsomes were also analyzed using an LC-QTOF/MS (Agilent iFunnel 6550A MS Q-TOF) equipped with an Agilent 1290 Infinity Binary pump and an Agilent 1290 Infinity autosampler. The HPLC and MS conditions are described in the tables below.

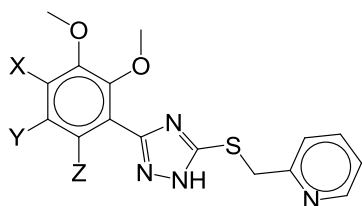
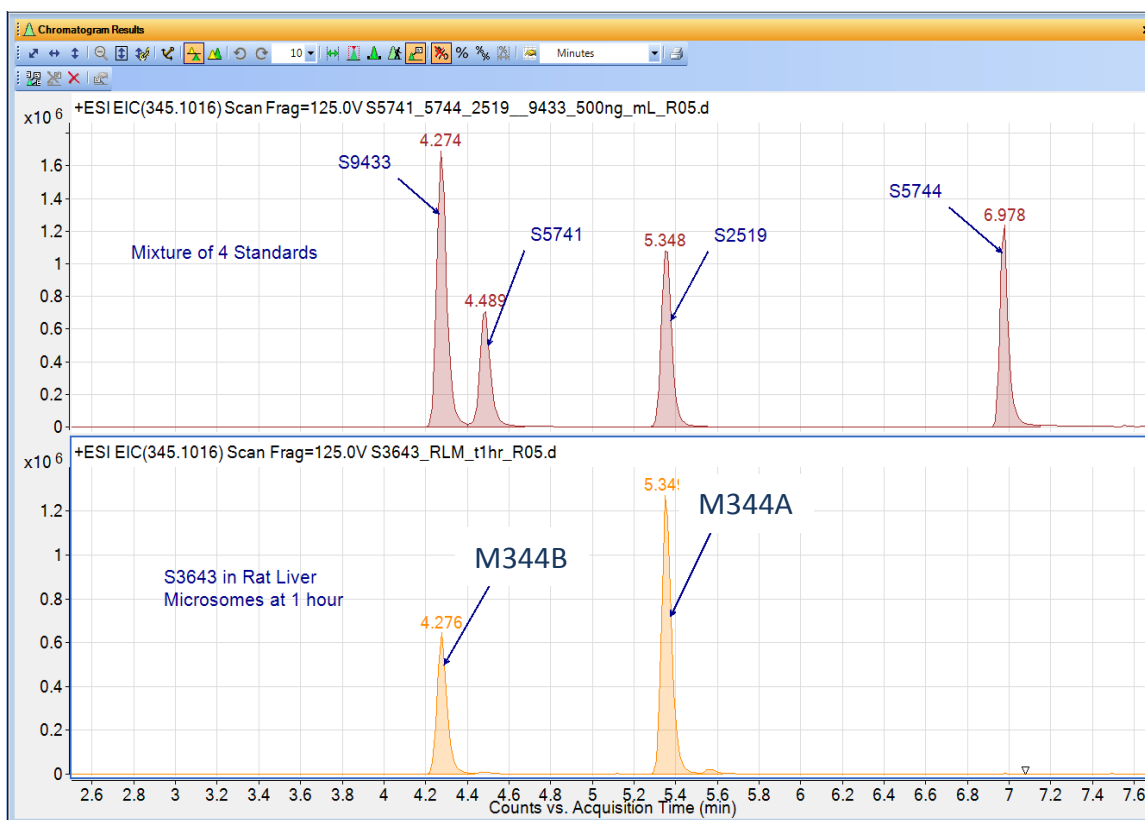
### ***Chromatographic Conditions***

HPLC pump	Agilent 1290 Infinity Binary pump		
Autosampler	Agilent 1290 Infinity Autosampler		
Column	Zorbax Eclipse Plus C18, 2.1 x 50 mm, 1.8 $\mu$ m		
Mobile Phase A	2 mM Ammonium acetate and 0.1 % formic acid in water		
Mobile Phase B	Methanol		
Flow Rate	1.0 mL/min		
Injection Volume	1.0 $\mu$ L		
Column Temperature	40 $^{\circ}$ C		
Gradient	Time (min)	%B	Valve switch
	0.0	5	1 => 2
	0.2	5	
	6.5	40	
	7.5	95	
	8.5	95	
	8.51	5	
10.0	5		
Acquisition Time	10.0 min		
S3643 Retention Time	~ 5.79 min		

### ***Mass Spectrometric Conditions***

Instrument	Agilent iFunnel 6550A MS Q-TOF
Ionization Source	Dual AJS ESI
Polarity	Positive
Gas Temp ( $^{\circ}$ C)	275
Gas Flow (L/min)	13
Nebulizer (psig)	30
SheathGasTemp ( $^{\circ}$ C)	375
SheathGasFlow (L/min)	12
VCap (V)	3250
Nozzle Voltage (V)	0
Fragmentor (V)	125
Ref Mass Enabled	Enabled
Ref Nebulizer (psig)	5
Reference Masses	121.0509, 922.0098

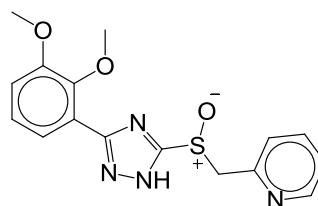
**Figure 1. +ESI Extracted Ion Chromatogram of Four Synthetic Standards and m/z 345.1016 Metabolites M344A (RT = 5.35 min) and M344 B (RT = 4.27 min) in Rat Liver Microsome Incubations (60 min)**



S9433 (X = OH, Y = Z = H)

S5741 (Y = OH, X = Z = H)

S5744 (Z = OH, X = Y = H)



S2519

The structure of metabolite M344A was confirmed to be the corresponding S3643-sulfoxide (*i.e.*, S2519). The structure of metabolite M344B was confirmed to be the 4'-hydroxy derivative of S3643 (*i.e.*, S9433). The corresponding 5'- and 6'-hydroxy analogs (S5741 and S5744, respectively) do not appear to be present in the rat liver microsomal preparations.

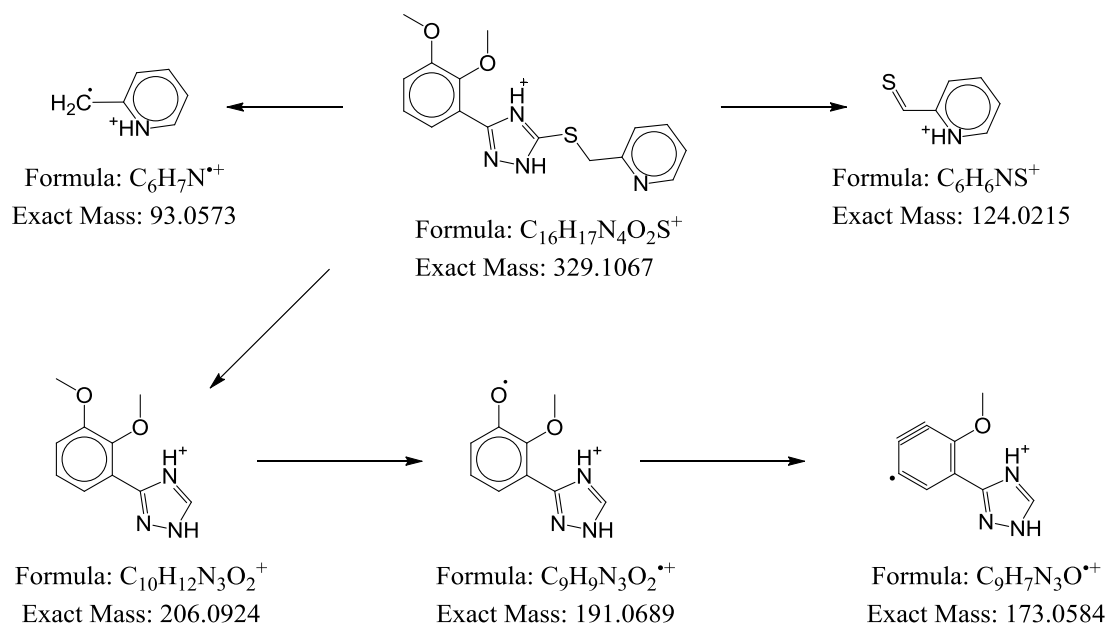


**Table 1. Major Metabolites of S3643 in Rat and Human Microsomal Incubations**

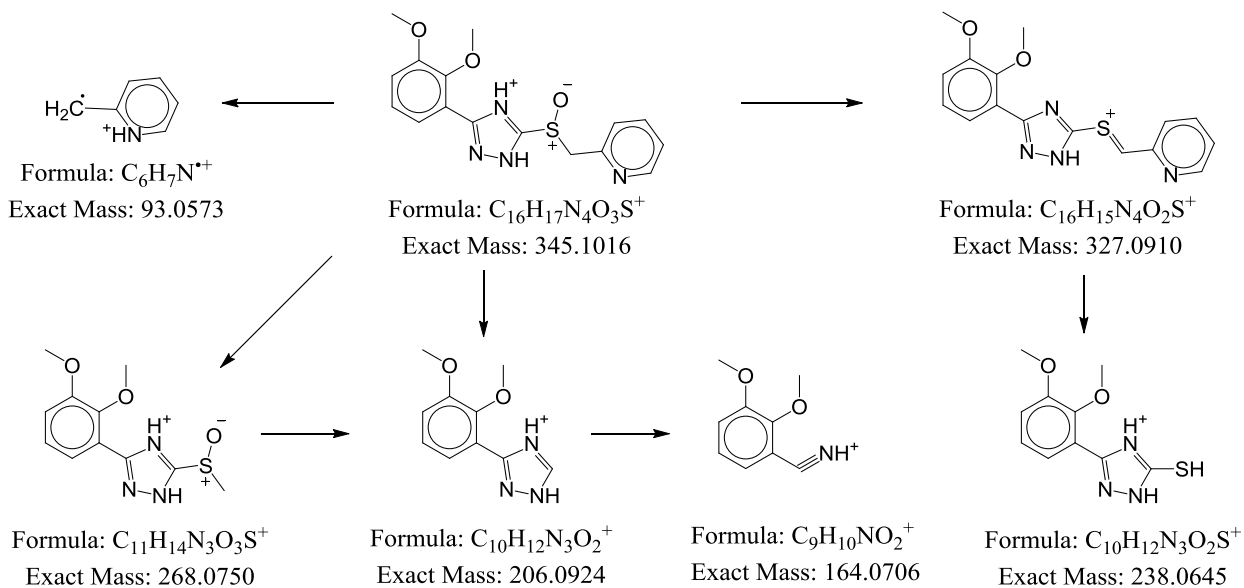
Metabolite	m/z (M+H)	Formula	Observed Parent and Fragment Ions (positive mode)	RT (min) <sup>a</sup>
S3643	329.1067	C <sub>16</sub> H <sub>17</sub> N <sub>4</sub> O <sub>2</sub> S <sup>+</sup>	329.1064 (M+H), 206.0922, 191.0688, 173.0586, 124.0210, 93.0573	5.79
M344A	345.1016	C <sub>16</sub> H <sub>17</sub> N <sub>4</sub> O <sub>3</sub> S <sup>+</sup>	345.1015 (M+H), 327.0901, 268.1082, 238.0641, 206.0921, 164.0705, 93.0569	5.46
M344B	345.1016	C <sub>16</sub> H <sub>17</sub> N <sub>4</sub> O <sub>3</sub> S <sup>+</sup>	345.1016 (M+H), 312.0672, 222.0873, 207.0641, 189.0535, 162.0661, 124.0212, 93.0571	4.42
M314A	315.0910	C <sub>15</sub> H <sub>15</sub> N <sub>4</sub> O <sub>2</sub> S <sup>+</sup>	315.0914 (M+H), 282.1112, 192.0765, 177.0534, 124.0214, 93.0572	5.46
M314B	315.0910	C <sub>15</sub> H <sub>15</sub> N <sub>4</sub> O <sub>2</sub> S <sup>+</sup>	315.0908 (M+H), 300.0667, 282.1107, 192.0765, 177.0534, 124.0209, 93.0571	4.26
M330A	331.0859	C <sub>15</sub> H <sub>15</sub> N <sub>4</sub> O <sub>3</sub> S <sup>+</sup>	331.0859 (M+H), 313.0766, 192.0773, 93.0570	4.97
M330B	331.0859	C <sub>15</sub> H <sub>15</sub> N <sub>4</sub> O <sub>3</sub> S <sup>+</sup>	331.057 (M+H), 299.0591, 192.0765, 93.0570	4.05
M330C	331.0859	C <sub>15</sub> H <sub>15</sub> N <sub>4</sub> O <sub>3</sub> S <sup>+</sup>	331.0849 (M+H), 254.0674, 208.0714, 193.0480, 176.0446, 124.0213, 93.0569	3.18
M330D	331.0859	C <sub>15</sub> H <sub>15</sub> N <sub>4</sub> O <sub>3</sub> S <sup>+</sup>	331.0836 (M+H), 299.0591, 192.0768, 108.0438, 78.0335	4.31
M300	301.0754	C <sub>14</sub> H <sub>13</sub> N <sub>4</sub> O <sub>2</sub> S <sup>+</sup>	301.0749 (M+H), 268.0958, 239.0820, 178.0609, 150.0653, 124.0213, 93.0573	4.00

a. Retention time using a Zorbax Eclipse Plus C18 column (50 x 2.1 mm, 1.8 μm) and 2 mM ammonium acetate/0.1% formic acid/water and methanol gradient system described above

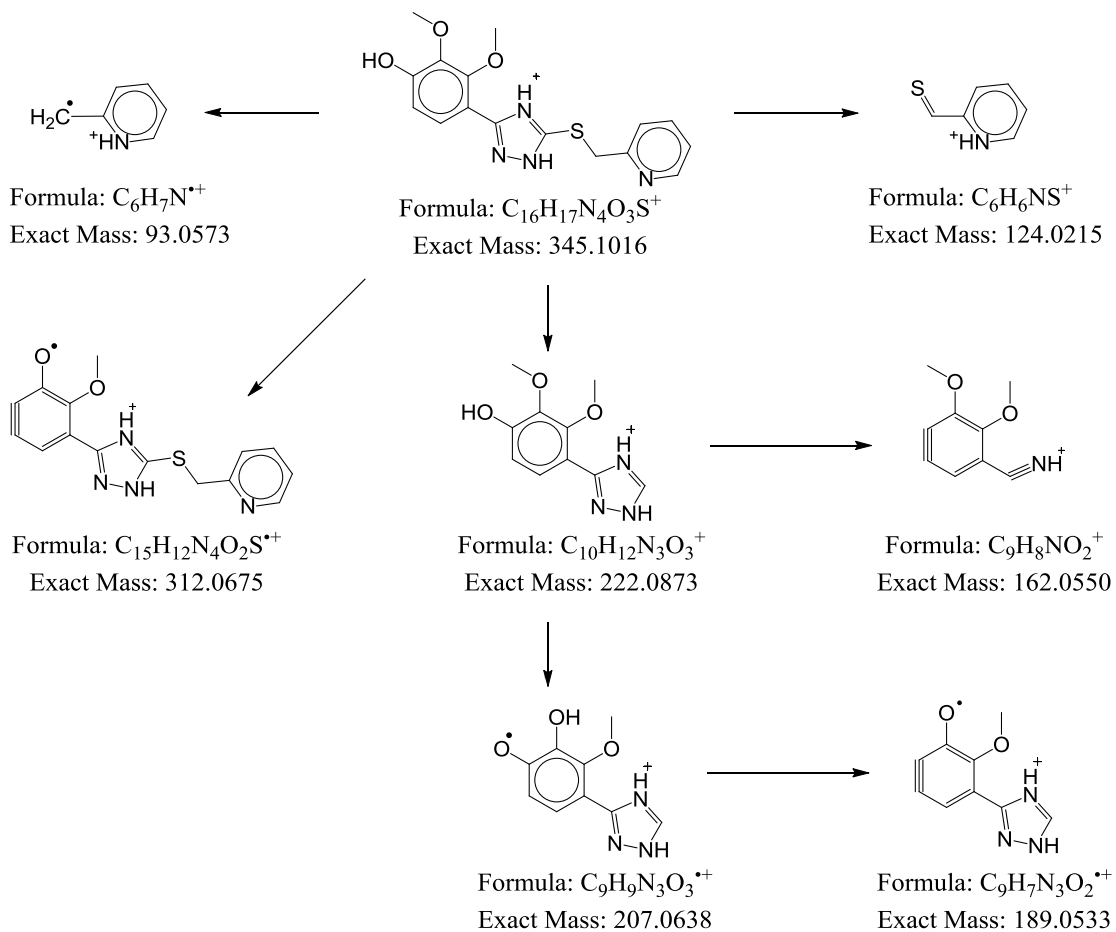
**Figure 2a. Proposed Fragmentation of S3643**



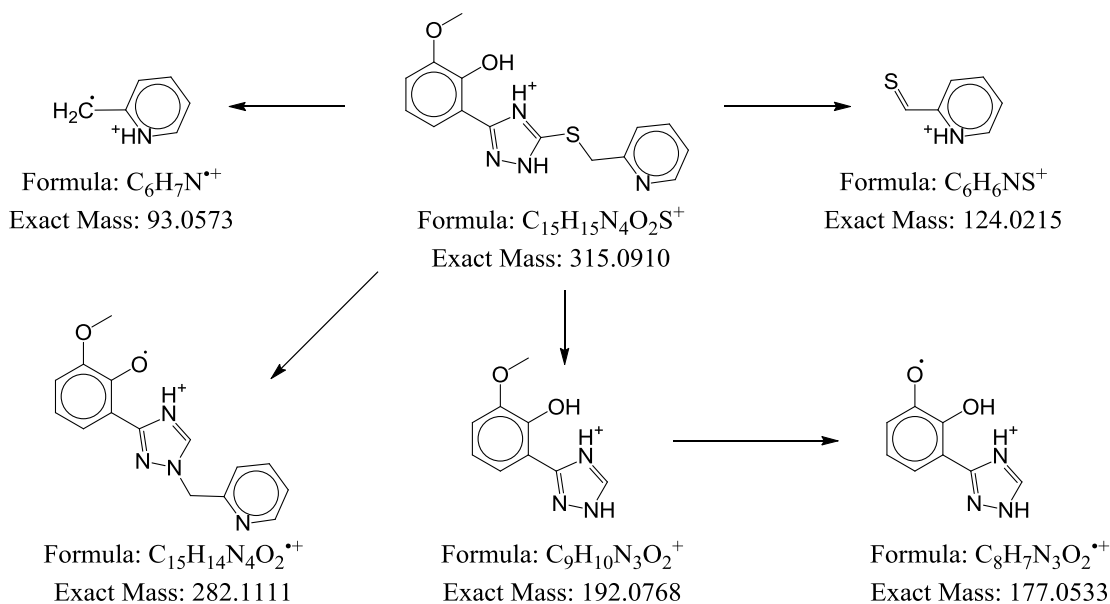
**Figure 2b. Proposed Fragmentation of M344A**



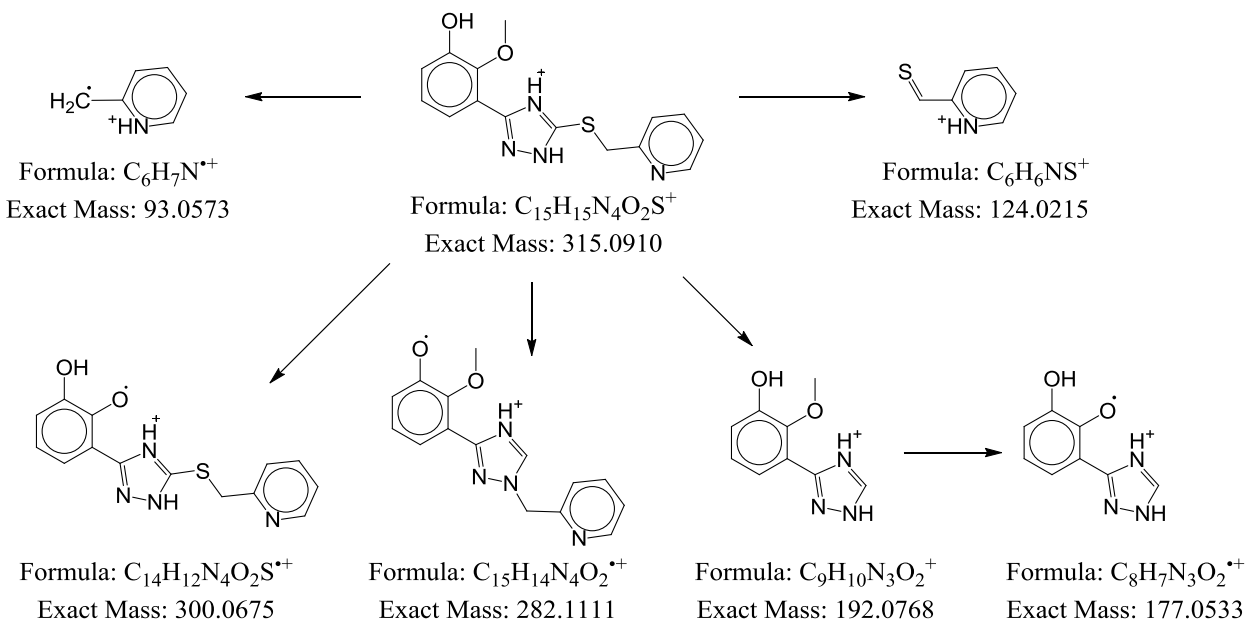
**Figure 2c. Proposed Fragmentation of M344B**



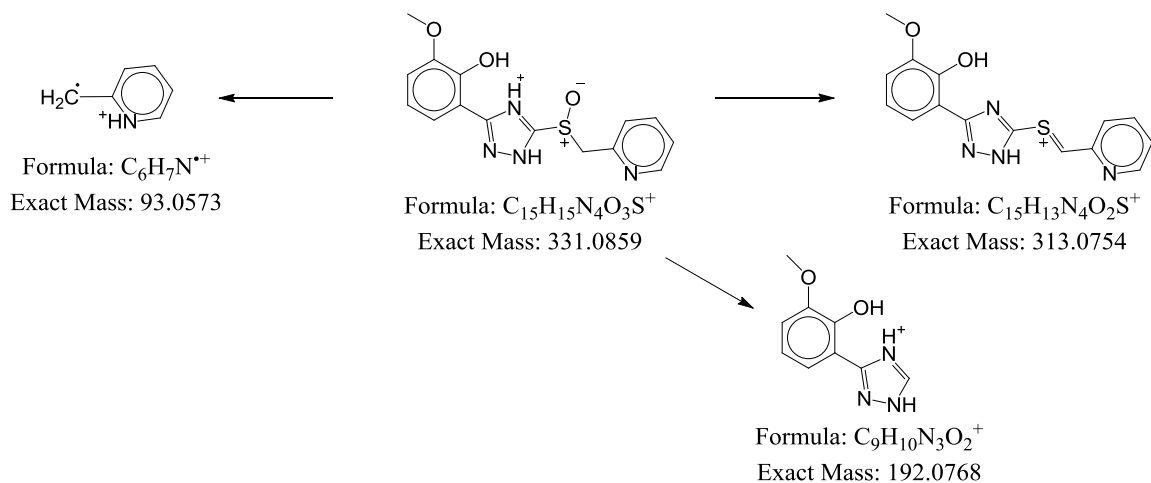
**Figure 2d. Proposed Fragmentation of M314A**



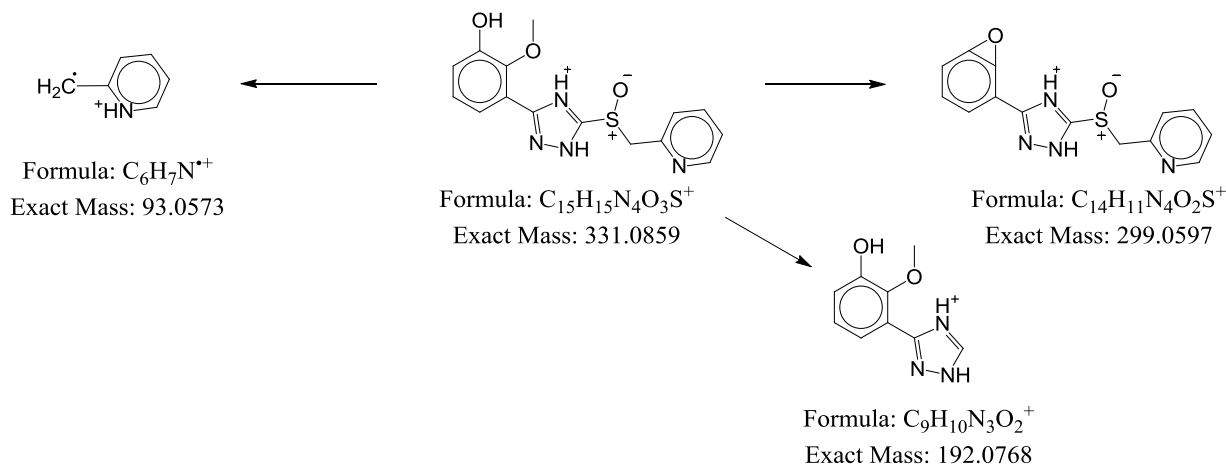
**Figure 2e. Proposed Fragmentation of M314B**



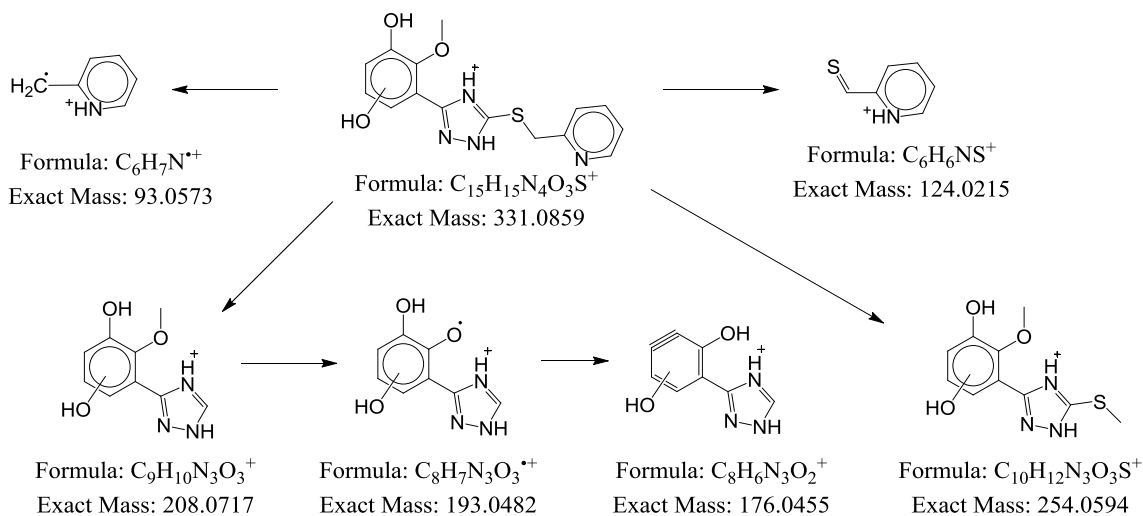
**Figure 2f. Proposed Fragmentation of M330A**



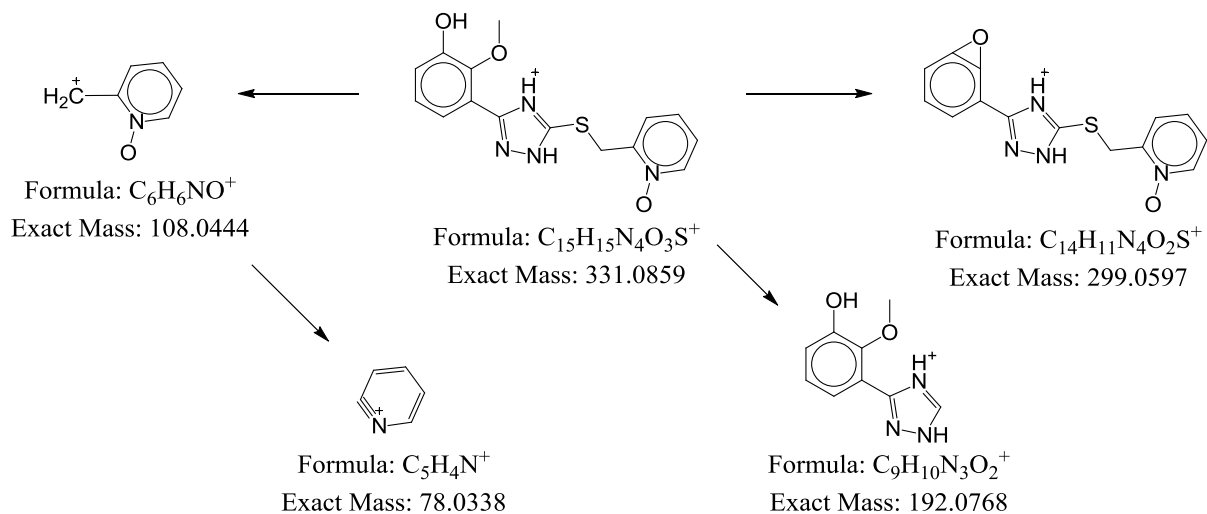
**Figure 2g. Proposed Fragmentation of M330B**



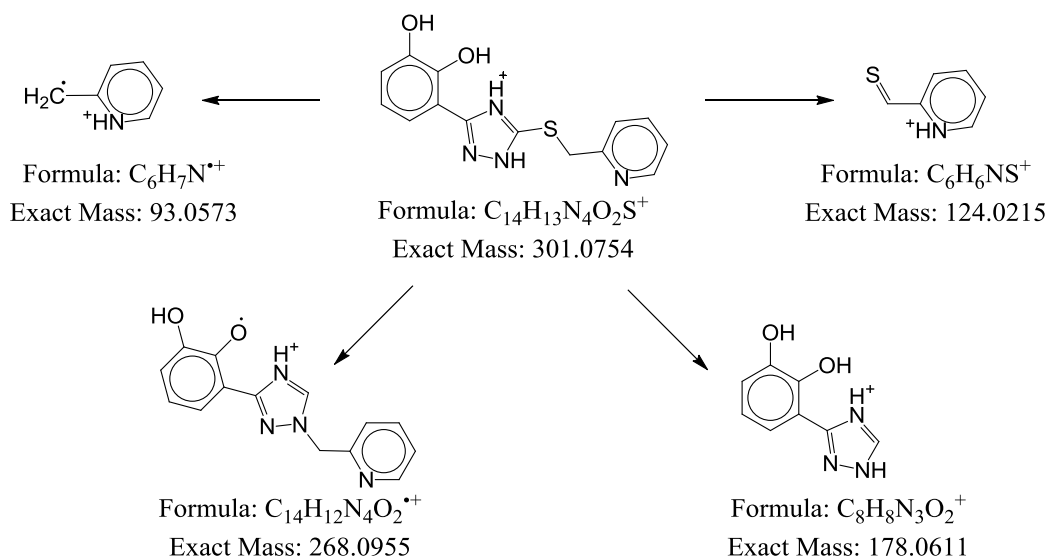
**Figure 2h. Proposed Fragmentation of M330C**



**Figure 2i. Proposed Fragmentation of M330D**



**Figure 2j. Proposed Fragmentation of M300**



## Pharmacokinetics and Bioavailability of S3643 in Sprague-Dawley Rats

Senomyx Study No. S3643-PK1

### Experimental Study Design

The sixteen male and sixteen female Sprague-Dawley rats were assigned to the study as presented in the table below.

Group	Test Article	Number of Animals	Dose Route	Formulation	Dose Level (mg/kg)	Gender
1	S3643	4	PO	1% methyl cellulose	10	Male
2	S3643	4	PO	1% methyl cellulose	30	Male
3	S3643	4	PO	1% methyl cellulose	100	Male
4	S3643	4	PO	1% methyl cellulose	10	Female
5	S3643	4	PO	1% methyl cellulose	30	Female
6	S3643	4	PO	1% methyl cellulose	100	Female
7	S3643	4	IV	10% ethanol in pH=7.4 buffer	1	Male
8	S3643	4	IV	10% ethanol in pH=7.4 buffer	1	Female

S3643 was administered once for group 1 to 6 via oral gavage and for group 7 to 8 via intravenous bolus injection. The dose levels for the treated group 1 to 6 were 10, 30, and 100 mg/kg at a dose volume of ~10 mL/kg. The dose level for the treated group 7 and 8 was 1 mg/kg at a dose volume of ~5 mL/kg. Each dose was based on the most recent body weight.

### Sample Collection, Handling, Storage, and Transfer

Blood samples were collected from a jugular catheter into tubes containing K<sub>2</sub>EDTA as the anticoagulant. Samples were collected from group 1 to 6 at approximately 0, 15, 30 min, 1, 2, 4, 8, and 24 hours post dose. Samples were collected from group 7 and 8 at approximately 0, 2, 5, 10, 30 min, 1, 2, 4, and 8 hours post-dose. The samples were stored on ice for no more than one hour until centrifuged at 2 to 7 °C. The plasma samples were placed on dry ice prior to storage at

approximately -70 °C. Samples were protected from direct sunlight during collection and processing. Samples were transferred to the Analytical Department at the test facility for analysis by liquid chromatography tandem mass spectrometry (LC-MS/MS).

### Plasma Sample Preparation

On the day of analysis, the plasma samples were thawed at room temperature . Proteins from plasma samples (25 µL) were precipitated by addition of 75 µL of acetonitrile containing 25 ng/mL of the internal standard (S9767). After 10 minutes of centrifugation (Sorvall Legend XTR, 6,000 rpm, 10 °C), 50 µL of the resulting supernatant was mixed with 100 µL deionized water. The solution was analyzed by LC-MS/MS.

### LC-MS/MS Analysis

The prepared plasma samples were analyzed using an LC-MS/MS (Applied Biosystems) equipped with an Agilent 1100 binary pump and a CTC PAL injector. S3643 and S9767 (internal standard = IS) were detected using the ion transitions (329.1/206.1 for S3643 and 297.1/174.1 for IS). The calibration curve, obtained by spiking known concentrations of S3643 to blank rat plasma, ranged from 2 ng/mL to 1000 ng/mL for both IV and oral dose. The lower limit of quantitation (LLOQ) for S3643 was 2 ng/mL. The HPLC and MS conditions are described in the tables below.

### Chromatographic Conditions

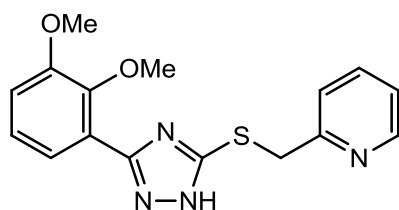
Column	SunFire™ C18, 2.1 mm x 50 mm, 3.5 µm, Waters		
Mobile Phase A	0.1% formic acid in water		
Mobile Phase B	0.1% formic acid in acetonitrile		
Flow Rate	0.7 mL/min		
Injection Volume	10 µL		
Column Temperature	Room temperature		
Gradient	Time (min)	%B	Valve switch
	0.0	5	Not used
	1.5	95	
	2.0	95	
	2.01	5	
	3.5	5	
Acquisition Time	3.5 min		
S3643 Retention Time	~ 1.78 min		
S9767 Retention Time	~ 1.89 min		

### Mass Spectrometric Conditions

Instrument	API 3200 Q Trap
Ionization Mode	TurboIonspray
Polarity	Positive

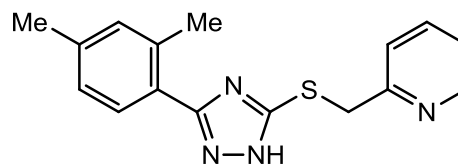
Scan Function	Multiple Reaction Monitoring (MRM)	
Parameters	S3643	S9767 (IS)
Precursor Ion	329.1	297.1
Product Ion	206.1	174.1
Dwell Time (ms)	100	100
DP - Declustering Potential (V)	55	55
CE - Collision Energy (eV)	28	28
CXP – Collision Cell Exit Potential (V)	4	4
EP-Entrance Potential (V)	10	10
IS – Ionspray Voltage (V)	4500	
TEM – Turbo Gas Temperature (°C)	600	
GS1 – Ion Source Gas 1	55.0	
GS2 – Ion Source Gas 2	50.0	
CUR – Curtain Gas	30.0	
CAD – Collision Gas	High	
Resolution	Unit	
Software	Analyst 1.4.2	

Figure 3. Structures of S3643 and Internal Standard S9767



**S3643**

Chemical Formula: C<sub>16</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub>S  
Molecular Weight: 328.39



**S9767**

Chemical Formula: C<sub>16</sub>H<sub>16</sub>N<sub>4</sub>S  
Molecular Weight: 296.39



**Table 2. Concentrations and Pharmacokinetic Parameters of S3643 in Plasma Following Single Intravenous Administration to Sprague-Dawley Rats**

Gender	Dose (mg/kg)	Subject	Time (hr)									AUC <sub>last</sub> (hr*ng/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	t <sub>1/2</sub> (hr)
			0.0	0.033	0.083	0.167	0.500	1.000	2.000	4.000	8.000				
			Concentration (ng/mL)												
male	1	Rat_13	LLOQ	12240	6770.2	3758.4	724.3	141.3	112.6	63.7	72.2	2955.9	12240.0	0.03	0.16
		Rat_14	LLOQ	11141	5318.2	3102.2	677.3	211.2	96.0	71.4	32.7	2629.0	11141.0	0.03	0.18
		Rat_15	LLOQ	11936	6208.4	3399.0	697.4	366.1	101.7	77.7	36.4	2946.6	11936.0	0.03	0.20
		Rat_16	LLOQ	8154.1	7534.2	2876.6	606.4	373.8	77.9	92.2	58.0	2627.0	8154.1	0.03	0.21
<b>N</b>			<b>0</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	
<b>Mean</b>				<b>10867.8</b>	<b>6457.8</b>	<b>3284.1</b>	<b>676.3</b>	<b>273.1</b>	<b>97.1</b>	<b>76.2</b>	<b>49.8</b>	<b>2789.6</b>	<b>10867.8</b>	<b>0.03</b>	<b>0.19</b>
<b>SD</b>				<b>1867.5</b>	<b>934.0</b>	<b>381.8</b>	<b>50.4</b>	<b>115.5</b>	<b>14.5</b>	<b>12.1</b>	<b>18.7</b>	<b>186.7</b>	<b>1867.5</b>	<b>0.00</b>	<b>0.02</b>
female	1	Rat_29	LLOQ	7938.2	4749.9	2770.2	581.2	113.3	38.7	35.2	17.5	1934.6	7938.2	0.03	0.16
		Rat_30	LLOQ	8522.1	4204.5	2283.4	383.6	100.7	77.1	40.5	33.9	1875.9	8522.1	0.03	0.16
		Rat_31	LLOQ	11484	5032.9	2495.3	299.7	88.1	43.8	17.1	12.8	1994.1	11484.0	0.03	0.14
		Rat_32	LLOQ	11430	5152.4	3164.2	636.9	147.5	94.6	83.1	34.7	2634.8	11430.0	0.03	0.16
<b>N</b>			<b>0</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	
<b>Mean</b>				<b>9843.6</b>	<b>4784.9</b>	<b>2678.3</b>	<b>475.3</b>	<b>112.4</b>	<b>63.6</b>	<b>43.9</b>	<b>24.7</b>	<b>2109.8</b>	<b>9843.6</b>	<b>0.03</b>	<b>0.16</b>
<b>SD</b>				<b>1878.3</b>	<b>422.2</b>	<b>380.3</b>	<b>159.8</b>	<b>25.6</b>	<b>26.8</b>	<b>27.9</b>	<b>11.2</b>	<b>353.3</b>	<b>1878.3</b>	<b>0.00</b>	<b>0.01</b>

LLOQ (lower limit of quantitation): 2.0 ng/mL

**Table 3. Concentrations and Pharmacokinetic Parameters of S3643 in Plasma Following Single Oral Administration to Sprague-Dawley Rats**

			Time (hr)											
			0.00	0.25	0.50	1.00	2.00	4.00	8.00	24.00				
Gender	Dose (mg/kg)	Subject	Concentration (ng/mL)								AUC <sub>last</sub> (hr*ng/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	t <sub>1/2</sub> (hr)
male	10	Rat_1	LLOQ	26621	18652	6480.4	275.2	76.8	15.1	3.6	19333	26621	0.25	0.78
		Rat_2	LLOQ	41239	26242	13662	1631	151.6	35.3	LLOQ	33369	41239	0.25	0.79
		Rat_3	LLOQ	29661	19320	11025	1565.7	639.3	26.5	LLOQ	27248	29661	0.25	0.82
		<b>N</b>	<b>0</b>	<b>3</b>	<b>3</b>	<b>3</b>	<b>3</b>	<b>3</b>	<b>3</b>	<b>1</b>	<b>3</b>	<b>3</b>	<b>3</b>	<b>3</b>
		<b>Mean</b>		<b>32507</b>	<b>21405</b>	<b>10389</b>	<b>1157.3</b>	<b>289.2</b>	<b>25.6</b>	<b>3.6</b>	<b>26650</b>	<b>32507</b>	<b>0.25</b>	<b>0.80</b>
		<b>SD</b>		<b>7713.4</b>	<b>4202.5</b>	<b>3632.8</b>	<b>764.6</b>	<b>305.4</b>	<b>10.1</b>		<b>7037</b>	<b>7713.4</b>	<b>0.00</b>	<b>0.02</b>
male	30	Rat_5	LLOQ	48512	62005	49740	7819.5	1055.8	324.5	11.2	90916	62005	0.50	0.97
		Rat_6	LLOQ	36166	34816	17817	4064.6	587.7	101.3	LLOQ	43523	36166	0.25	0.90
		Rat_7	LLOQ	51638	53219	48248	19585	4744.1	170.8	4.8	114409	53219	0.50	0.89
		Rat_8	LLOQ	43164	52130	30719	7529.8	2296.5	455.7	LLOQ	72475	52130	0.50	1.13
		<b>N</b>	<b>0</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>2</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>
		<b>Mean</b>		<b>44870</b>	<b>50543</b>	<b>36631</b>	<b>9749.7</b>	<b>2171</b>	<b>263.1</b>	<b>8</b>	<b>80330</b>	<b>50880</b>	<b>0.44</b>	<b>0.97</b>
		<b>SD</b>		<b>6775.9</b>	<b>11378</b>	<b>15229</b>	<b>6775.1</b>	<b>1860.8</b>	<b>158.7</b>	<b>4.5</b>	<b>29944</b>	<b>10760</b>	<b>0.13</b>	<b>0.11</b>
male	100	Rat_9	LLOQ	64104	49438	28525	17133	7796.1	1837.4	9.8	123499	64104	0.25	1.67
		Rat_10	LLOQ	58982	84190	69190	31746	18176	2268.7	14.7	223161	84190	0.50	1.46
		Rat_11	LLOQ	83440	69046	51380	24270	4972.1	6537	43.5	202327	83440	0.25	2.12
		Rat_12	LLOQ	81360	79993	59164	26163	10553	1808.4	71.3	184268	81360	0.25	1.39
		<b>N</b>	<b>0</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>
		<b>Mean</b>		<b>71972</b>	<b>70667</b>	<b>52065</b>	<b>24828</b>	<b>10374.3</b>	<b>3112.9</b>	<b>34.8</b>	<b>183314</b>	<b>78274</b>	<b>0.31</b>	<b>1.66</b>
		<b>SD</b>		<b>12252</b>	<b>15526</b>	<b>17304</b>	<b>6032.3</b>	<b>5678.3</b>	<b>2292.4</b>	<b>28.5</b>	<b>42926</b>	<b>9521.9</b>	<b>0.13</b>	<b>0.33</b>
female	10	Rat_17	LLOQ	4248.6	2096.4	895.5	574.9	244.4	16.3	LLOQ	4148	4248.6	0.25	1.20
		Rat_18	LLOQ	22112	12491	3361.1	448.7	95.3	6.6	LLOQ	13705	22112	0.25	0.74
		Rat_19	LLOQ	19296	17101	10874	2817.7	702.2	14.3	LLOQ	25754	19296	0.25	0.74
		Rat_20	LLOQ	13896	8321.4	4618.4	1321	408.3	20.7	LLOQ	13306	13896	0.25	0.89
		<b>N</b>	<b>0</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>0</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>
		<b>Mean</b>		<b>14888</b>	<b>10003</b>	<b>4937.3</b>	<b>1290.6</b>	<b>362.5</b>	<b>14.5</b>		<b>14228</b>	<b>14888</b>	<b>0.25</b>	<b>0.89</b>
		<b>SD</b>		<b>7869.7</b>	<b>6374.8</b>	<b>4249.2</b>	<b>1088.4</b>	<b>260</b>	<b>5.9</b>		<b>8861.5</b>	<b>7869.7</b>	<b>0.00</b>	<b>0.22</b>
female	30	Rat_21	LLOQ	48829	34617	20031	5021.6	2354.4	25.1	2.9	55081	48829	0.25	0.75
		Rat_23	LLOQ	39603	35316	28252	13498	4608.7	3402.4	5.4	112473	39603	0.25	1.91
		Rat_24	LLOQ	47699	34496	18881	4884.8	2190.4	30.9	LLOQ	52982	47699	0.25	0.77
		<b>N</b>	<b>0</b>	<b>3</b>	<b>3</b>	<b>3</b>	<b>3</b>	<b>3</b>	<b>3</b>	<b>2</b>	<b>3</b>	<b>3</b>	<b>3</b>	<b>3</b>
		<b>Mean</b>		<b>45377</b>	<b>34810</b>	<b>22388</b>	<b>7801.5</b>	<b>3051.2</b>	<b>1152.8</b>	<b>4.1</b>	<b>73512</b>	<b>45377</b>	<b>0.25</b>	<b>1.14</b>
		<b>SD</b>		<b>5032.2</b>	<b>442.7</b>	<b>5110.8</b>	<b>4933.8</b>	<b>1351.4</b>	<b>1948.2</b>	<b>1.8</b>	<b>33758</b>	<b>5032.2</b>	<b>0.00</b>	<b>0.67</b>
female	100	Rat_25	LLOQ	85304	94121	63234	36145	7437.9	930.8	14.6	190003	94121	0.50	1.12
		Rat_26	LLOQ	109550	117250	93617	53711	21022	13037	10.1	415652	117250	0.50	2.35
		Rat_27	LLOQ	73801	73574	42074	20727	5212.5	2696.3	4.6	151324	73801	0.25	1.61
		Rat_28	LLOQ	110470	108320	49888	26957	7125.6	3279.9	7.3	200324	110470	0.25	1.57
		<b>N</b>	<b>0</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>	<b>4</b>
		<b>Mean</b>		<b>94781</b>	<b>98316</b>	<b>62203</b>	<b>34385</b>	<b>10200</b>	<b>4986</b>	<b>9.2</b>	<b>239326</b>	<b>98911</b>	<b>0.38</b>	<b>1.66</b>
		<b>SD</b>		<b>18205</b>	<b>19047</b>	<b>22692</b>	<b>14356</b>	<b>7281.8</b>	<b>5459.4</b>	<b>4.3</b>	<b>119428</b>	<b>19351</b>	<b>0.14</b>	<b>0.51</b>

LLOQ: 2.0 ng/mL

**Table 4. Comparison of S3643 Exposure (AUC<sub>last</sub> and C<sub>max</sub>) in Plasma Between Female and Male Following Single IV and Oral Administration to Sprague-Dawley Rats**

<b>Route</b>	<b>PK Parameter</b>	<b>Dose (mg/kg)</b>	<b>Ratio of Mean (Female/Male)</b>	<b>Standard Deviation</b>
IV	AUC <sub>last</sub>	1	0.76	0.14
	C <sub>max</sub>	1	0.91	0.23
PO	AUC <sub>last</sub>	10	0.53	0.36
	AUC <sub>last</sub>	30	0.92	0.54
	AUC <sub>last</sub>	100	1.31	0.72
	C <sub>max</sub>	10	0.46	0.27
	C <sub>max</sub>	30	0.89	0.21
	C <sub>max</sub>	100	1.26	0.29

**Table 5. Absolute Bioavailability of S3643 in Plasma Following Single IV and Oral Administration to Sprague-Dawley Rats**

<b>Gender</b>	<b>Route</b>	<b>Dose (mg/kg)</b>	<b>Mean %F</b>	<b>Standard Deviation</b>
male	PO	10	95.5	26.0
		30	96.0	36.4
		100	65.7	16.0
female	PO	10	67.4	43.5
		30	116.1	56.8
		100	113.4	59.7

## ***In Vivo* Metabolism of S3643 in Rats**

Senomyx Study No. S3643-PK2

### **Experimental Study Design**

The four male and four female Sprague-Dawley rats were assigned to the study as presented in the table below.

<b>Group</b>	<b>Test Article</b>	<b>Number of Animals</b>	<b>Dose Route</b>	<b>Formulation</b>	<b>Dose Level (mg/kg)</b>	<b>Gender</b>
1	S3643	4	PO	1% methyl cellulose	100	Male
2	S3643	4	PO	1% methyl cellulose	100	Female

S3643 was administered once for Group 1 and 2 via oral gavage at a dose volume of ~10 mL/kg. The dose was based on the most recent body weight.

### **Sample Collection, Handling, Storage, and Transfer**

Blood samples were collected from a jugular catheter into tubes containing K<sub>2</sub>EDTA as the anticoagulant. Samples were collected from Groups 1 and 2 at approximately 0, 15, 30 min, 1, 2, 4, 8, and 24 hours post dose. The samples were stored on ice for no more than one hour until centrifuged at 2 to 7 °C. The plasma samples were placed on dry ice prior to storage at approximately -70 °C. Samples were protected from direct sunlight during collection and processing. Samples were transferred to the Analytical Department at the Test Facility for analysis by liquid chromatography quadrupole time-of-flight mass spectrometry (LC-QTOF/MS).

### **Plasma Sample Preparation**

On the day of analysis, the plasma samples were thawed at room temperature (RT). Plasma (10 µL) from each animal was pooled together by each time point. Proteins from plasma samples (80 µL) were precipitated by addition of 240 µL of acetonitrile. After 10 minutes of centrifugation (Sorvall Legend XTR, 6,000 rpm, 10 °C), 50 µL of the resulting supernatant was mixed with 100 µL deionized water. The solution was analyzed by LC-QTOF/MS.

### **LC-QTOF/MS Analysis**

The prepared plasma samples were analyzed using an LC-QTOF/MS (Agilent iFunnel 6550A MS Q-TOF) equipped with an Agilent 1290 Infinity Binary pump and an Agilent 1290 Infinity autosampler. The HPLC and MS conditions are described in the tables below.

### Chromatographic Conditions

HPLC pump	Agilent 1290 Infinity Binary pump		
Autosampler	Agilent 1290 Infinity Autosampler		
Column	Zorbax Eclipse Plus C18, 2.1 x 50 mm, 1.8 $\mu$ m		
Mobile Phase A	2 mM Ammonium acetate and 0.1 % formic acid in water		
Mobile Phase B	Methanol		
Flow Rate	1.0 mL/min		
Injection Volume	1.0 $\mu$ L		
Column Temperature	40 $^{\circ}$ C		
Gradient	Time (min)	%B	Valve switch
	0.0	5	1 => 2
	0.2	5	
	6.5	40	
	7.5	95	
	8.5	95	
	8.51	5	
10.0	5		
Acquisition Time	10.0 min		
S3643 Retention Time	~ 5.79 min		

### Mass Spectrometric Conditions

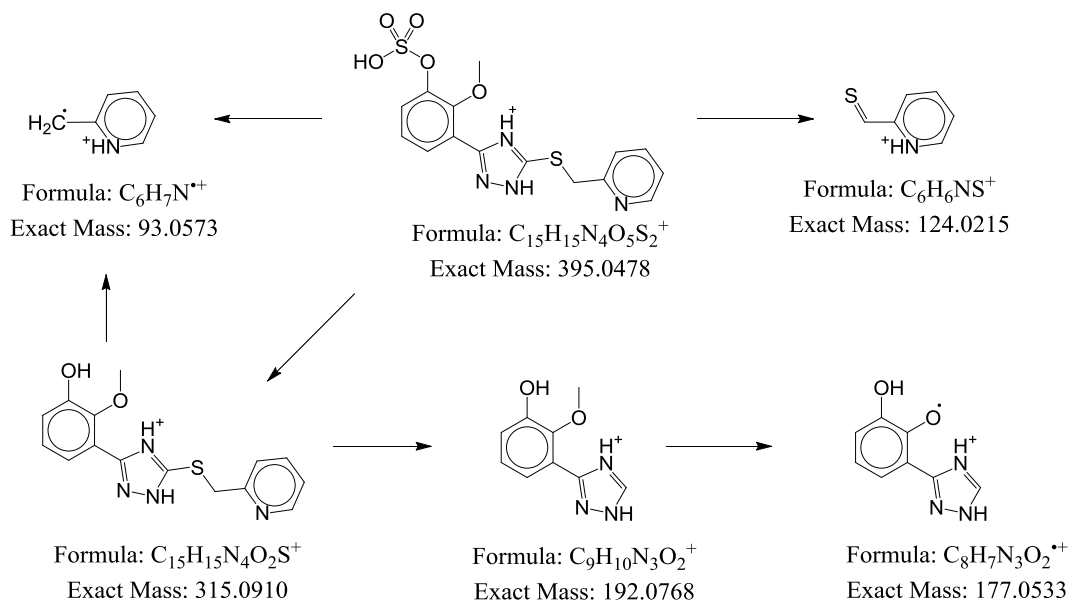
Instrument	Agilent iFunnel 6550A MS Q-TOF
Ionization Source	Dual AJS ESI
Polarity	Positive
Gas Temp ( $^{\circ}$ C)	275
Gas Flow (L/min)	13
Nebulizer (psig)	30
SheathGasTemp ( $^{\circ}$ C)	375
SheathGasFlow (L/min)	12
VCap (V)	3250
Nozzle Voltage (V)	0
Fragmentor (V)	125
Ref Mass Enabled	Enabled
Ref Nebulizer (psig)	5
Reference Masses	121.0509, 922.0098

**Table 6. Phase II Metabolites of S3643 Observed in Rat Plasma**

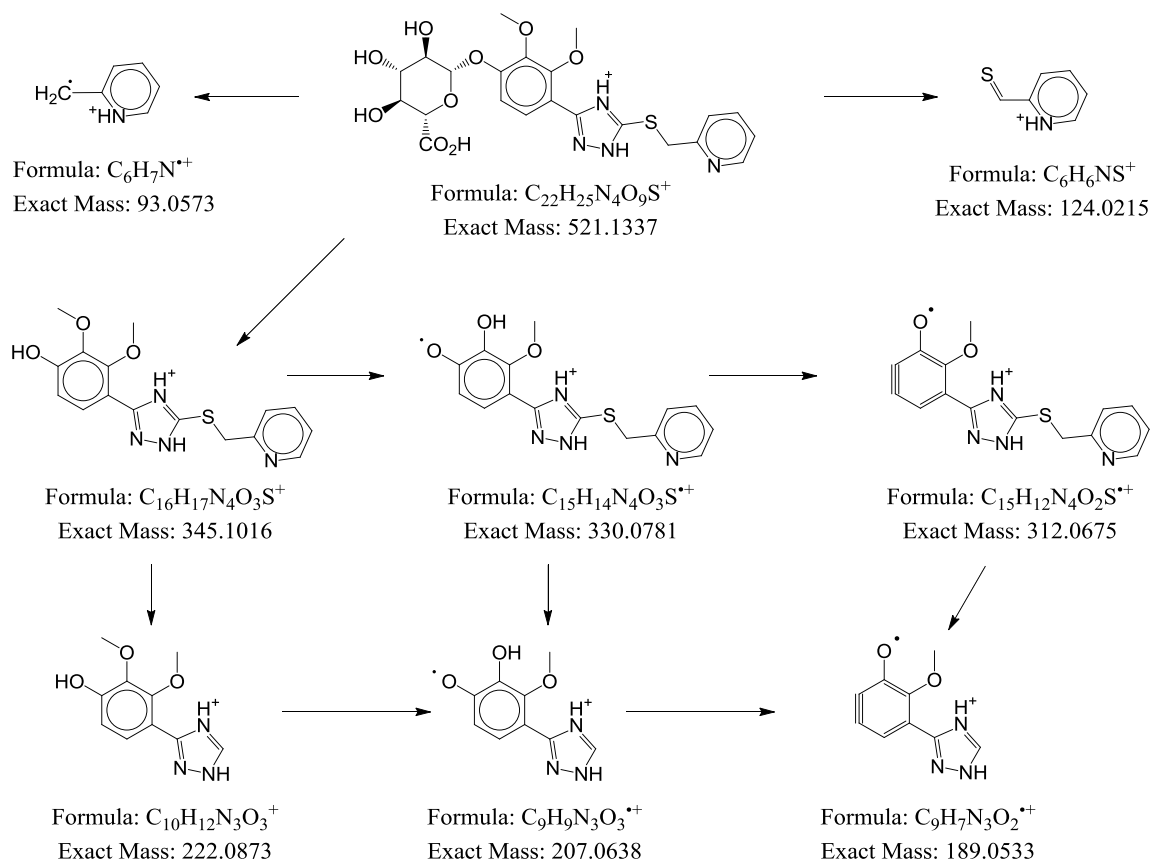
Metabolite	m/z (M+H)	Formula	Observed Parent and Fragment Ions (positive mode)	RT (min) <sup>a</sup>
M394	395.0478	C <sub>15</sub> H <sub>15</sub> N <sub>4</sub> O <sub>5</sub> S <sub>2</sub> <sup>+</sup>	395.0436 (M+H), 315.0909, 300.0662, 192.0766, 177.0531, 124.0213, 93.0568	3.22
M520	521.1337	C <sub>16</sub> H <sub>17</sub> N <sub>4</sub> O <sub>3</sub> S <sup>+</sup>	521.1337 (M+H), 345.1016, 330.0778, 312.0680, 222.0872, 207.0626, 189.0522, 124.0210, 93.0568	2.74

a. Retention time using a Zorbax Eclipse Plus C18 column (50 x 2.1 mm, 1.8  $\mu$ m) and 2 mM ammonium acetate/0.1% formic acid/water and methanol gradient system described above

**Figure 4a. Proposed Fragmentation of M394**



**Figure 4b. Proposed Fragmentation of M520**



## Reverse Bacterial Mutation Assay: S3643

**Table 7. Plate Incorporation Assay**

Nucro-Technics Project No. 257958

<b>S3643</b>					
<b>mg per plate</b>	<b>Colony Counts</b>			<b>Mean ± SD</b>	<b>Lawn</b>
<b><u>TA98, -S9</u></b>					
* 0	24	20	18		NL
* 0	25	19	14	20 ± 4	NL
0.016	19	11	16	15 ± 4	NL
0.031	18	15	16	16 ± 2	NL
0.063	16	23	21	20 ± 4	NL
0.13	29	22	31	27 ± 5	NL
0.25	11	22	13	15 ± 6	NL
0.50	26	13	27	22 ± 8	NL
1.0	15	25	24	21 ± 6	NL
2.0	18	22	13	18 ± 5	NL
* 2-NF, 5 µg	1875	2069	1825	1987 ± 133	NL
	2166	2070	1919		NL
<b><u>TA98, +S9</u></b>					
0	35	38	31	35 ± 4	NL
0.13	34	31	37	34 ± 3	NL
0.25	21	30	26	26 ± 5	NL
0.50	27	43	33	34 ± 8	NL
1.0	29	25	21	25 ± 4	NL
2.0	19	11	20	17 ± 5	NL
B[α]P, 5 µg	425	399	433	419 ± 18	NL
<b><u>TA100, -S9</u></b>					
* 0	114	108	106		NL
* 0	114	107	108	110 ± 4	NL
0.016	112	104	103	106 ± 5	NL
0.031	123	106	101	110 ± 12	NL
0.063	106	92	105	101 ± 8	NL
0.13	106	109	110	108 ± 2	NL
0.25	111	108	105	108 ± 3	NL
0.50	108	111	114	111 ± 3	NL
1.0	83	100	131	105 ± 24	NL
2.0	120	102	98	107 ± 12	NL
* NaAz, 5 µg	1898	1887	1960	1879 ± 204	NL
	2036	2014	1481		NL
<b><u>TA100, +S9</u></b>					
0	115	102	117	111 ± 8	NL
0.13	110	106	104	107 ± 3	NL
0.25	96	100	120	105 ± 13	NL
0.50	96	108	108	104 ± 7	NL
1.0	116	121	98	112 ± 12	NL
2.0	98	108	104	103 ± 5	NL
B[α]P, 5 µg	1168	1167	1029	1121 ± 80	NL

**Table 7. Plate Incorporation Assay (continued)**

Nucro-Technics Project No. 257958

<b>S3643</b>	<b>Colony Counts</b>			<b>Mean ± SD</b>	<b>Lawn</b>
<b>mg per plate</b>					
<b><u>TA1535, -S9</u></b>					
* 0	14	15	17		NL
* 0	19	6	18	15 ± 5	NL
0.016	19	18	17	18 ± 1	NL
0.031	15	13	17	15 ± 2	NL
0.063	18	22	19	20 ± 2	NL
0.13	13	8	17	13 ± 5	NL
0.25	11	17	13	14 ± 3	NL
0.50	13	14	10	12 ± 2	NL
1.0	16	8	18	14 ± 5	NL
2.0	6	12	7	8 ± 3	NL
* NaAz, 5 µg	1953	1975	2091	1914 ± 113	NL
	1828	1799	1835		NL
<b><u>TA1535, +S9</u></b>					
0	18	13	18	16 ± 3	NL
0.13	12	12	19	14 ± 4	NL
0.25	16	15	17	16 ± 1	NL
0.50	14	12	12	13 ± 1	NL
1.0	19	15	17	17 ± 2	NL
2.0	8	12	4	8 ± 4	NL
CP, 100 µg	129	114	137	127 ± 12	NL
<b><u>TA1537, -S9</u></b>					
* 0	10	12	15		NL
* 0	9	10	10	11 ± 2	NL
0.016	11	6	7	8 ± 3	NL
0.031	6	7	7	7 ± 1	NL
0.063	9	13	9	10 ± 2	NL
0.13	12	9	11	11 ± 2	NL
0.25	10	10	12	11 ± 1	NL
0.50	4	18	8	10 ± 7	NL
1.0	2	9	5	5 ± 4	NL
2.0	2	5	2	3 ± 2	NL
* 9-AA, 100 µg	1259	1233	1315	1541 ± 312	NL
	1974	1725	1737		NL
<b><u>TA1537, +S9</u></b>					
0	29	20	15	19 ± 3	NL
0.13	19	14	12	15 ± 4	NL
0.25	21	16	17	18 ± 3	NL
0.50	13	16	13	14 ± 2	NL
1.0	9	8	8	8 ± 1	NL
2.0	5	3	8	4 ± 1	NL
B[α]P, 5 µg	198	228	192	206 ± 19	NL



**Table 7. Plate Incorporation Assay (continued)**

Nucro-Technics Project No. 257958

<b>S3643</b>	<b>Colony Counts</b>			<b>Mean ± SD</b>	<b>Lawn</b>
<b>mg per plate</b>					
<b><u>WP2 <i>uvrA</i>, -S9</u></b>					
0	31	33	31	32 ± 1	NL
0.25	33	31	24	29 ± 5	NL
0.50	33	23	36	31 ± 7	NL
1.0	23	21	25	23 ± 2	NL
2.0	32	28	31	30 ± 2	NL
5.0	20	25	29	25 ± 5	NL
MMS, 1 µl	407	423	396	409 ± 14	NL
<b><u>WP2 <i>uvrA</i>, +S9</u></b>					
0	49	46	40	45 ± 5	NL
0.25	39	45	39	41 ± 3	NL
0.50	47	38	37	41 ± 6	NL
1.0	48	46	43	46 ± 3	NL
2.0	45	34	51	43 ± 9	NL
5.0	44	42	25	37 ± 10	NL
2-AMA, 100 µg	142	161	155	153 ± 10	NL

Note:

9-AA, 9-aminoacridine  
 2-AMA, 2-aminoanthracene  
 2-NF, 2-nitrofluorene  
 NaAz, sodiumazide  
 B[α]P, benzo[α]pyrene  
 CP, cyclophosphamide  
 MMS, methyl methanesulfonate

\*, A portion of the experiment was repeated  
 thus the mean of all six negative and positive  
 controls was reported

Note:

NL, Normal Background Lawn  
 SR, Slight Reduction of Lawn  
 MR, Moderate Reduction of Lawn  
 ER, Extreme Reduction of Lawn

**Table 8. Preincubation Assay**

Nuero-Technics Project No. 257958

<b>S3643</b>	<b>Colony Counts</b>			<b>Mean ± SD</b>	<b>Lawn</b>
<b>mg per plate</b>					
<b><u>TA98, -S9</u></b>					
0	18	21	29	23 ± 6	NL
0.13	26	23	19	23 ± 4	NL
0.25	25	17	14	19 ± 6	NL
0.50	19	20	24	21 ± 3	NL
1.0	11	15	22	16 ± 6	NL
2.0	5	6	5	5 ± 1	NL
2-NF, 5 µg	1313	1496	1300	1370 ± 110	NL
<b><u>TA98, +S9</u></b>					
0	32	33	26	30 ± 4	NL
0.031	24	27	39	30 ± 8	NL
0.063	26	28	23	26 ± 3	NL
0.13	24	29	23	25 ± 3	NL
0.25	28	21	30	26 ± 5	NL
0.50	14	17	26	19 ± 6	NL
1.0	6	5	9	7 ± 2	NL
B[α]P, 5 µg	437	476	475	463 ± 22	NL
<b><u>TA100, -S9</u></b>					
0	126	122	136	128 ± 7	NL
0.13	126	123	135	128 ± 6	NL
0.25	140	123	116	126 ± 12	NL
0.50	127	121	122	123 ± 3	NL
1.0	95	100	117	104 ± 12	NL
2.0	122	109	119	117 ± 7	NL
NaAz, 5 µg	1896	1874	1881	1884 ± 11	NL
<b><u>TA100, +S9</u></b>					
0	162	148	147	152 ± 8	NL
0.031	152	143	144	146 ± 5	NL
0.063	141	150	137	143 ± 7	NL
0.13	145	131	158	145 ± 14	NL
0.25	153	132	137	141 ± 11	NL
0.50	147	127	150	141 ± 13	NL
1.0	128	139	122	130 ± 9	NL
B[α]P, 5 µg	1061	998	938	999 ± 62	NL

**Table 8. Preincubation Assay (continued)**

Nucro-Technics Project No. 257958

<b>S3643</b>	<b>Colony Counts</b>			<b>Mean ± SD</b>	<b>Lawn</b>
<u>mg per plate</u>					
<b><u>TA1535, -S9</u></b>					
0	14	18	15	16 ± 2	NL
0.13	15	9	20	15 ± 6	NL
0.25	20	15	12	16 ± 4	NL
0.50	10	23	16	16 ± 7	NL
1.0	10	16	16	14 ± 3	NL
2.0	3	7	6	5 ± 2	NL
NaAz, 5 µg	1628	1848	1563	1680 ± 149	NL
<b><u>TA1535, +S9</u></b>					
0	20	13	21	18 ± 4	NL
0.031	16	12	9	12 ± 4	NL
0.063	18	19	14	17 ± 3	NL
0.13	8	19	17	15 ± 6	NL
0.25	17	19	15	17 ± 2	NL
0.50	13	11	13	12 ± 1	NL
1.0	11	11	10	11 ± 1	NL
CP, 100 µg	203	189	190	194 ± 8	NL
<b><u>TA1537, -S9</u></b>					
0	9	7	9	8 ± 1	NL
0.063	15	8	5	9 ± 5	NL
0.13	5	6	7	6 ± 1	NL
0.25	14	5	10	10 ± 5	NL
0.50	6	6	4	5 ± 1	NL
1.0	7	5	5	6 ± 1	NL
2.0	0	2	2	1 ± 1	NL
9-AA, 100 µg	937	1091	983	1004 ± 79	NL
<b><u>TA1537, +S9</u></b>					
0	22	11	9	14 ± 7	NL
0.031	17	13	11	14 ± 3	NL
0.063	15	16	11	14 ± 3	NL
0.13	11	18	12	14 ± 4	NL
0.25	10	5	9	8 ± 3	NL
0.50	14	5	11	10 ± 5	NL
1.0	7	8	5	7 ± 2	NL
B[α]P, 5 µg	230	205	214	216 ± 13	NL

**Table 8. Preincubation Assay (continued)**

Nucro-Technics Project No. 257958

<b>S3643</b>	<b>Colony Counts</b>			<b>Mean <math>\pm</math> SD</b>	<b>Lawn</b>
<b>mg per plate</b>					
<b><u>WP2 <i>uvrA</i>, -S9</u></b>					
0	10	10	13	11 $\pm$ 2	NL
0.25	10	17	12	13 $\pm$ 4	NL
0.50	9	9	13	10 $\pm$ 2	NL
1.0	12	13	13	13 $\pm$ 1	NL
2.0	10	12	10	11 $\pm$ 1	NL
5.0	12	9	15	12 $\pm$ 3	NL
MMS, 1 $\mu$ l	1062	1141	1064	1089 $\pm$ 45	NL
<b><u>WP2 <i>uvrA</i>, +S9</u></b>					
0	17	21	18	19 $\pm$ 2	NL
0.25	26	26	19	24 $\pm$ 4	NL
0.50	20	19	26	22 $\pm$ 4	NL
1.0	11	15	21	16 $\pm$ 5	NL
2.0	18	13	18	16 $\pm$ 3	NL
5.0	20	23	26	23 $\pm$ 3	NL
2-AMA, 100 $\mu$ g	135	138	119	131 $\pm$ 10	NL

Note:

*9-AA*, 9-aminoacridine  
*2-AMA*, 2-aminoanthracene  
*2-NF*, 2-nitrofluorene  
*NaN<sub>3</sub>*, sodium azide  
*B[ $\alpha$ ]P*, benzo[ $\alpha$ ]pyrene  
*CP*, cyclophosphamide  
*MMS*, methyl methanesulfonate

Note:

*NL*, Normal Background Lawn  
*SR*, Slight Reduction of Lawn  
*MR*, Moderate Reduction of Lawn  
*ER*, Extreme Reduction of Lawn

## *In Vitro* Chromosome Aberration Test of S3643 in Human Lymphocytes

**Table 9. Relative Cell Growth**

Nucro-Technics Project No. 257957

3 hrs -S9				3 hrs +S9				20 hrs -S9			
S3643 (mg/mL)	Cells (x 10 <sup>6</sup> )	Mean (x 10 <sup>6</sup> )	RCG (%)	S3643 (mg/mL)	Cells (x 10 <sup>6</sup> )	Mean (x 10 <sup>6</sup> )	RCG (%)	S3643 (mg/mL)	Cells (x 10 <sup>6</sup> )	Mean (x 10 <sup>6</sup> )	RCG (%)
0	2.505	2.59	100	0	2.265	2.17	100	0	3.210	3.32	100
	2.670				2.070				3.435		
0.063	2.700	2.59	100	0.031	2.025	2.04	94	0.063	3.465	3.36	101
	2.475				2.055				3.255		
0.13	2.445	2.41	93	0.063	1.890	1.85	85	0.13	3.180	3.26	98
	2.370				1.815				3.330		
0.25	2.535	2.57	99	0.13	1.380	1.58	73	0.25	3.150	2.86	86
	2.610				1.770				2.565		
0.50	2.160	2.15	83	0.25	1.725	1.69	78	0.50	1.725	1.69	51
	2.130				1.650				1.650		

RCG = Relative Cell Growth

**Table 10. Relative Mitotic Index**  
 Nucro-Technics Project No. 257957

3 hrs -S9			
S3643 (mg/mL)	M/500 cells	MI (%)	RMI (%)
0	28	5.3	100
	25		
0.063	22	4.7	89
	25		
0.13	23	5.0	94
	27		
0.25	15	3.4	64
	19		
0.50	8	2.2	42
	14		

3 hrs +S9			
S3643 (mg/mL)	M/500 cells	MI (%)	RMI (%)
0	24	4.5	100
	21		
0.031	25	5.1	113
	26		
0.063	22	4.2	93
	20		
0.13	20	3.4	76
	14		
0.25	12	2.7	60
	15		

20 hrs -S9			
S3643 (mg/mL)	M/500 cells	MI (%)	RMI (%)
0	22	4.5	100
	23		
0.063	17	3.9	87
	22		
0.13	13	2.8	62
	15		
0.25	7	1.2	27
	5		
0.50	-	-	-
	-		

M = Metaphases    MI = Mitotic Index    RMI = Relative Mitotic Index

"-" Not counted due to extreme toxicity

**Table 11-1. Structural Chromosome Aberrations, 3 Hours , -S9**  
 Nucro-Technics Project No. 257957

S3643 (mg/mL)	Cells• (Diploid)	Chromatid Type								Chromosome Type					Aberrations /100 Cells	Aberrant Cells (%)		
		Simple		Complex						Simple		Complex					Other	
		tg*	tb	isb	tr	qr	cr	id	ci	sg*	sb	d	r	dm				
0	100	1	1														1	1
	100																0	0
																	0.5	0.5
0.13	100	1															0	0
	100	1	1														1	1
																	0.5	0.5
0.25	100		1														1	1
	100	1															0	0
																	0.5	0.5
0.5	100	1															0	0
	100		2														2	2
																	1.0	1.0
MMC (0.2 µg/mL)	50	1	4		1												10	10
	100	3	5						1		1						7	7
																	8.5	8.5

\* aberrations not included in calculations of Aberrations/100 Cells and Aberrant Cells (%)

**Table 11-2. Structural Chromosome Aberrations, 3 Hours , +S9**  
 Nucro-Technics Project No. 257957

S3643 (mg/mL)	Cells• (Diploid)	Chromatid Type								Chromosome Type					Aberrations /100 Cells	Aberrant Cells (%)	
		Simple				Complex				Simple		Complex					Other
		tg*	tb	isb	tr	qr	cr	id	ci	sg*	sb	d	r	dm			
0	100	1	1													1	1
	100	1	1													1	1
																1.0	1.0
0.063	100	2	2													2	2
	100	1														0	0
																1.0	1.0
0.13	100	1	1													1	1
	100	2	1													1	1
																1.0	1.0
0.25	100	3	2								1					3	3
	100	4	3													3	3
																3.0	3.0
CP (10 µg/mL)	43	4	4		1						1					14	14
	46	4	5						1		1					15	13
																14.6	13.5

\* aberrations not included in calculations of Aberrations/100 Cells and Aberrant Cells (%)



**Table 11-3. Structural Chromosome Aberrations, 20 Hours , -S9**  
 Nucro-Technics Project No. 257957

S3643 (mg/mL)	Cells* (Diploid)	Chromatid Type								Chromosome Type					Aberrations /100 Cells	Aberrant Cells (%)		
		Simple			Complex					Simple		Complex					Other	
		tg*	tb	isb	tr	qr	cr	id	ci	sg*	sb	d	r	dm				
0	100	1	1														1	1
	100	2	1														1	1
																	1.0	1.0
0.063	100	1	1														1	1
	100	2								1							1	1
																	1.0	1.0
0.13	100	1															0	0
	100	2	2														2	2
																	1.0	1.0
0.25	100	1															0	0
	100	3	3														3	3
																	1.5	1.5
MMC (0.1 µg/mL)	50	2	6								1						14	12
	50	1	4		1						1						12	10
																	13.0	11.0

\* aberrations not included in calculations of Aberrations/100 Cells and Aberrant Cells (%)

**Table 11-4. Numerical Chromosome Aberrations**

Nucro-Technics Project No. 257957

3 hours -S9						3 hours +S9						20 hours -S9					
S3643 (mg/mL)	Cells•	e	pp	Aberrant Cells (%)	Mean	S3643 (mg/mL)	Cells•	e	pp	Aberrant Cells (%)	Mean	S3643 (mg/mL)	Cells•	e	pp	Aberrant Cells (%)	Mean
0	100			0	0.0	0	100			0	0.0	0	100			0	0.0
	100			0			100			0			100			0	
0.13	100			0	0.0	0.063	100			0	0.0	0.031	100			0	0.0
	100			0			100			0			100			0	
0.25	100			0	0.0	0.13	100			0	0.0	0.063	100			0	0.0
	100			0			100			0			100			0	
0.50	100			0	0.0	0.25	100			0	0.0	0.13	100			0	0.0
	100			0			101			0			100			0	

Total cells (diploid, endoreduplicated and polyploid cells)

## In Vitro Micronucleus Test of S3643 in Chinese Hamster Ovary Cells

**Table 12-1. Cytostasis**

Nucro-Technics Project No. 257956

3 Hours -S9							3 Hours +S9						19 Hours -S9							
Dose (µg/mL)	Nuclei Frequency			Total Cells	CBPI	CYT (%)	Dose (µg/mL)	Nuclei Frequency			Total Cells	CBPI	CYT (%)	Dose (µg/mL)	Nuclei Frequency			Total Cells	CBPI	CYT (%)
	1	2	3+					1	2	3+					1	2	3+			
0	75	393	32	500	1.93	0	0	87	391	22	500	1.89	0	0	84	900	16	1000	1.93	0
	62	401	37	500				71	407	22	500				95	887	18	1000		
100	55	417	28	500	1.93	1	50	89	382	29	500	1.89	-1	16	187	801	12	1000	1.83	10
	83	380	37	500				77	395	28	500				175	811	14	1000		
200	64	417	19	500	1.93	0	100	76	389	35	500	1.90	-2	31	308	668	24	1000	1.72	22
	59	405	36	500				78	399	23	500				282	708	11	1001		
300	168	321	11	500	1.70	25	200	197	295	8	500	1.63	29	63	571	429	0	1000	1.46	50
	161	318	21	500				187	304	9	500				505	495	0	1000		
450	455	45	0	500	1.07	93	300	465	35	0	500	1.08	91	80	873	127	0	1000	1.13	87
	476	24	0	500				454	46	0	500				877	123	0	1000		
*600	-	-	-	-	-	-	**450	-	-	-	-	-	-	130	925	75	0	1000	1.06	93
	-	-	-	-				-	-	-	-				951	49	0	1000		
*600	-	-	-	-	-	-	*600	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-				-	-	-	-				-	-	-			

Nuclei Frequency = Number of mono-, bi- and multi-nucleated cells

CBPI = Cytokinesis-Block Proliferation Index = (mononucleated cells + 2X binucleated cells + 3X multinucleated cells) / total cells

CYT (%) = % Cytostasis =  $100 - 100 \{ (CBPI_T - 1) / (CBPI_C - 1) \}$  where T = Test Substance and C = Negative Control

"\*\*" Cells were altered in morphology and were only single binucleated cells

"\*" Cells were not harvested due to cell death

**Table 12-2. Micronuclei Incidence**

Nucro-Technics Project No. 257956

3 Hours -S9							3 Hours +S9						19 Hours -S9							
Dose (µg/mL)	Number of BN with MN			Total BN Cells	MN per BN	% BN with MN	Dose (µg/mL)	Number of BN with MN			Total BN Cells	MN per BN	% BN with MN	Dose (µg/mL)	Number of BN with MN			Total BN Cells	MN per BN	% BN with MN
	1	2	3+					1	2	3+					1	2	3+			
0	10	0	1	1000	0.011	1.0	0	12	0	0	1000	0.018	1.6	0	8	0	0	1000	0.011	1.1
	8	0	0	1000				17	2	1	1000				14	0	0	1000		
100	7	2	0	1000	0.014	1.2	50	10	2	0	1000	0.014	1.2	16	17	0	0	1000	0.014	1.4
	12	2	0	1000				10	2	0	1000				9	1	0	1000		
200	14	0	0	1000	0.015	1.4	100	7	2	0	1000	0.020	1.7	31	8	2	0	1000	0.014	1.3
	13	1	0	1000				21	2	1	1000				16	0	0	1000		
300	7	1	0	1000	0.013	1.1	200	17	2	1	1000	0.025	2.1	63	18	0	0	1000	0.020	1.9
	12	2	0	1000				20	1	1	1000				19	1	0	1000		
COL 8	52	4	2	1000	0.063	5.3	CP 7.5	52	14	3	300	0.29	23.5	COL 0.16	42	8	2	1000	0.074	5.8
	40	5	3	1000				61	7	4	300				45	15	3	1000		

MN = Micronuclei

BN = Binucleated Cell(s)

Number of BN with MN = Refers to the number of binucleated cells with 1, 2 or 3+ micronuclei

MN per BN= ((#BN with one MN)+2 (#BN with two MN)+3 (# of BN with three or more MN))/(Total BN analyzed)

% BN with MN= ((# of BN with MN)/(Total BN)) X 100

## 28-Day Range Finding Toxicology Study of S3643 in Sprague-Dawley Rats

### Study Design

Three treatment groups of five male and five female CD<sup>®</sup> [CrI:CD<sup>®</sup>(SD)] rats were administered the test article at dose levels of 10, 30, and 100 mg/kg bw/day. One additional group of five animals/sex served as the control and received untreated (vehicle) diet. The vehicle or test article diet was available *ad libitum* for 28 consecutive days. Body weights were measured and recorded on Days - 1, 4, 7, 11, 14, 21, and 28. Food consumption was measured and recorded on Days 4, 7, 11, 14, 21, and 28. Compound consumption was calculated at the same intervals as food consumption. Ophthalmoscopic examinations were conducted pretest and prior to the terminal necropsy. Blood and urine samples for clinical pathology evaluations were collected from all animals prior to the terminal necropsy. At study termination, necropsy examinations were performed, organ weights were recorded, and only the liver was microscopically examined for animals at 0 and 100 mg/kg bw/day.

**Table 13. Pathology Procedures**

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination	
			1, 4	2, 3
Adrenal gland	X	X		
Aorta		X		
Bone with bone marrow, femur		X		
Bone with bone marrow, sternum		X		
Bone marrow smear		X		
Brain (cerebrum, midbrain, cerebellum, medulla/pons)	X	X		
Epididymis	X	X		
Esophagus		X		
Eye (with optic nerve)		X		
GALT (Gut-Associated Lymphoid Tissue)		X		
Heart	X	X		
Joint, tibiofemoral		X		
Kidney	X	X		
Lacrimal gland, exorbital		X		
Large intestine, cecum		X		
Large intestine, colon		X		
Large intestine, rectum		X		
Larynx		X		
Liver	X	X	X	
Lung with bronchi	X	X		
Lymph node, mandibular		X		

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination	
			1, 4	2, 3
Lymph node, mesenteric		X		
Mammary gland (process females only)		X		
Nerve, sciatic		X		
Ovary with Oviducts	X	X		
Pancreas		X		
Pituitary	X	X		
Prostate	X	X		
Salivary gland, mandibular	X	X		
Salivary gland, parotid		X		
Salivary gland, sublingual		X		
Seminal vesicles		X		
Skeletal muscle, biceps femoris		X		
Skin		X		
Small intestine, duodenum		X		
Small intestine, ileum		X		
Small intestine, jejunum		X		
Spinal cord, cervical		X		
Spinal cord, lumbar		X		
Spinal cord, thoracic		X		
Spleen	X	X		
Stomach, glandular		X		
Stomach, nonglandular		X		
Target Organs		X	X	X
Testis	X	X		
Thymus	X	X		
Thyroid gland (with parathyroid)	X	X		
Tongue		X		
Trachea		X		
Ureters		X		
Urinary bladder		X		
Uterus with cervix	X	X		
Vagina		X		
Gross lesions		X		
Tissue masses with regional lymph node		X		

**Table 14-1. Summary of Body Weights - Male**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	Study Interval (Day)	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight g	-1	186.4	7.64	5	186.0	6.96	5	187.6	9.84	5	188.2	8.23	5
	1	186.0	8.25	5	187.4	6.88	5	187.0	11.60	5	188.4	8.38	5
	4	216.2	8.70	5	217.0	9.77	5	217.4	13.70	5	216.8	11.95	5
	7	239.2	10.43	5	240.4	12.20	5	238.2	15.77	5	241.2	11.90	5
	11	266.8	14.18	5	275.0	19.43	5	264.4	15.65	5	272.6	13.94	5
	14	285.8	14.53	5	291.4	18.64	5	284.2	20.13	5	291.4	16.33	5
	21	332.6	16.47	5	338.8	27.64	5	330.8	26.68	5	335.4	17.64	5
	28	358.8	24.18	5	368.0	33.20	5	357.0	25.16	5	361.0	18.28	5

**Table 14-2. Summary of Body Weights – Female**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	Study Interval (Day)	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight g	-1	170.0	6.20	5	169.6	5.98	5	169.4	6.66	5	170.6	6.80	5
	1	167.0	7.84	5	166.0	5.83	5	164.8	7.60	5	167.2	5.93	5
	4	183.0	8.66	5	180.6	6.31	5	177.8	9.44	5	181.2	5.02	5
	7	191.6	12.10	5	187.6	4.77	5	186.2	8.67	5	185.6	5.22	5
	11	201.4	12.76	5	196.4	5.59	5	196.8	10.55	5	195.8	5.12	5
	14	205.8	13.39	5	201.4	8.71	5	199.2	11.21	5	199.4	8.20	5
	21	226.4	14.33	5	220.8	9.23	5	218.4	11.55	5	215.6	7.33	5
	28	231.4	15.19	5	228.2	10.11	5	219.8	8.98	5	220.6	6.19	5

N – Number of measures  
SD – Standard Deviation

**Table 15-1. Summary of Food Consumption - Male**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	Study Interval (Day)	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Consumption g/animal/day	4	22.00	1.616	5	21.73	1.362	5	21.53	2.305	5	21.93	1.877	5
	7	24.20	2.545	5	24.47	1.924	5	22.60	2.229	5	24.13	1.556	5
	11	25.40	3.338	5	25.15	1.755	5	24.05	3.099	5	24.75	1.591	5
	14	24.67	1.563	5	25.20	1.909	5	23.40	2.253	5	24.67	1.130	5
	21	25.34	1.889	5	25.20	2.300	5	24.09	2.074	5	24.57	1.208	5
	28	25.09	2.685	5	25.63	2.549	5	23.89	1.251	5	24.09	2.173	5

**Table 15-2. Summary of Food Consumption - Female**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	Study Interval (Day)	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Consumption g/animal/day	4	16.73	0.983	5	15.60	0.596	5	15.80	1.677	5	15.20	1.346	5
	7	16.73	1.362	5	16.60	0.863	5	16.00	1.546	5	16.33	2.906	5
	11	17.15	1.040	5	16.40	1.537	5	15.85	1.055	5	15.80	1.165	5
	14	16.87	0.901	5	17.20	1.980	5	15.73	1.090	5	16.93	3.227	5
	21	17.69	1.197	5	17.00	1.781	5	17.23	1.123	5	16.31	0.950	5
	28	17.06	1.154	5	17.00	1.857	5	15.49	0.831	5	15.34	0.884	5

N – Number of measures  
SD – Standard Deviation



**Table 16-1. Summary of Hematology Values – Male**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Leukocytes 10 <sup>3</sup> /μL	Terminal	16.14	6.748	5	17.26	4.222	5	16.78	3.642	5	14.54	2.042	5
Erythrocytes 10 <sup>6</sup> /μL	Terminal	8.942	0.5719	5	8.382	0.1699	5	8.232 <sup>a</sup>	0.4456	5	8.386	0.3360	5
Hemoglobin g/dL	Terminal	16.82	1.031	5	15.84	0.434	5	16.14	0.493	5	16.16	0.662	5
Hematocrit %	Terminal	56.62	4.717	5	52.66	1.324	5	53.98	1.551	5	53.86	1.705	5
MCV fL	Terminal	63.32	2.129	5	62.82	2.572	5	65.68	3.268	5	64.24	1.119	5
MCH pg	Terminal	18.84	0.532	5	18.90	0.667	5	19.60	0.604	5	19.30	0.557	5
MCHC g/dL	Terminal	29.76	0.760	5	30.12	0.687	5	29.88	0.576	5	30.02	0.559	5

N – Number of measures

SD – Standard Deviation

<sup>a</sup>. Significantly different from control

**Table 16-1. Summary of Hematology Values – Male (continued)**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Platelets 103/ $\mu$ L	Terminal	1158.8	196.60	5	1367.2	403.34	5	1204.4	129.15	5	1242.8	187.44	5
Absolute Reticulocytes 103/ $\mu$ L	Terminal	211.38	30.552	5	232.18	65.234	5	205.04	16.549	5	198.66	14.173	5
Neutrophils 103/ $\mu$ L	Terminal	1.618	0.6377	5	2.574	1.6555	5	1.888	0.4845	5	1.534	0.6831	5
Lymphocytes 103/ $\mu$ L	Terminal	13.668	6.2339	5	13.904	3.6383	5	14.018	2.9900	5	12.332	1.9908	5
Monocytes 103/ $\mu$ L	Terminal	0.322	0.1303	5	0.354	0.2067	5	0.374	0.1399	5	0.228	0.0672	5
Eosinophils 103/ $\mu$ L	Terminal	0.122	0.0522	5	0.106	0.0451	5	0.108	0.0507	5	0.092	0.0606	5
Basophils 103/ $\mu$ L	Terminal	0.130	0.0762	5	0.122	0.0192	5	0.110	0.0406	5	0.098	0.0217	5
Other Cells 103/ $\mu$ L	Terminal	0.284	0.2294	5	0.200	0.0612	5	0.264	0.1097	5	0.238	0.0898	5

N – Number of measures  
SD – Standard Deviation

**Table 16-2. Summary of Hematology Values – Female**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Leukocytes 103/ $\mu$ L	Terminal	9.32	1.695	5	12.42	3.168	5	11.04	3.477	5	13.30	3.261	5
Erythrocytes 106/ $\mu$ L	Terminal	8.680	0.3766	5	8.722	0.3993	5	8.528	0.2452	5	8.686	0.5126	5
Hemoglobin g/dL	Terminal	16.48	0.602	5	16.42	0.918	5	16.10	0.671	5	16.60	0.946	5
Hematocrit %	Terminal	53.20	1.783	5	52.44	3.331	5	52.32	2.386	5	53.14	2.640	5
MCV fL	Terminal	61.36	1.524	5	60.10	1.079	5	61.32	1.452	5	61.26	2.485	5
MCH pg	Terminal	18.98	0.421	5	18.80	0.292	5	18.82	0.476	5	19.12	0.421	5
MCHC g/dL	Terminal	30.94	0.623	5	31.32	0.669	5	30.74	0.658	5	31.26	0.744	5

N – Number of measures  
SD – Standard Deviation

**Table 16-2. Summary of Hematology Values – Female (continued)**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Platelets 103/ $\mu$ L	Terminal	1075.8	89.28	5	1222.4	148.83	5	1196.6	250.11	5	1191.6	108.54	5
Absolute Reticulocytes 103/ $\mu$ L	Terminal	162.28	19.416	5	167.84	29.928	5	172.82	29.914	5	187.52	29.635	5
Neutrophils 103/ $\mu$ L	Terminal	1.312	0.7662	5	1.314	0.7362	5	1.226	0.7842	5	1.112	0.5633	5
Lymphocytes 103/ $\mu$ L	Terminal	7.446	1.5756	5	10.522	2.7059	5	9.250	2.8096	5	11.472 <sup>a</sup>	2.7606	5
Monocytes 103/ $\mu$ L	Terminal	0.230	0.0846	5	0.224	0.0439	5	0.220	0.0930	5	0.244	0.1038	5
Eosinophils 103/ $\mu$ L	Terminal	0.116	0.0767	5	0.084	0.0251	5	0.076	0.0270	5	0.124	0.0358	5
Basophils 103/ $\mu$ L	Terminal	0.068	0.0192	5	0.094	0.0195	5	0.072	0.0179	5	0.088	0.0370	5
Other Cells 103/ $\mu$ L	Terminal	0.142	0.0268	5	0.188	0.0421	5	0.178	0.1145	5	0.272	0.1910	5

N – Number of measures

SD – Standard Deviation

<sup>a</sup> Significantly different from control (p<0.05)

**Table 17-1. Summary of Coagulation Values – Male**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
APTT sec	Terminal	17.24	2.691	5	16.62	1.207	5	17.58	1.434	5	18.88	1.849	5
Prothrombin Time sec	Terminal	17.00	1.432	5	16.50	0.652	5	16.64	0.541	5	16.48	0.814	5

**Table 17-2. Summary of Coagulation Values – Female**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
APTT sec	Terminal	15.92	1.668	5	16.84	1.443	5	17.36	2.952	5	15.26	3.752	5
Prothrombin Time sec	Terminal	16.78	1.310	5	16.22	0.665	5	16.46	0.594	5	16.06	0.445	5

N – Number of measures  
SD – Standard Deviation

**Table 18-1. Summary of Clinical Chemistry Values – Male**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Sodium mEq/L	Terminal	144.6	0.55	5	144.2	1.10	5	145.2	0.45	5	144.8	1.10	5
Potassium mEq/L	Terminal	6.62	1.018	5	7.10	1.387	5	6.68	0.342	5	6.82	0.545	5
Chloride mEq/L	Terminal	99.2	1.48	5	99.4	0.55	5	100.2	0.45	5	99.0	1.58	5
Calcium mg/dL	Terminal	11.98	0.719	5	11.96	0.182	5	11.76	0.416	5	11.98	0.517	5
Phosphorus mg/dL	Terminal	11.16	0.709	5	11.56	1.537	5	11.26	0.385	5	10.98	0.482	5
Alkaline Phosphatase U/L	Terminal	207.0	21.77	5	190.6	44.88	5	185.0	35.23	5	192.2	48.56	5
Total Bilirubin mg/dL	Terminal	0.12	0.045	5	0.14	0.055	5	0.10	0.000	5	0.10	0.000	5

N – Number of measures  
SD – Standard Deviation

**Table 18-1. Summary of Clinical Chemistry Values – Male (continued)**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
GGT U/L	Terminal <sup>#</sup>	1.5	0.71	2	1.0	0.00	4	1.0	0.00	2	1.0	0.00	4
AST U/L	Terminal	132.2	137.09	5	72.8	7.89	5	70.6	7.23	5	72.8	4.27	5
ALT U/L	Terminal	78.0	83.26	5	31.8	6.02	5	31.4	6.35	5	29.2	1.30	5
Urea Nitrogen mg/dL	Terminal	16.8	2.77	5	14.0	1.58	5	16.4	3.21	5	15.4	2.70	5
Creatinine mg/dL	Terminal	0.38	0.045	5	0.34	0.055	5	0.36	0.055	5	0.34	0.055	5
Total Protein g/dL	Terminal	6.48	0.438	5	6.40	0.367	5	6.20	0.158	5	6.60	0.374	5
Albumin g/dL	Terminal	3.44	0.230	5	3.34	0.182	5	3.34	0.089	5	3.50	0.141	5

N – Number of measures

SD – Standard Deviation

<sup>#</sup> No statistics performed due to lack of variability or sample size

**Table 18-1. Summary of Clinical Chemistry Values – Male (continued)**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Globulin g/dL	Terminal	3.04	0.230	5	3.06	0.219	5	2.86	0.195	5	3.10	0.265	5
Albumin/Globulin Ratio	Terminal	1.12	0.045	5	1.06	0.055	5	1.16	0.114	5	1.14	0.055	5
Triglyceride mg/dL	Terminal	66.6	4.28	5	58.6	25.92	5	55.4	26.85	5	39.8	12.85	5
Cholesterol mg/dL	Terminal	61.4	12.42	5	62.2	7.16	5	57.6	9.13	5	61.4	17.50	5
Glucose mg/dL	Terminal	243.8	62.96	5	234.4	56.77	5	200.2	32.83	5	201.0	28.22	5

N – Number of measures

SD – Standard Deviation

# No statistics performed due to lack of variability or sample size



**Table 18-2. Summary of Clinical Chemistry Values – Female**  
 MPI Research Study No. 1646-015  
 S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Sodium mEq/L	Terminal	143.0	0.71	5	144.6	1.52	5	143.2	1.64	5	143.2	1.30	5
Potassium mEq/L	Terminal	7.64	0.404	5	7.06	0.673	5	8.10	1.488	5	7.78	1.110	5
Chloride mEq/L	Terminal	101.6	1.67	5	100.6	1.95	5	102.0	1.00	5	100.6	1.14	5
Calcium mg/dL	Terminal	11.88	0.205	5	11.66	0.573	5	11.80	0.648	5	12.28	0.512	5
Phosphorus mg/dL	Terminal	10.42	0.311	5	9.90	0.667	5	10.66	1.322	5	10.52	0.729	5
Alkaline Phosphatase U/L	Terminal	132.2	41.75	5	105.0	21.99	5	81.8 <sup>a</sup>	18.71	5	91.8	18.10	5
Total Bilirubin mg/dL	Terminal	0.14	0.055	5	0.12	0.045	5	0.10	0.000	5	0.12	0.045	5

N – Number of measures

SD – Standard Deviation

<sup>a</sup> Significantly different from control (p<0.05)

**Table 18-2. Summary of Clinical Chemistry Values – Female (continued)**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
GGT U/L	Terminal	1.0	0.00	5	1.0	0.00	5	1.4	0.55	5	1.3	0.50	4
AST U/L	Terminal	76.6	14.50	5	68.6	8.91	5	79.4	17.34	5	69.6	5.50	5
ALT U/L	Terminal	29.2	10.85	5	27.2	6.42	5	26.6	10.14	5	25.8	4.09	5
Urea Nitrogen mg/dL	Terminal	14.0	1.41	5	16.0	3.54	5	17.6	4.22	5	17.4	2.07	5
Creatinine mg/dL	Terminal	0.38	0.045	5	0.42	0.084	5	0.38	0.084	5	0.40	0.000	5
Total Protein g/dL	Terminal	6.90	0.381	5	6.98	0.545	5	6.84	0.573	5	7.12	0.563	5
Albumin g/dL	Terminal	3.72	0.179	5	3.68	0.286	5	3.68	0.327	5	3.82	0.311	5

N – Number of measures  
SD – Standard Deviation

**Table 18-2. Summary of Clinical Chemistry Values – Female (continued)**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Globulin g/dL	Terminal	3.18	0.217	5	3.30	0.292	5	3.16	0.251	5	3.30	0.274	5
Albumin/Globulin Ratio	Terminal	1.16	0.055	5	1.10	0.071	5	1.16	0.055	5	1.16	0.055	5
Triglyceride mg/dL	Terminal	32.0	9.87	5	31.2	5.22	5	33.4	8.91	5	35.4	8.99	5
Cholesterol mg/dL	Terminal	75.6	13.16	5	62.0	18.10	5	75.4	8.41	5	70.8	20.00	5
Glucose mg/dL	Terminal	141.6	27.92	5	169.4	42.79	5	147.8	26.56	5	195.8 <sup>a</sup>	23.21	5

N – Number of measures

SD – Standard Deviation

<sup>a</sup> Significantly different from control (p<0.05)

**Table 19-1. Summary of Urinalysis Values – Male**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Volume mL	Terminal	3.80	1.483	5	4.20	2.515	5	3.70	4.932	5	8.50	4.093	5
Specific Gravity	Terminal	1.0718	0.01651	5	1.0628	0.01680	4	1.0210 <sup>a</sup>	NA	1	1.0338 <sup>a</sup>	0.01228	4
pH	Terminal	6.70	0.274	5	6.80	0.274	5	7.10	0.822	5	6.80	0.274	5

**Table 19-2. Summary of Urinalysis Values – Female**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Volume mL	Terminal	4.20	1.789	5	4.20	4.751	5	1.88	1.322	5	1.70	0.908	5
Specific Gravity	Terminal	1.0528	0.01819	5	1.0510	0.03387	3	1.0555	0.00071	2	1.0770	0.00909	4
pH	Terminal	6.60	0.224	5	6.60	0.418	5	6.63	0.479	4	6.50	0.500	5

N – Number of measures  
SD – Standard Deviation

NA – Not applicable/not available

<sup>a</sup> Significantly different from control (p<0.05)

**Table 20-1. Summary of Macroscopic Observations – Male**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

<b>Tissue</b>		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Observation	Severity				
Number of Animals Examined		5	5	5	5
<b>all tissues</b>					
within normal limits		5	3	5	5
<b>kidneys</b>					
dilatation, pelvic		0	2	0	0
	- mild	0	1	0	0
	- moderate	0	1	0	0

**Table 20-2. Summary of Macroscopic Observations – Female**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

<b>Tissue</b>		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Observation	Severity				
Number of Animals Examined		5	5	5	5
<b>all tissues</b>					
within normal limits		5	5	4	5
<b>uterus with cervix</b>					
enlarged	- mild	0	0	1	0

**Table 21-1. Summary of Organ Weights – Male**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Body weight</b> g	334	22	5	342	29	5	333	29	5	333	17	5
<b>Brain</b> g	1.928	0.028	5	1.947	0.072	5	1.926	0.044	5	1.966	0.083	5
Brain/BWt %	0.5794	0.0370	5	0.5728	0.0590	5	0.5808	0.0387	5	0.5902	0.0224	5
<b>Adrenal gl</b> g	0.063	0.012	5	0.066	0.009	5	0.077	0.025	5	0.069	0.024	5
Adrenal gl/BWt %	0.0190	0.0042	5	0.0193	0.0021	5	0.0232	0.0076	5	0.0205	0.0061	5
Adrenal gl/BrWt ratio	0.0327	0.0058	5	0.0340	0.0044	5	0.0399	0.0129	5	0.0348	0.0109	5

N – Number of measures

SD – Standard Deviation

**Table 21-1. Summary of Organ Weights – Male (continued)**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Epididymides</b>												
g	0.846	0.049	5	0.836	0.057	5	0.916	0.129	5	0.917	0.077	5
Epididymides/BWt %	0.2545	0.0247	5	0.2460	0.0311	5	0.2779	0.0547	5	0.2749	0.0167	5
Epididymides/BrWt ratio	0.4388	0.0228	5	0.4289	0.0197	5	0.4763	0.0733	5	0.4664	0.0346	5
<b>Heart</b>												
g	1.286	0.144	5	1.382	0.202	5	1.235	0.098	5	1.327	0.092	5
Heart/BWt %	0.3847	0.0223	5	0.4033	0.0395	5	0.3708	0.0057	5	0.3984	0.0301	5
Heart/BrWt ratio	0.6674	0.0746	5	0.7095	0.0982	5	0.6404	0.0379	5	0.6751	0.0431	5

N – Number of measures  
SD – Standard Deviation

**Table 21-1. Summary of Organ Weights – Male (continued)**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Kidneys</b>												
g	2.980	0.279	5	3.168	0.302	5	3.092	0.231	5	3.252	0.254	5
Kidneys/BWt %	0.8918	0.0315	5	0.9264	0.0540	5	0.9301	0.0575	5	0.9750 <sup>a</sup>	0.0435	5
Kidneys/BrWt ratio	1.5462	0.1432	5	1.6278	0.1570	5	1.6040	0.0971	5	1.6533	0.0849	5
<b>Liver</b>												
g	10.971	0.822	5	12.319	1.237	5	11.532	2.099	5	12.486	1.323	5
Liver/BWt %	3.2892	0.1857	5	3.6084	0.3480	5	3.4431	0.4042	5	3.7390	0.2455	5
Liver/BrWt ratio	5.6922	0.4320	5	6.3251	0.5992	5	5.9716	0.9840	5	6.3410	0.4529	5

N – Number of measures

SD – Standard Deviation

<sup>a</sup> Significantly different from control



**Table 21-1. Summary of Organ Weights – Male (continued)**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Lung w/ bronchi</b> g	1.531	0.062	5	1.543	0.098	5	1.404	0.185	5	1.549	0.125	5
Lung w/ bronchi/BWt %	0.4597	0.0228	5	0.4519	0.0205	5	0.4215	0.0407	5	0.4654	0.0423	5
Lung w/ bronchi/BrWt ratio	0.7947	0.0381	5	0.7929	0.0529	5	0.7283	0.0883	5	0.7894	0.0740	5
<b>Pituitary gl</b> g	0.0126	0.0011	5	0.0135	0.0024	5	0.0131	0.0021	5	0.0136	0.0023	5
Pituitary gl/BWt %	0.0038	0.0004	5	0.0039	0.0004	5	0.0040	0.0006	5	0.0040	0.0005	5
Pituitary gl/BrWt ratio	0.0066	0.0006	5	0.0069	0.0013	5	0.0068	0.0010	5	0.0069	0.0009	5

N – Number of measures

SD – Standard Deviation

**Table 21-1. Summary of Organ Weights – Male (continued)**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Prostate gl</b>												
g	0.870	0.226	5	1.016	0.305	5	1.050	0.139	5	0.940	0.211	5
Prostate gl/BWt %	0.2605	0.0659	5	0.2973	0.0824	5	0.3163	0.0430	5	0.2825	0.0647	5
Prostate gl/BrWt ratio	0.4517	0.1180	5	0.5258	0.1745	5	0.5446	0.0686	5	0.4785	0.1084	5
<b>Sal. gl, mand.</b>												
g	0.636	0.020	5	0.635	0.040	5	0.697	0.128	5	0.714	0.085	5
Sal. gl, mand./BWt %	0.1912	0.0145	5	0.1869	0.0241	5	0.2099	0.0393	5	0.2140	0.0230	5
Sal. gl, mand./BrWt ratio	0.3299	0.0072	5	0.3258	0.0126	5	0.3617	0.0660	5	0.3628	0.0389	5

N – Number of measures

SD – Standard Deviation

**Table 21-1. Summary of Organ Weights – Male (continued)**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Spleen</b>												
g	0.673	0.084	5	0.793	0.193	5	0.698	0.136	5	0.807	0.163	5
Spleen/BWt %	0.2016	0.0227	5	0.2301	0.0427	5	0.2094	0.0334	5	0.2410	0.0380	5
Spleen/BrWt ratio	0.3489	0.0416	5	0.4082	0.1028	5	0.3620	0.0669	5	0.4089	0.0669	5
<b>Testes</b>												
g	3.173	0.206	5	3.130	0.226	5	3.365	0.300	5	3.206	0.405	5
Testes/BWt %	0.9535	0.0828	5	0.9214	0.1239	5	1.0170	0.1354	5	0.9608	0.0956	5
Testes/BrWt ratio	1.6453	0.0879	5	1.6066	0.0875	5	1.7476	0.1584	5	1.6279	0.1524	5

N – Number of measures  
SD – Standard Deviation

**Table 21-1. Summary of Organ Weights – Male (continued)**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Thymus</b> g	0.585	0.147	5	0.604	0.122	5	0.525	0.083	5	0.533	0.108	5
Thymus/BWt %	0.1745	0.0394	5	0.1752	0.0231	5	0.1595	0.0337	5	0.1596	0.0297	5
Thymus/BrWt ratio	0.3032	0.0761	5	0.3104	0.0643	5	0.2733	0.0468	5	0.2705	0.0483	5
<b>Thyroid/parathyroid gl</b> g	0.025	0.004	5	0.021	0.003	5	0.019 <sup>a</sup>	0.003	5	0.022	0.003	5
Thyroid/parathyroid gl/BWt %	0.0075	0.0010	5	0.0060 <sup>a</sup>	0.0009	5	0.0058 <sup>a</sup>	0.0006	5	0.0066	0.0008	5
Thyroid/parathyroid gl/BrWt ratio	0.0131	0.0019	5	0.0105 <sup>a</sup>	0.0013	5	0.0100 <sup>a</sup>	0.0014	5	0.0112	0.0014	5

N – Number of measures

SD – Standard Deviation

<sup>a</sup> Significantly different from control

**Table 21-2. Summary of Organ Weights – Female**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Body weight</b> g	211	14	5	206	9	5	201	10	5	200	7	5
<b>Brain</b> g	1.890	0.029	5	1.838	0.066	5	1.927	0.166	5	1.804	0.157	5
Brain/BWt %	0.8995	0.0599	5	0.8911	0.0239	5	0.9594	0.1054	5	0.9007	0.0666	5
<b>Adrenal gl</b> g	0.076	0.017	5	0.072	0.004	5	0.075	0.016	5	0.084	0.019	5
Adrenal gl/BWt %	0.0358	0.0061	5	0.0349	0.0033	5	0.0375	0.0083	5	0.0422	0.0109	5
Adrenal gl/BrWt ratio	0.0401	0.0084	5	0.0392	0.0035	5	0.0392	0.0086	5	0.0472	0.0133	5

N – Number of measures

SD – Standard Deviation

**Table 21-2. Summary of Organ Weights – Female (continued)**  
 MPI Research Study No. 1646-015  
 S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Heart</b>												
g	0.870	0.107	5	0.871	0.041	5	0.821	0.051	5	0.881	0.028	5
Heart/BWt %	0.4119	0.0252	5	0.4223	0.0188	5	0.4076	0.0174	5	0.4401	0.0112	5
Heart/BrWt ratio	0.4604	0.0534	5	0.4738	0.0151	5	0.4276	0.0330	5	0.4910	0.0413	5
<b>Kidneys</b>												
g	1.808	0.206	5	1.754	0.114	5	1.822	0.144	5	1.752	0.075	5
Kidneys/BWt %	0.8562	0.0531	5	0.8508	0.0570	5	0.9057	0.0776	5	0.8761	0.0495	5
Kidneys/BrWt ratio	0.9573	0.1104	5	0.9550	0.0624	5	0.9486	0.0839	5	0.9782	0.1068	5

N – Number of measures  
 SD – Standard Deviation

**Table 21-2. Summary of Organ Weights – Female (continued)**  
 MPI Research Study No. 1646-015  
 S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Liver</b>												
g	7.119	0.649	5	6.926	0.325	5	6.954	0.609	5	6.940	0.340	5
Liver/BWt %	3.3739	0.1462	5	3.3651	0.2900	5	3.4566	0.3093	5	3.4680	0.1574	5
Liver/BrWt ratio	3.7689	0.3578	5	3.7753	0.2879	5	3.6278	0.4405	5	3.8705	0.3764	5
<b>Lung w/ bronchi</b>												
g	1.159	0.139	5	1.211	0.132	5	1.520	0.934	5	1.112	0.102	5
Lung w/ bronchi/BWt %	0.5488	0.0345	5	0.5897	0.0923	5	0.7615	0.4879	5	0.5566	0.0598	5
Lung w/ bronchi/BrWt ratio	0.6133	0.0693	5	0.6606	0.0903	5	0.7640	0.3810	5	0.6224	0.0954	5

N – Number of measures  
 SD – Standard Deviation

**Table 21-2. Summary of Organ Weights – Female (continued)**  
 MPI Research Study No. 1646-015  
 S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Ovaries w/ oviducts</b>												
g	0.130	0.016	5	0.117	0.021	5	0.112	0.023	5	0.131	0.007	5
Ovaries w/ oviducts/BWt %	0.0616	0.0058	5	0.0571	0.0111	5	0.0555	0.0117	5	0.0658	0.0052	5
Ovaries w/ oviducts/BrWt ratio	0.0688	0.0089	5	0.0642	0.0132	5	0.0581	0.0124	5	0.0736	0.0106	5
<b>Pituitary gl</b>												
g	0.0149	0.0006	5	0.0136	0.0041	5	0.0149	0.0031	5	0.0137	0.0012	5
Pituitary gl/BWt %	0.0071	0.0006	5	0.0065	0.0018	5	0.0074	0.0013	5	0.0068	0.0005	5
Pituitary gl/BrWt ratio	0.0079	0.0003	5	0.0074	0.0020	5	0.0079	0.0021	5	0.0076	0.0001	5

N – Number of measures  
 SD – Standard Deviation



**Table 21-2. Summary of Organ Weights – Female (continued)**  
 MPI Research Study No. 1646-015  
 S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Sal. gl, mand.</b>												
g	0.494	0.037	5	0.475	0.040	5	0.480	0.051	5	0.461	0.061	5
Sal. gl, mand./BWt %	0.2355	0.0261	5	0.2304	0.0172	5	0.2389	0.0304	5	0.2308	0.0333	5
Sal. gl, mand./BrWt ratio	0.2614	0.0166	5	0.2587	0.0213	5	0.2492	0.0202	5	0.2572	0.0393	5
<b>Spleen</b>												
g	0.492	0.067	5	0.511	0.057	5	0.520	0.067	5	0.495	0.035	5
Spleen/BWt %	0.2328	0.0238	5	0.2472	0.0196	5	0.2580	0.0272	5	0.2474	0.0209	5
Spleen/BrWt ratio	0.2602	0.0347	5	0.2780	0.0293	5	0.2707	0.0346	5	0.2765	0.0367	5

N – Number of measures  
 SD – Standard Deviation

**Table 21-2. Summary of Organ Weights – Female (continued)**  
 MPI Research Study No. 1646-015  
 S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Thymus</b>												
g	0.486	0.095	5	0.461	0.041	5	0.447	0.072	5	0.383	0.071	5
Thymus/BWt %	0.2299	0.0371	5	0.2236	0.0203	5	0.2225	0.0400	5	0.1909	0.0333	5
Thymus/BrWt ratio	0.2566	0.0476	5	0.2513	0.0271	5	0.2309	0.0199	5	0.2108	0.0232	5
<b>Thyroid/parathyroid gl</b>												
g	0.019	0.003	5	0.017	0.002	5	0.016	0.001	5	0.017	0.002	5
Thyroid/parathyroid gl/BWt %	0.0088	0.0012	5	0.0084	0.0011	5	0.0078	0.0008	5	0.0087	0.0008	5
Thyroid/parathyroid gl/BrWt ratio	0.0099	0.0015	5	0.0094	0.0011	5	0.0081	0.0002	5	0.0097	0.0013	5

N – Number of measures  
 SD – Standard Deviation

**Table 21-2. Summary of Organ Weights – Female (continued)**  
 MPI Research Study No. 1646-015  
 S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Uterus w/ cervix</b> g	0.631	0.266	5	0.671	0.302	5	0.511	0.240	5	0.644	0.137	5
Uterus w/ cervix/BWt %	0.2989	0.1202	5	0.3245	0.1433	5	0.2553	0.1236	5	0.3232	0.0764	5
Uterus w/ cervix/BrWt ratio	0.3330	0.1373	5	0.3634	0.1579	5	0.2668	0.1288	5	0.3606	0.0920	5

N – Number of measures  
 SD – Standard Deviation

**Table 22-1. Summary of Microscopic Observations – Male**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

		0 mg/kg/day	100 mg/kg/day
<b>Tissue</b>			
Observation	Severity		
Number of Animals Examined		5	5
<b>liver</b>		(5)	(5)
infiltration, mononuclear cell	- minimal	5	5

( ) – Number observed

**Table 22-2. Summary of Microscopic Observations – Female**

MPI Research Study No. 1646-015

S3643: A 4-Week Dietary Administration Toxicity Study in Rats (non-GLP)

		0 mg/kg/day	100 mg/kg/day
<b>Tissue</b>			
Observation	Severity		
Number of Animals Examined		5	5
<b>liver</b>		(5)	(5)
infiltration, mononuclear cell	- minimal	5	5
necrosis, focal	- minimal	1	0
vacuolation, focal	- minimal	0	1
vacuolation, periportal	- minimal	1	0

( ) – Number observed

## 90-Day Subchronic Toxicology Study of S3643 in Sprague-Dawley Rats

### Study Design

Compound was administered in the diet to four groups of twenty male and twenty female CD<sup>®</sup> [CrI:CD<sup>®</sup>(SD)] rats at dose levels of 0 (control), 10, 30, and 100 mg/kg/day. Additionally, one control group of three animals/sex and three treated groups of six animals/sex/group served as toxicokinetic (TK) animals and received the vehicle or test article diet in the same manner as the main study groups at respective dose levels of 0, 10, 30, and 100 mg/kg/day. The vehicle or test article diet was available *ad libitum* for 13 weeks. Samples for hematology and clinical chemistry evaluations were collected from all the main study animals on Days 14 and 45, and again prior to termination. Urinalysis and samples for coagulation evaluations were collected prior to termination only.

### Sample Collection for Toxicokinetic Analysis

Blood samples (approximately 0.5 mL) were collected from the TK animals via the sublingual vein for determination of the plasma concentrations of S3643. Samples were collected from 1 cohort of 3 animals/sex (control animals) at 1 hour post the start of the dark cycle on Days 7 and 90. Samples were collected from 2 cohorts of 3 animals/sex (treated animals) at 1, 3, 6, 12, and 24 hours post the start of the dark cycle (18:00) on Days 7 and 90. Samples were collected from the treated TK animals between 17:00 and 18:00 during the predose collection on Days 7 and 90. The animals were not fasted prior to blood collection. Samples were placed in tubes containing K<sub>2</sub>EDTA as an anticoagulant. The blood samples were placed on wet ice after collection and centrifuged under refrigeration. The samples were contained in tightly capped, pre-labeled, plastic vials and were stored frozen at -50 to -90°C until analyzed.

### Sample Preparation for Toxicokinetic Analysis

Each 25 µL aliquot of sample was mixed with 25 µL of working internal standard (IS, S9767) solution (2000 ng/mL). The plate was vortexed, a 400 µL aliquot of methanol was added, and the plate was vortexed and centrifuged. A 50 µL aliquot of the resulting supernatant was transferred to a clean plate, 950 µL of water/methanol (55:45, v/v) was added, and the plate was mixed. A 50 µL aliquot of the resulting solution was added to a clean autosampler plate and a 600 µL aliquot of water/methanol (55:45, v/v) was added, the plate was mixed, centrifuged, and an aliquot was injected onto an LC-MS/MS system for analysis.

### Analytical Method

The liquid chromatography system used an ACE 5 C18-PFP column, 2.1 x 50 mm (5 µm particle size) with an isocratic flow of 10 mM ammonium acetate in water/methanol/acetonitrile (550:225:225, v/v/v) at a flow rate of 450 µL/minute. The analyte (S3643) and internal standard (S9767) were detected using an Applied Biosystems/MDS Sciex API 5000 triple quadrupole LC-MS/MS system equipped with an ESI (TurboIonSpray<sup>®</sup>) ionization source operated in the positive ion mode. The following MRM transitions of the respective [M+H]<sup>+</sup> ions were used to monitor S3643 and S9767 and may have been slightly modified to optimize system response. Actual transitions and retention times were documented in the data.

Compound	Transition Monitored	Retention Time
S3643 (analyte)	<i>m/z</i> 328.9 → 206	0.8 – 1.1 min
S9767 (IS)	<i>m/z</i> 297.1 → 174.2	1.4 – 1.7 min

**Table 23-1. Concentration Analysis of S3643 in Plasma of Sprague-Dawley Rats on Day 7**

			Time Point (hr)					
			0	1	3	6	12	24
Sex	Dose Group	Animal No.	Concentration (ng/mL)					
Male	10 mg/kg/d	6001	79.2		373		447	
		6002	BLLQ		137		256	
		6003	71.5		91.5		232	
		6004		106		299		113
		6005		BLLQ		272		190
		6006		123		220		216
		Mean (M)		50.2	76	201	264	312
SD		43.7	67	151	40.2	118	53.6	
Female	10 mg/kg/d	6501	BLLQ		257		204	
		6502	BLLQ		111		105	
		6503	BLLQ		BLLQ		245	
		6504		153		BLLQ		168
		6505		199		524		BLLQ
		6506		279		338		165
		Mean (F)		0	210	123	287	185
SD		0	64	129	266	72	96	
<b>Mean (M + F)</b>			<b>25.1</b>	<b>143</b>	<b>162</b>	<b>276</b>	<b>248</b>	<b>142</b>
<b>SD</b>			<b>39.0</b>	<b>93.8</b>	<b>133</b>	<b>170</b>	<b>112</b>	<b>77</b>
Male	30 mg/kg/d	7001	401		850		635	
		7002	119		166		743	
		7003	235		838		1040	
		7004		1210		2510		685
		7005		BLLQ		472		62.1
		7006		258		1280		96.6
		Mean (M)		252	489	618	1421	806
SD		142	637	391	1026	210	350	
Female	30 mg/kg/d	7501	BLLQ		312		2360	
		7502	399		1820		1970	
		7503	BLLQ		585		2200	
		7504		613		2670		288
		7505		611		2130		1040
		7506		842		3270		1280
		Mean (F)		133	689	906	2690	2177
SD		230	133	804	570.3	196	518	
<b>Mean (M + F)</b>			<b>192</b>	<b>589</b>	<b>762</b>	<b>2055</b>	<b>1491</b>	<b>575</b>
<b>SD</b>			<b>183</b>	<b>426</b>	<b>587</b>	<b>1017</b>	<b>772</b>	<b>510</b>
Male	100 mg/kg/d	8001	190		4530		5290	
		8002	1500		3880		9600	
		8003	5020		6710		5700	
		8004		3720		7900		3720
		8005		1450		5130		4390
		8006		4550		3870		790
		Mean (M)		2237	3240	5040	5633	6863
SD		2498	1605	1482	2062	2379	1915	
Female	100 mg/kg/d	8501	BLLQ		128		728	
		8502	196		4190		7180	
		8503	2290		8550		8910	
		8504		1930		939		BLLQ
		8505		4560		5710		BLLQ
		8506		2180		4750		1970
		Mean (F)		829	2890	4289	3800	5606
SD		1269	1452	4212	2523	4312	1137	
<b>Mean (M + F)</b>			<b>1533</b>	<b>3065</b>	<b>4665</b>	<b>4717</b>	<b>6235</b>	<b>1812</b>
<b>SD</b>			<b>1933</b>	<b>1382</b>	<b>2854</b>	<b>2293</b>	<b>3190</b>	<b>1893</b>

LLQ = 50 ng/mL

BLLQ < 50 ng/mL

**Table 23-2. Concentration Analysis of S3643 in Plasma of Sprague-Dawley Rats on Day 90**

			Time Point (hr)					
			0	1	3	6	12	24
Sex	Dose Group	Animal No.	Concentration (ng/mL)					
Male	10 mg/kg/d	6001	543		720		666	
		6002	357		683		1070	
		6003	248		145		499	
		6004		364		805		275
		6005		710		627		430
		6006		462		2090		91.7
		Mean (M)		383	512	516	1174	745
		SD	149	178	322	798	294	169
Female	10 mg/kg/d	6501	298		653		158	
		6502	135		252		300	
		6503	BLLQ		444		454	
		6504		360		184		68.3
		6505		659		1230		BLLQ
		6506		247		139		103
		Mean (F)		144	422	450	518	304
		SD	149	213	201	617	148	52
<b>Mean (M + F)</b>			<b>264</b>	<b>467</b>	<b>483</b>	<b>846</b>	<b>525</b>	<b>161</b>
<b>SD</b>			<b>187</b>	<b>182</b>	<b>243</b>	<b>732</b>	<b>319</b>	<b>160</b>
Male	30 mg/kg/d	7001	1320		1060		2540	
		7002	668		436		2350	
		7003	560		3960		1560	
		7004		2860		4140		252
		7005		1210		629		BLLQ
		7006		938		2770		263
		Mean (M)		849	1669	1819	2513	2150
		SD	411	1040	1881	1770	520	149
Female	30 mg/kg/d	7501	731		171		2480	
		7502	478		4600		3530	
		7503	924		3110		4680	
		7504		514		3570		116
		7505		1230		5390		90.8
		7506		1420		2440		1680
		Mean (F)		711	1055	2627	3800	3563
		SD	224	478	2254	1488.4	1100	910
<b>Mean (M + F)</b>			<b>780</b>	<b>1362</b>	<b>2223</b>	<b>3157</b>	<b>2857</b>	<b>400</b>
<b>SD</b>			<b>306</b>	<b>798</b>	<b>1908</b>	<b>1623</b>	<b>1092</b>	<b>635</b>
Male	100 mg/kg/d	8001	8360		15200		7370	
		8002	6760		9650		14200	
		8003	12400		17100		19000	
		8004		6530		13600		153
		8005		5910		10700		7800
		8006		5170		4260		9590
		Mean (M)		9173	5870	13983	9520	13523
		SD	2907	681	3871	4781	5844	5012
Female	100 mg/kg/d	8501	BLLQ		352		942	
		8502	374		9500		3930	
		8503	3960		10500		16000	
		8504		778		1690		BLLQ
		8505		1700		9710		73
		8506		7150		9330		1880
		Mean (F)		1445	3209	6784	6910	6957.333
		SD	2186	3444	5593	4525	7972	1065
<b>Mean (M + F)</b>			<b>5309</b>	<b>4540</b>	<b>10384</b>	<b>8215</b>	<b>10240</b>	<b>3249</b>
<b>SD</b>			<b>4818</b>	<b>2656</b>	<b>5836</b>	<b>4402</b>	<b>7213</b>	<b>4313</b>

LLQ = 50 ng/mL

BLLQ < 50 ng/mL

**Table 24. Pathology Procedures**

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination	
			1, 4	2, 3
Adrenal gland	X	X	X	
Aorta		X	X	
Bone with bone marrow, femur		X	X	
Bone with bone marrow, sternum		X	X	
Bone marrow smear		X	X	
Brain (cerebrum, midbrain, cerebellum, medulla/pons)	X	X	X	
Epididymis	X	X	X	
Esophagus		X	X	
Eye (with optic nerve)		X	X	
GALT (Gut-Associated Lymphoid Tissue)		X	X	
Heart	X	X	X	
Joint, tibiofemoral		X	X	
Kidney	X	X	X	
Lacrimal gland, exorbital		X	X	
Large intestine, cecum		X	X	
Large intestine, colon		X	X	
Large intestine, rectum		X	X	
Larynx		X	X	
Liver	X	X	X	
Lung with bronchi	X	X	X	
Lymph node, mandibular		X	X	
Lymph node, mesenteric		X	X	
Mammary gland (process females only)		X	X	
Nerve, sciatic		X	X	
Ovary with Oviducts	X	X	X	
Pancreas		X	X	
Pituitary	X	X	X	
Prostate	X	X	X	
Salivary gland, mandibular		X	X	
Salivary gland, parotid		X	X	
Salivary gland, sublingual		X	X	
Seminal vesicles	X	X	X	
Skeletal muscle, biceps femoris		X	X	
Skin		X	X	
Small intestine, duodenum		X	X	



Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination	
			1, 4	2, 3
Small intestine, ileum		X	X	
Small intestine, jejunum		X	X	
Spinal cord, cervical		X	X	
Spinal cord, lumbar		X	X	
Spinal cord, thoracic		X	X	
Spleen	X	X	X	
Stomach, glandular		X	X	
Stomach, nonglandular		X	X	
Target Organs		X	X	X
Testis	X	X	X	
Thymus	X	X	X	
Thyroid gland (with parathyroid)	X	X	X	
Tongue		X	X	
Trachea		X	X	
Ureters		X	X	
Urinary bladder		X	X	
Uterus with cervix	X	X	X	
Vagina		X	X	
Gross lesions		X	X	X
Tissue masses with regional lymph node		X	X	X

**Table 25-1. Summary of Body Weights - Male**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Week)	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight g	-1	253.4	16.16	20	250.9	14.91	20	255.0	15.63	20	252.5	14.44	20
	1	306.2	21.26	20	306.3	18.92	20	308.7	20.93	20	301.6	19.31	20
	2	316.3	23.24	20	318.2	24.08	20	317.9	23.43	20	316.4	20.84	20
	3	375.7	27.60	20	377.0	28.79	20	377.0	31.05	20	374.9	30.66	20
	4	402.3	41.62	20	413.8	35.28	20	411.5	34.37	20	409.9	34.92	20
	5	433.2	36.68	20	441.2	39.48	20	437.9	43.24	20	436.8	37.66	20
	6	460.7	39.03	20	464.4	42.40	20	463.9	46.72	20	460.7	41.13	20
	7	477.4	40.27	20	477.6	43.36	20	480.7	46.72	20	476.5	41.92	20
	8	502.6	43.11	20	502.3	48.32	20	502.9	49.49	20	495.5	43.15	20
	9	518.9	45.07	20	518.9	50.41	20	519.5	54.50	20	515.2	45.33	20
	10	536.9	47.78	20	539.1	51.77	20	535.5	55.50	20	533.3	47.38	20
	11	542.0	48.25	20	549.2	55.77	20	539.9	55.33	20	535.5	53.52	20
	12	557.3	51.10	20	562.4	59.37	20	553.9	58.08	20	545.9	52.11	20
	13	555.4	52.78	20	560.5	57.87	20	554.8	60.52	20	547.2	52.68	20

N - Number of measures used to calculate mean  
SD – Standard Deviation

**Table 25-2. Summary of Body Weights - Female**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Week)	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight													
g	-1	193.4	10.43	20	192.8	14.11	20	194.4	13.72	20	192.0	8.59	20
	1	212.8	12.69	20	213.8	18.27	20	213.1	15.87	20	203.9	13.11	20
	2	209.4	14.38	20	210.4	18.20	20	210.6	16.26	20	201.6	10.97	20
	3	240.5	16.62	20	241.2	19.58	20	238.6	21.24	20	229.1	12.34	20
	4	249.1	20.51	20	251.2	19.42	20	248.1	23.11	20	237.7	15.07	20
	5	259.8	20.56	20	257.9	20.01	20	256.5	23.96	20	242.7 <sup>a</sup>	17.10	20
	6	264.3	22.35	20	267.6	23.58	20	265.4	22.89	20	252.3	14.93	20
	7	271.4	22.88	20	269.1	20.60	20	269.0	25.66	20	252.6 <sup>a</sup>	19.74	20
	8	278.8	24.02	20	279.1	21.59	20	277.1	24.86	20	262.8	17.35	20
	9	282.4	23.78	20	284.0	21.88	20	280.7	25.09	20	263.9 <sup>a</sup>	15.32	20
	10	287.9	25.16	20	287.6	23.30	20	285.4	25.05	20	269.3 <sup>a</sup>	14.48	20
	11	291.2	24.99	20	293.5	23.26	20	288.0	22.68	20	271.7 <sup>a</sup>	14.92	20
	12	294.0	25.83	20	295.8	24.78	20	294.1	25.86	20	275.8 <sup>a</sup>	16.62	20
	13	293.7	26.27	20	294.0	22.31	20	294.2	24.28	20	275.4 <sup>a</sup>	19.17	20

N - Number of measures used to calculate mean

SD – Standard Deviation

<sup>a</sup>. Significantly different from control; (p< 0.05)

**Table 25-3. Summary of Toxicokinetic Body Weights - Male**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Week)	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight g	1	316.0	18.60	4	307.9	17.13	8	309.4	16.95	8	306.3	20.07	8
	2	359.3	19.36	4	346.6	20.91	8	349.0	18.28	8	342.8	21.49	8
	3	395.3	19.52	4	386.5	23.16	8	388.3	20.14	8	378.5	26.05	8
	4	429.8	23.71	4	423.9	25.82	8	421.5	23.12	8	411.6	30.67	8
	5	434.8	31.87	4	451.4	29.48	8	448.9	22.78	8	434.5	31.54	8
	6	474.5	22.04	4	475.1	33.00	8	475.1	26.90	8	455.4	32.19	8
	7	496.8	24.19	4	496.5	37.05	8	495.4	28.84	8	470.3	33.15	8
	8	519.3	31.14	4	519.9	38.71	8	515.1	30.23	8	487.5	34.94	8
	9	533.3	36.85	4	534.1	40.26	8	528.6	32.99	8	500.4	37.21	8
	10	553.0	42.29	4	556.9	41.69	8	543.0	32.08	8	516.6	38.78	8
	11	558.8	46.56	4	562.4	45.19	8	546.1	32.25	8	517.4	38.86	8
	12	563.0	48.72	4	569.8	46.00	8	554.1	35.17	8	521.3	40.37	8
	13	570.0	55.20	4	578.4	48.51	8	560.9	42.80	8	519.4	54.13	8

N - Number of measures used to calculate mean

SD – Standard Deviation

No statistical analysis performed

**Table 25-4. Summary of Toxicokinetic Body Weights - Female**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Week)	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight g	1	204.8	16.50	4	215.1	12.60	8	215.1	9.33	8	206.5	8.18	8
	2	214.0	23.11	4	226.6	11.29	8	233.1	8.77	8	218.1	8.43	8
	3	231.0	21.02	4	243.4	13.93	8	249.5	16.24	8	226.9	10.70	8
	4	238.5	22.40	4	249.9	13.43	8	260.9	22.71	8	249.1	9.63	8
	5	246.8	22.97	4	258.1	14.94	8	268.5	21.75	8	245.5	12.51	8
	6	255.3	26.42	4	269.3	15.65	8	280.9	25.97	8	253.0	9.90	8
	7	262.3	26.08	4	275.1	14.09	8	294.1	28.29	8	264.8	13.49	8
	8	264.5	26.03	4	279.9	16.66	8	305.3	30.76	8	269.4	11.93	8
	9	270.8	29.07	4	284.4	17.32	8	302.1	27.49	8	269.9	13.03	8
	10	269.3	16.74	4	293.4	18.33	8	309.0	31.61	8	278.3	12.06	8
	11	276.3	27.80	4	292.0	19.04	8	307.8	33.13	8	276.5	15.64	8
	12	280.3	30.25	4	291.1	18.60	8	310.6	27.42	8	278.0	14.91	8
	13	280.3	31.74	4	292.4	22.88	8	309.1	31.05	8	280.3	13.96	8

N - Number of measures used to calculate mean

SD – Standard Deviation

No statistical analysis performed

**Table 26-1. Summary of Food Consumption Values - Male**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Week)	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Consumption g/animal/day													
	1	24.21	1.892	20	23.56	1.555	20	23.86	1.831	20	23.32	1.370	19
	2	22.29	1.550	20	22.81	1.908	20	22.39	1.815	20	22.57	1.531	20
	3	25.00	1.566	20	25.30	2.012	19	25.41	1.950	20	25.49	2.077	20
	4	23.44	4.777	20	25.20	2.266	20	25.09	2.585	20	24.91	2.304	20
	5	25.19	2.212	20	24.69	2.474	20	24.19	3.629	20	24.79	2.049	20
	6	25.21	2.042	20	25.31	2.380	20	25.26	2.714	20	25.30	2.532	20
	7	23.81	1.637	20	23.65	2.030	20	23.83	2.193	20	24.19	2.043	20
	8	25.91	2.006	20	25.69	2.279	20	25.89	2.820	20	25.94	2.134	20
	9	25.75	2.615	20	25.73	2.468	20	25.47	3.295	20	25.72	2.325	20
	10	26.17	2.228	20	26.46	2.256	20	25.64	2.715	20	26.71	2.624	20
	11	26.00	2.280	19	26.39	2.642	20	25.61	2.465	20	25.31	3.424	20
	12	26.19	2.605	20	26.15	2.606	20	25.29	2.375	20	25.94	2.030	20
	13	24.49	2.550	20	24.50	2.448	20	23.91	2.665	20	24.02	2.359	20

N - Number of measures used to calculate mean

SD – Standard Deviation

**Table 26-2. Summary of Food Consumption Values - Female**  
 MPI Research Study No. 1646-014  
 S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Week)	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Consumption g/animal/day	1	17.24	1.314	20	16.95	1.658	20	16.33	1.458	20	14.81 <sup>b</sup>	1.881	20
	2	14.61	1.283	20	15.50	1.567	20	15.19	1.130	20	14.41	1.365	20
	3	18.04	1.621	20	18.21	2.128	20	17.61	1.767	20	17.02	1.566	20
	4	17.91	3.647	20	18.69	3.175	20	16.72	2.897	20	15.34 <sup>a</sup>	1.540	20
	5	16.36	1.324	20	16.29	1.387	20	15.83	1.449	20	15.00 <sup>D</sup>	1.447	20
	6	16.56	1.452	20	17.33	1.739	20	16.74	1.348	20	16.01	1.006	20
	7	16.18	1.883	20	16.10	1.359	20	15.79	1.662	20	13.89 <sup>D</sup>	1.793	20
	8	17.27	2.189	20	17.45	1.501	20	17.04	1.459	20	16.19	1.409	20
	9	16.99	2.281	20	17.01	1.553	20	15.84	1.425	20	15.31 <sup>D</sup>	0.767	20
	10	16.80	3.243	19	17.54	2.135	20	17.11	1.460	20	15.98	1.081	20
	11	17.27	2.000	20	17.51	1.549	20	16.62	2.151	19	15.82 <sup>a</sup>	1.128	20
	12	16.44	1.568	20	17.29	1.179	20	17.04	1.367	20	15.94	1.144	20
	13	15.89	1.554	19	16.21	1.175	20	16.29	2.166	20	14.71	1.414	20

N - Number of measures used to calculate mean

SD – Standard Deviation

<sup>a</sup>. Significantly different from control; (p< 0.05)

<sup>b</sup>. Significantly different from control; (p< 0.01)

**Table 27-1. Summary of Hematology Values – Male**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Leukocytes 10 <sup>3</sup> /μL	Day 14	9.41	2.421	20	7.87	1.668	20	8.05	2.327	20	8.21	1.808	20
	Day 45	10.51	2.693	20	10.07	2.429	20	10.69	2.300	20	10.46	1.897	20
	Terminal	13.96	2.587	20	13.06	1.960	20	13.13	2.428	20	13.00	2.365	20
Erythrocytes 10 <sup>6</sup> /μL	Day 14	8.311	0.5189	20	7.963 <sup>a</sup>	0.3494	20	7.992	0.3574	20	7.997	0.4392	20
	Day 45	8.806	0.3530	20	8.546	0.3724	20	8.668	0.3304	20	8.681	0.3610	20
	Terminal	9.084	0.6947	20	8.955	0.4450	20	9.021	0.5544	20	9.004	0.3947	20
Hemoglobin g/dL	Day 14	16.29	0.833	20	15.97	0.612	20	15.83	0.745	20	15.64 <sup>a</sup>	0.767	20
	Day 45	15.95	0.483	20	15.64	0.669	20	15.80	0.558	20	15.74	0.499	20
	Terminal	15.60	1.212	20	15.56	0.655	20	15.57	0.804	20	15.49	0.607	20
Hematocrit %	Day 14	49.37	2.384	20	48.12	1.817	20	47.73	2.306	20	47.43 <sup>a</sup>	2.455	20
	Day 45	48.55	1.813	20	47.40	2.178	20	47.77	2.055	20	47.77	1.782	20
	Terminal	50.36	3.905	20	50.08	2.013	20	50.19	2.445	20	49.50	2.107	20
MCV fL	Day 14	59.46	2.018	20	60.47	1.949	20	59.76	1.814	20	59.34	1.300	20
	Day 45	55.16	1.499	20	55.50	1.863	20	55.11	1.423	20	55.04	1.352	20
	Terminal	55.46	1.736	20	55.98	1.774	20	55.69	1.971	20	55.00	1.326	20
MCH pg	Day 14	19.61	0.493	20	20.09 <sup>a</sup>	0.766	20	19.81	0.614	20	19.57	0.565	20
	Day 45	18.13	0.427	20	18.31	0.777	20	18.25	0.580	20	18.15	0.521	20
	Terminal	17.18	0.576	20	17.39	0.713	20	17.28	0.757	20	17.21	0.493	20

N - Number of measures used to calculate mean

SD - Standard Deviation

<sup>a</sup>. Significantly different from control; (p< 0.05)



**Table 27-1. Summary of Hematology Values – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
MCHC g/dL	Day 14	33.00	0.732	20	33.22	0.870	20	33.15	0.739	20	33.01	0.489	20
	Day 45	32.87	0.582	20	33.00	0.798	20	33.10	0.772	20	32.95	0.533	20
	Terminal	30.99	0.421	20	31.05	0.679	20	31.03	0.614	20	31.31	0.438	20
Platelets 10 <sup>3</sup> /μL	Day 14	916.3	239.69	20	872.0	222.57	20	925.5	206.06	20	879.7	131.70	20
	Day 45	811.1	160.14	20	777.4	125.46	20	793.9	267.60	20	791.8	202.96	20
	Terminal	1032.9	100.97	20	1045.3	130.61	20	1125.5	194.08	20	1131.6	162.58	20
Absolute Reticulocytes 10 <sup>3</sup> /μL	Day 14	264.73	36.622	20	266.29	36.041	20	262.05	45.935	20	280.11	34.246	20
	Day 45	208.10	42.302	20	214.35	34.830	20	204.52	39.341	20	226.97	39.664	20
	Terminal	169.59	39.076	20	181.73	36.618	20	194.91	118.411	20	181.10	27.608	20
Neutrophils 10 <sup>3</sup> /μL	Day 14	1.644	0.6623	20	1.342	0.5354	20	1.459	0.9791	20	1.513	1.0591	20
	Day 45	1.464	0.4232	20	1.529	0.4180	20	1.547	0.5776	20	1.543	0.6527	20
	Terminal	1.951	0.8109	20	1.678	0.5294	20	1.606	0.5300	20	1.644	0.5920	20
Band Neutrophils 10 <sup>3</sup> /μL	Day 14 <sup>#</sup>	0.00	NA	1	NA	NA	0	0.00	NA	1	NA	NA	0
	Day 45 <sup>#</sup>	0.00	NA	1	NA	NA	0	NA	NA	0	NA	NA	0
	Terminal <sup>#</sup>	0.00	NA	1	NA	NA	0	NA	NA	0	NA	NA	0
Lymphocytes 10 <sup>3</sup> /μL	Day 14	7.235	2.4345	20	6.134	1.1550	20	6.124	1.9982	20	6.288	1.3337	20
	Day 45	8.289	2.5159	20	7.977	2.1527	20	8.581	1.9331	20	8.286	1.7049	20
	Terminal	11.111	2.5448	20	10.599	1.7700	20	10.775	2.2073	20	10.564	2.1486	20

N - Number of measures used to calculate mean

SD - Standard Deviation

NA – Not applicable/not available

<sup>#</sup> No statistics performed due to lack of variability or sample size

**Table 27-1. Summary of Hematology Values – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Monocytes 10 <sup>3</sup> /μL	Day 14	0.167	0.0522	20	0.163	0.0787	20	0.171	0.0823	20	0.164	0.0575	20
	Day 45	0.195	0.0780	20	0.197	0.0538	20	0.177	0.0723	20	0.227	0.0596	20
	Terminal	0.383	0.1828	20	0.349	0.1112	20	0.299	0.0889	20	0.347	0.0821	20
Eosinophils 10 <sup>3</sup> /μL	Day 14	0.093	0.0704	20	0.077	0.0373	20	0.088	0.0604	20	0.120	0.1190	20
	Day 45	0.120	0.0433	20	0.106	0.0419	20	0.125	0.0447	20	0.120	0.0488	20
	Terminal	0.182	0.0886	20	0.151	0.0432	20	0.159	0.0571	20	0.165	0.0626	20
Basophils 10 <sup>3</sup> /μL	Day 14	0.077	0.0667	20	0.092	0.0913	20	0.076	0.0932	20	0.068	0.0595	20
	Day 45	0.181	0.1023	20	0.175	0.0713	20	0.177	0.0770	20	0.204	0.1009	20
	Terminal	0.135	0.0670	20	0.122	0.0427	20	0.117	0.0490	20	0.122	0.0548	20
Other Cells 10 <sup>3</sup> /μL	Day 14	0.189	0.4924	20	0.053	0.0227	20	0.123	0.3109	20	0.050	0.0243	20
	Day 45	0.245	0.7201	20	0.077	0.0262	20	0.073	0.0283	20	0.077	0.0351	20
	Terminal	0.200	0.0908	20	0.164	0.0615	20	0.169	0.0534	20	0.150	0.0459	20

N - Number of measures used to calculate mean  
SD - Standard Deviation

**Table 27-2. Summary of Hematology Values – Female**  
MPI Research Study No. 1646-014  
S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Leukocytes 10 <sup>3</sup> /μL	Day 14	6.68	2.210	20	6.98	2.373	20	6.19	1.731	20	7.02	1.670	20
	Day 45	7.69	2.443	20	8.06	2.326	20	6.73	1.654	20	7.67	1.391	20
	Terminal	9.74	1.760	20	11.24	3.083	20	10.27	2.196	20	10.99	1.928	20
Erythrocytes 10 <sup>6</sup> /μL	Day 14	8.098	0.3619	20	7.964	0.4848	20	8.154	0.3109	20	8.332	0.4293	20
	Day 45	8.398	0.2822	20	8.385	0.3018	20	8.424	0.3069	20	8.489	0.4256	20
	Terminal	8.408	0.3236	20	8.502	0.3356	20	8.471	0.3691	20	8.595	0.4546	20
Hemoglobin g/dL	Day 14	15.93	0.633	20	15.41 <sup>a</sup>	0.861	20	15.78	0.543	20	16.07	0.607	20
	Day 45	15.62	0.464	20	15.53	0.397	20	14.93	3.113	20	15.68	0.519	20
	Terminal	15.26	0.511	20	15.26	0.571	20	15.24	0.533	20	15.50	0.638	20
Hematocrit %	Day 14	46.16	2.151	20	45.21	2.459	20	46.27	1.740	20	47.07	2.140	20
	Day 45	46.86	1.580	20	46.56	1.302	20	46.52	1.379	20	46.90	2.075	20
	Terminal	48.27	1.713	20	48.36	1.797	20	48.25	1.880	20	49.02	2.289	20
MCV fL	Day 14	57.01	1.594	20	56.81	1.628	20	56.77	1.320	20	56.53	1.212	20
	Day 45	55.82	1.478	20	55.56	1.166	20	55.26	1.240	20	55.27	1.058	20
	Terminal	57.45	1.689	20	56.88	1.441	20	57.00	1.486	20	57.06	1.303	20
MCH pg	Day 14	19.68	0.666	20	19.36	0.566	20	19.37	0.453	20	19.30	0.510	20
	Day 45	18.60	0.529	20	18.54	0.552	20	17.71	3.689	20	18.47	0.446	20
	Terminal	18.19	0.621	20	17.95	0.588	20	18.01	0.515	20	18.05	0.451	20

N - Number of measures used to calculate mean  
SD - Standard Deviation  
<sup>a</sup>. Significantly different from control; (p< 0.05)

**Table 27-2. Summary of Hematology Values – Female (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
MCHC g/dL	Day 14	34.53	1.011	20	34.08	0.616	20	34.12	0.580	20	34.15	0.843	20
	Day 45	33.35	0.639	20	33.35	0.551	20	32.04	6.632	20	33.45	0.678	20
	Terminal	31.67	0.612	20	31.57	0.552	20	31.60	0.508	20	31.63	0.486	20
Platelets 10 <sup>3</sup> /μL	Day 14	928.7	199.81	20	942.7	193.78	20	912.0	184.29	20	910.9	182.66	20
	Day 45	749.2	168.92	20	778.3	130.94	20	777.4	194.16	20	775.7	145.71	20
	Terminal	1041.8	137.10	20	1123.7	154.43	20	1074.3	128.69	20	1080.6	92.87	20
Absolute Reticulocytes 10 <sup>3</sup> /μL	Day 14	170.24	29.162	20	176.71	48.471	20	164.84	36.302	20	160.09	39.784	20
	Day 45	166.08	32.085	20	176.50	49.006	20	171.18	45.157	20	161.46	30.133	20
	Terminal	145.55	29.740	20	153.63	47.211	20	138.02	22.191	20	144.08	29.894	20
Neutrophils 10 <sup>3</sup> /μL	Day 14	1.166	0.5400	20	1.397	1.5650	20	0.976	0.3380	20	1.067	0.5230	20
	Day 45	1.140	0.5089	20	1.170	0.7138	20	0.985	0.5077	20	0.924	0.4253	20
	Terminal	1.090	0.4471	20	1.355	0.8217	20	1.153	0.4697	20	1.057	0.4357	20
Band Neutrophils 10 <sup>3</sup> /μL	Day 14 <sup>#</sup>	NA	NA	0	NA	NA	0	NA	NA	0	0.00	NA	1
	Day 45 <sup>#</sup>	NA	NA	0	NA	NA	0	NA	NA	0	NA	NA	0
	Terminal <sup>#</sup>	NA	NA	0	NA	NA	0	NA	NA	0	NA	NA	0
Lymphocytes 10 <sup>3</sup> /μL	Day 14	5.163	1.8302	20	5.227	1.8041	20	4.924	1.6725	20	5.569	1.4514	20
	Day 45	6.085	2.0550	20	6.419	2.1113	20	5.396	1.3534	20	6.337	1.3767	20
	Terminal	7.980	1.6583	20	9.187	2.4771	20	8.485	1.9923	20	9.317	1.7863	20

N - Number of measures used to calculate mean

SD - Standard Deviation

NA – Not applicable/not available

<sup>#</sup> No statistics performed due to lack of variability or sample size

**Table 27-2. Summary of Hematology Values – Female (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Monocytes 10 <sup>3</sup> /μL	Day 14	0.125	0.0599	20	0.155	0.1020	20	0.113	0.0488	20	0.122	0.0508	20
	Day 45	0.155	0.0487	20	0.166	0.0980	20	0.104 <sup>a</sup>	0.0390	20	0.133	0.0533	20
	Terminal	0.266	0.0942	20	0.313	0.1593	20	0.269	0.0612	20	0.246	0.0834	20
Eosinophils 10 <sup>3</sup> /μL	Day 14	0.126	0.1242	20	0.081	0.0265	20	0.093	0.0467	20	0.108	0.0574	20
	Day 45	0.117	0.0622	20	0.110	0.0444	20	0.084	0.0376	20	0.098	0.0402	20
	Terminal	0.123	0.0566	20	0.130	0.0555	20	0.121	0.0582	20	0.112	0.0437	20
Basophils 10 <sup>3</sup> /μL	Day 14	0.048	0.0487	20	0.067	0.0775	20	0.042	0.0331	20	0.093	0.1184	20
	Day 45	0.118	0.0639	20	0.145	0.0838	20	0.099	0.0557	20	0.109	0.0499	20
	Terminal	0.095	0.0343	20	0.094	0.0390	20	0.083	0.0342	20	0.096	0.0373	20
Other Cells 10 <sup>3</sup> /μL	Day 14	0.048	0.0253	20	0.045	0.0176	20	0.042	0.0278	20	0.060	0.0589	20
	Day 45	0.053	0.0245	20	0.052	0.0238	20	0.042	0.0209	20	0.062	0.0274	20
	Terminal	0.181	0.0903	20	0.157	0.0675	20	0.154	0.0442	20	0.151	0.0745	20

N - Number of measures used to calculate mean

SD - Standard Deviation

<sup>a</sup>. Significantly different from control; (p< 0.05)

**Table 28-1. Summary of Coagulation Values – Male**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
APTT sec	Terminal	18.69	1.673	20	18.67	2.323	20	18.43	2.587	20	19.10	1.709	20
Prothrombin Time sec	Terminal	15.57	0.536	20	15.65	0.551	20	15.74	0.765	20	15.53	0.631	20

N - Number of measures used to calculate mean  
SD - Standard Deviation

**Table 28-2. Summary of Coagulation Values – Female**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
APTT sec	Terminal	15.55	1.399	20	16.03	1.417	20	16.00	2.017	20	15.97	2.061	20
Prothrombin Time sec	Terminal	15.60	0.789	20	15.63	0.381	20	15.67	0.652	20	15.82	0.826	20

N - Number of measures used to calculate mean  
SD - Standard Deviation

**Table 29-1. Summary of Clinical Chemistry Values – Male**  
 MPI Research Study No. 1646-014  
 S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Sodium mEq/L	Day 14	141.5	1.32	20	141.9	1.39	20	142.0	1.12	20	141.4	1.60	20
	Day 45	142.2	1.44	20	141.5	1.05	20	142.1	1.32	20	141.7	1.87	20
	Terminal	145.3	1.69	20	145.7	2.32	20	145.4	1.46	20	144.9	1.45	20
Potassium mEq/L	Day 14	5.58	0.464	20	5.92	0.647	20	5.87	0.820	20	5.98	0.425	20
	Day 45	5.47	0.323	20	5.88 <sup>a</sup>	0.401	20	5.66	0.358	20	5.84 <sup>a</sup>	0.616	20
	Terminal	6.30	0.849	20	6.20	1.053	20	6.30	0.972	20	6.20	0.827	20
Chloride mEq/L	Day 14	100.0	1.43	20	100.3	1.16	20	100.6	1.60	20	100.0	1.59	20
	Day 45	100.8	1.74	20	100.5	1.28	20	100.5	1.50	20	99.8	2.17	20
	Terminal	99.1	1.59	20	98.9	1.79	20	99.0	1.26	20	98.7	1.59	20
Calcium mg/dL	Day 14	10.22	0.246	20	10.28	0.245	20	10.16	0.278	20	10.11	0.286	20
	Day 45	10.26	0.258	20	10.19	0.399	20	10.18	0.245	20	10.38	0.330	20
	Terminal	11.43	0.423	20	11.43	0.337	20	11.44	0.416	20	11.44	0.356	20

N - Number of measures used to calculate mean

SD - Standard Deviation

<sup>a</sup>. Significantly different from control; (p< 0.05)

**Table 29-1. Summary of Clinical Chemistry Values – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Phosphorus mg/dL	Day 14	8.74	0.583	20	8.94	0.701	20	8.89	0.672	20	8.88	0.471	20
	Day 45	7.57	0.407	20	7.47	0.590	20	7.39	0.499	20	7.81	0.381	20
	Terminal	8.29	0.880	20	8.19	0.835	20	8.17	0.773	20	8.34	0.724	20
Alkaline Phosphatase U/L	Day 14	239.5	39.62	20	222.3	45.23	20	249.7	39.81	20	231.1	48.58	20
	Day 45	178.2	35.29	20	161.7	48.48	20	174.5	36.66	20	162.9	41.98	20
	Terminal	99.1	19.52	20	91.5	25.71	20	94.0	27.73	20	86.8	17.03	20
Total Bilirubin mg/dL	Day 14	0.11	0.031	20	0.11	0.031	20	0.10	0.000	20	0.11	0.022	20
	Day 45	0.16	0.050	20	0.16	0.051	20	0.15	0.051	20	0.13	0.044	20
	Terminal	0.13	0.044	20	0.11	0.022	20	0.10 <sup>a</sup>	0.000	20	0.11	0.031	20
AST U/L	Day 14	133.3	23.12	20	129.3	23.35	20	123.6	21.06	20	129.7	19.06	20
	Day 45	108.3	18.17	20	112.7	23.10	20	110.2	19.00	20	111.2	14.31	20
	Terminal	71.4	8.76	20	70.1	15.84	20	69.0	13.25	20	64.2	10.13	20

N - Number of measures used to calculate mean

SD - Standard Deviation

<sup>a</sup>. Significantly different from control; (p< 0.05)



**Table 29-1. Summary of Clinical Chemistry Values – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
ALT													
U/L	Day 14	34.5	6.91	20	31.9	4.97	20	31.4	4.32	20	33.3	4.46	20
	Day 45	36.7	4.56	20	37.7	5.98	20	36.9	3.41	20	36.8	5.53	20
	Terminal	34.5	7.98	20	33.8	10.53	20	32.5	7.09	20	30.5	3.03	20
Urea Nitrogen													
mg/dL	Day 14	12.3	1.77	20	11.0 <sup>a</sup>	1.23	20	11.8	1.68	20	12.1	1.62	20
	Day 45	11.7	1.66	20	12.2	1.79	20	12.1	1.62	20	12.8	1.96	20
	Terminal	14.1	2.63	20	14.2	1.73	20	13.9	1.57	20	13.8	1.89	20
Creatinine													
mg/dL	Day 14	0.35	0.051	20	0.34	0.075	20	0.33	0.044	20	0.32	0.037	20
	Day 45	0.34	0.050	20	0.34	0.050	20	0.35	0.051	20	0.34	0.050	20
	Terminal	0.42	0.037	20	0.41	0.022	20	0.42	0.041	20	0.40	0.046	20
Total Protein													
g/dL	Day 14	6.17	0.320	20	6.09	0.216	20	6.17	0.274	20	6.02	0.230	20
	Day 45	6.51	0.258	20	6.45	0.298	20	6.62	0.250	20	6.62	0.333	20
	Terminal	6.47	0.281	20	6.53	0.283	20	6.57	0.359	20	6.68	0.334	20

N - Number of measures used to calculate mean

SD - Standard Deviation

<sup>a</sup>. Significantly different from control; (p< 0.05)

**Table 29-1. Summary of Clinical Chemistry Values – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Albumin g/dL	Day 14	3.41	0.194	20	3.36	0.119	20	3.40	0.130	20	3.30	0.156	20
	Day 45	3.41	0.162	20	3.34	0.142	20	3.43	0.097	20	3.44	0.139	20
	Terminal	3.28	0.224	20	3.30	0.169	20	3.31	0.161	20	3.29	0.162	20
Globulin g/dL	Day 14	2.76	0.198	20	2.73	0.162	20	2.77	0.193	20	2.72	0.176	20
	Day 45	3.10	0.182	20	3.11	0.220	20	3.20	0.233	20	3.18	0.231	20
	Terminal	3.19	0.253	20	3.23	0.200	20	3.26	0.241	20	3.39 <sup>a</sup>	0.223	20
Albumin/Globulin Ratio	Day 14	1.25	0.094	20	1.25	0.089	20	1.24	0.088	20	1.22	0.106	20
	Day 45	1.11	0.076	20	1.07	0.080	20	1.08	0.077	20	1.09	0.067	20
	Terminal	1.05	0.115	20	1.03	0.085	20	1.02	0.075	20	0.98	0.070	20
Triglyceride mg/dL	Day 14	54.5	15.03	20	55.9	15.70	20	47.9	12.73	20	56.0	15.73	20
	Day 45	82.8	32.07	20	70.7	24.47	20	71.3	24.49	20	73.5	19.61	20
	Terminal	70.2	34.27	20	74.0	34.36	20	64.0	26.15	20	65.6	25.92	20

N - Number of measures used to calculate mean

SD - Standard Deviation

<sup>a</sup>. Significantly different from control; (p< 0.05)

**Table 29-1. Summary of Clinical Chemistry Values – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Cholesterol mg/dL	Day 14	56.4	9.69	20	64.2	14.99	20	57.0	11.42	20	62.8	9.59	20
	Day 45	63.7	11.19	20	73.1	20.78	20	69.3	14.75	20	81.8 <sup>b</sup>	13.89	20
	Terminal	58.9	15.55	20	70.8	24.95	20	66.4	15.99	20	79.5 <sup>b</sup>	14.81	20
Glucose mg/dL	Day 14	81.5	6.79	20	83.5	6.58	20	79.7	8.70	20	81.7	6.64	20
	Day 45	93.2	9.86	20	95.4	9.63	20	90.6	10.14	20	91.7	9.53	20
	Terminal	196.5	40.48	20	190.9	44.48	20	203.7	56.20	20	180.6	34.10	20

N - Number of measures used to calculate mean

SD - Standard Deviation

<sup>a</sup> - Significantly different from control; (p< 0.05)

**Table 29-2. Summary of Clinical Chemistry Values – Female**  
 MPI Research Study No. 1646-014  
 S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Sodium mEq/L	Day 14	139.9	1.68	20	140.0	1.62	20	139.3	1.12	20	139.6	1.98	20
	Day 45	140.8	1.40	20	140.7	1.42	20	141.1	1.80	20	140.5	1.40	20
	Terminal	142.9	0.99	20	143.6	1.31	20	143.0	1.59	20	143.2	1.35	20
Potassium mEq/L	Day 14	5.30	0.479	20	5.80 <sup>a</sup>	0.659	20	5.41	0.343	20	5.76 <sup>a</sup>	0.571	20
	Day 45	5.32	0.492	20	5.47	0.594	20	5.20	0.588	20	5.43	0.566	20
	Terminal	7.06	0.536	20	6.95	0.561	20	6.88	1.023	20	7.02	0.653	20
Chloride mEq/L	Day 14	100.9	1.74	20	101.0	1.12	20	100.2	1.32	20	100.4	1.43	20
	Day 45	101.7	2.43	20	101.1	1.39	20	101.5	1.90	20	101.2	1.61	20
	Terminal	99.8	1.33	20	100.2	1.61	20	99.4	1.63	20	99.6	1.60	20
Calcium mg/dL	Day 14	10.22	0.358	20	10.24	0.372	20	10.25	0.310	20	10.19	0.270	20
	Day 45	10.44	0.428	20	10.31	0.501	20	10.27	0.333	20	10.35	0.319	20
	Terminal	11.90	0.502	20	11.84	0.365	20	12.06	0.538	20	11.90	0.405	20

N - Number of measures used to calculate mean

SD - Standard Deviation

<sup>a</sup>. Significantly different from control; (p< 0.05)

**Table 29-2. Summary of Clinical Chemistry Values – Female (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Phosphorus mg/dL	Day 14	7.27	0.553	20	7.87 <sup>a</sup>	0.825	20	7.47	0.598	20	7.42	0.672	20
	Day 45	5.96	0.763	20	6.37	0.615	20	5.79	0.735	20	5.99	0.769	20
	Terminal	7.80	0.732	20	8.03	0.759	20	8.07	0.668	20	8.21	0.841	20
Alkaline Phosphatase U/L	Day 14	127.5	31.16	20	138.1	36.02	20	137.7	34.50	20	126.6	27.00	20
	Day 45	99.1	25.96	20	100.5	35.95	20	103.7	34.95	20	91.8	28.31	20
	Terminal	45.2	9.94	20	53.4	21.40	20	55.8	21.78	20	50.8	12.25	20
Total Bilirubin mg/dL	Day 14	0.13	0.047	20	0.12	0.037	20	0.13	0.047	20	0.13	0.044	20
	Day 45	0.15	0.051	20	0.17	0.049	20	0.15	0.051	20	0.15	0.051	20
	Terminal	0.13	0.044	20	0.12	0.037	20	0.14	0.049	20	0.11	0.031	20
AST U/L	Day 14	119.3	23.14	20	112.9	27.53	20	107.7	19.85	20	122.6	20.52	20
	Day 45	100.2	19.32	20	100.8	20.98	20	96.2	17.39	20	102.2	32.02	20
	Terminal	101.0	100.72	20	75.3	34.06	20	77.4	62.06	20	62.1	9.88	20

N - Number of measures used to calculate mean

SD - Standard Deviation

<sup>a</sup>. Significantly different from control; (p< 0.05)

**Table 29-2. Summary of Clinical Chemistry Values – Female (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
ALT													
U/L	Day 14	32.0	3.61	20	30.5	5.32	20	29.2	4.94	20	30.3	4.12	20
	Day 45	40.0	6.93	20	36.2	7.84	20	35.1	5.76	20	34.7	18.43	20
	Terminal	54.2	78.04	20	35.8	22.31	20	37.3	25.83	20	27.7	5.14	20
Urea Nitrogen													
mg/dL	Day 14	15.3	1.89	20	14.4	2.23	20	13.9	1.21	20	14.2	1.96	20
	Day 45	13.4	1.47	20	12.9	2.68	20	13.7	2.18	20	13.2	2.35	20
	Terminal	14.1	1.77	20	15.3	4.01	20	15.5	3.19	20	14.9	2.47	20
Creatinine													
mg/dL	Day 14	0.39	0.059	20	0.35	0.051	20	0.36	0.051	20	0.38	0.095	20
	Day 45	0.40	0.056	20	0.37	0.047	20	0.40	0.032	20	0.40	0.051	20
	Terminal	0.46	0.051	20	0.45	0.051	20	0.46	0.051	20	0.47	0.047	20
Total Protein													
g/dL	Day 14	6.52	0.308	20	6.26 <sup>a</sup>	0.289	20	6.50	0.280	20	6.54	0.349	20
	Day 45	7.11	0.411	20	6.79 <sup>a</sup>	0.294	20	7.12	0.354	20	7.14	0.362	20
	Terminal	7.17	0.493	20	6.94	0.390	20	7.14	0.550	20	7.01	0.400	20

N - Number of measures used to calculate mean

SD - Standard Deviation

<sup>a</sup>. Significantly different from control; (p< 0.05)

**Table 29-2. Summary of Clinical Chemistry Values – Female (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Albumin g/dL	Day 14	3.68	0.207	20	3.55	0.147	20	3.67	0.149	20	3.67	0.187	20
	Day 45	3.84	0.260	20	3.66 <sup>a</sup>	0.193	20	3.86	0.209	20	3.85	0.214	20
	Terminal	3.82	0.312	20	3.66	0.230	20	3.81	0.352	20	3.70	0.229	20
Globulin g/dL	Day 14	2.84	0.176	20	2.71	0.192	20	2.83	0.183	20	2.87	0.218	20
	Day 45	3.27	0.232	20	3.13	0.262	20	3.26	0.224	20	3.29	0.174	20
	Terminal	3.35	0.212	20	3.28	0.221	20	3.33	0.275	20	3.31	0.220	20
Albumin/Globulin Ratio	Day 14	1.30	0.100	20	1.32	0.075	20	1.30	0.086	20	1.29	0.088	20
	Day 45	1.19	0.102	20	1.19	0.125	20	1.20	0.108	20	1.17	0.047	20
	Terminal	1.16	0.076	20	1.13	0.085	20	1.15	0.105	20	1.12	0.077	20
Triglyceride mg/dL	Day 14	43.1	13.76	20	38.2	12.06	20	41.9	14.63	20	35.9	9.80	20
	Day 45	50.6	19.69	20	37.4 <sup>a</sup>	8.31	20	37.5 <sup>a</sup>	10.03	20	37.4 <sup>a</sup>	8.64	20
	Terminal	41.3	12.46	20	40.8	12.77	20	46.2	14.25	20	41.6	10.52	20

N - Number of measures used to calculate mean

SD - Standard Deviation

<sup>a</sup>. Significantly different from control; (p< 0.05)

**Table 29-2. Summary of Clinical Chemistry Values – Female (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Cholesterol mg/dL	Day 14	71.0	13.83	20	63.4	11.68	20	67.2	11.77	20	67.0	11.76	20
	Day 45	79.6	15.36	20	74.8	11.24	20	80.0	14.99	20	75.2	12.33	20
	Terminal	77.3	15.38	20	67.1	10.18	20	75.5	16.89	20	71.5	15.89	20
Glucose mg/dL	Day 14	87.9	9.68	20	86.8	7.91	20	87.4	9.79	20	86.9	9.34	20
	Day 45	95.0	13.81	20	92.7	11.97	20	94.6	16.11	20	91.1	13.75	20
	Terminal	181.1	34.18	20	169.3	18.78	20	181.6	23.55	20	182.2	32.45	20

N - Number of measures used to calculate mean

SD - Standard Deviation



**Table 30-1. Summary of Urinalysis Values – Male**  
 MPI Research Study No. 1646-014  
 S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Volume mL	Terminal	5.83	4.948	20	5.45	2.753	20	7.33	6.340	20	5.65	2.351	20
Specific Gravity	Terminal	1.0621	0.02210	16	1.0651	0.01845	16	1.0608	0.02233	18	1.0628	0.01566	17
pH	Terminal	6.78	0.302	20	6.80	0.299	20	6.80	0.377	20	6.85	0.328	20

**Table 30-2. Summary of Urinalysis Values – Female**  
 MPI Research Study No. 1646-014  
 S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Volume mL	Terminal	3.25	2.262	20	4.87	4.402	20	3.85	2.283	20	3.39	1.830	20
Specific Gravity	Terminal	1.0621	0.02007	16	1.0499	0.02463	14	1.0614	0.02060	17	1.0620	0.02011	18
pH	Terminal	6.58	0.373	20	6.68	0.606	19	6.75	0.344	20	6.82	0.533	19

N - Number of measures used to calculate mean  
 SD - Standard Deviation

**Table 31-1. Summary of Macroscopic Observations – Male**  
 MPI Research Study No. 1646-014  
 S3643: A 13 Week Dietary Administration Toxicity Study in Rats

		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
<b>Tissue</b>	<b>Severity</b>				
<b>Observation</b>					
Number of Animals Examined		20	20	20	20
<b>all tissues</b>					
within normal limits		19	20	19	19
<b>epididymides</b>					
small	- mild	0	0	1	0
<b>lung with bronchi</b>					
discoloration, red	- moderate	0	0	0	1
<b>pituitary gland</b>					
cyst	- mild	1	0	0	0
<b>testes</b>					
small	- mild	0	0	1	0

**Table 31-2. Summary of Macroscopic Observations – Female**  
 MPI Research Study No. 1646-014  
 S3643: A 13 Week Dietary Administration Toxicity Study in Rats

		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
<b>Tissue</b>	<b>Severity</b>				
<b>Observation</b>					
Number of Animals Examined		20	20	20	20
<b>all tissues</b>					
within normal limits		19	17	19	19
<b>clitoral glands</b>					
enlarged	- moderate	0	1	0	0
<b>kidneys</b>					
absent	- no grade	0	0	0	1
dilatation, pelvic	- mild	1	1	0	0
focus/foci, red	- mild	0	1	0	0
irregular surface	- moderate	0	1	0	0
<b>thyroid gland</b>					
small	- moderate	0	0	1	0
<b>ureters</b>					
absent	- no grade	0	0	0	1
dilatation	- mild	1	0	0	0
distended with urine	- mild	0	1	0	0
<b>urinary bladder</b>					
calculus/calculi	- moderate	0	1	0	0
<b>uterus with cervix</b>					
absent, portion	- no grade	0	0	0	1
enlarged	- moderate	0	1	0	0

**Table 32-1. Summary of Organ Weight Values – Male**  
 MPI Research Study No. 1646-014  
 S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Body weight</b>												
g	524	51	20	531	57	20	522	60	20	516	51	20
<b>Brain</b>												
g	2.177	0.111	20	2.151	0.123	20	2.171	0.120	20	2.161	0.119	20
Brain/BWt												
%	0.4184	0.0367	20	0.4087	0.0399	20	0.4197	0.0387	20	0.4219	0.0355	20
<b>Adrenal gl</b>												
g	0.075	0.019	20	0.063	0.013	20	0.070	0.016	20	0.074	0.024	20
Adrenal gl/BWt												
%	0.0142	0.0029	20	0.0120	0.0031	20	0.0134	0.0035	20	0.0143	0.0039	20
Adrenal gl/BrWt												
ratio	0.0345	0.0088	20	0.0292	0.0067	20	0.0320	0.0073	20	0.0342	0.0105	20

N - Number of measures used to calculate mean  
 SD - Standard Deviation

**Table 32-1. Summary of Organ Weight Values – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Epididymides</b>												
g	1.521	0.167	20	1.377 <sup>a</sup>	0.131	20	1.455	0.148	19	1.524	0.225	20
Epididymides/BWt %	0.2919	0.0350	20	0.2620 <sup>a</sup>	0.0346	20	0.2845	0.0474	19	0.2954	0.0330	20
Epididymides/BrWt ratio	0.7001	0.0816	20	0.6409	0.0566	20	0.6716	0.0747	19	0.7050	0.0989	20
<b>Heart</b>												
g	1.773	0.238	20	1.772	0.248	20	1.791	0.229	20	1.794	0.206	20
Heart/BWt %	0.3394	0.0409	20	0.3343	0.0346	20	0.3455	0.0456	20	0.3488	0.0332	20
Heart/BrWt ratio	0.8161	0.1183	20	0.8262	0.1239	20	0.8246	0.0961	20	0.8310	0.0944	20

N - Number of measures used to calculate mean

SD - Standard Deviation

<sup>a</sup>. Significantly different from control; (p< 0.05)

**Table 32-1. Summary of Organ Weight Values – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Kidneys</b>												
g	3.874	0.397	20	3.935	0.434	20	3.912	0.393	20	4.013	0.524	20
Kidneys/BWt %	0.7407	0.0478	20	0.7432	0.0560	20	0.7536	0.0670	20	0.7781	0.0651	20
Kidneys/BrWt ratio	1.7807	0.1668	20	1.8332	0.2087	20	1.8000	0.1239	20	1.8583	0.2446	20
<b>Liver</b>												
g	14.752	1.966	20	16.116	2.643	20	15.689	2.602	20	16.589	3.078	20
Liver/BWt %	2.8089	0.1446	20	3.0278 <sup>a</sup>	0.2746	20	2.9976	0.2576	20	3.2054 <sup>b</sup>	0.3854	20
Liver/BrWt ratio	6.7763	0.8231	20	7.5014	1.2074	20	7.2034	0.9425	20	7.6929 <sup>a</sup>	1.4712	20

N - Number of measures used to calculate mean

SD - Standard Deviation

<sup>a</sup>. Significantly different from control; (p< 0.05)<sup>b</sup>. Significantly different from control; (p< 0.01)

**Table 32-1. Summary of Organ Weight Values – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Lung w/ bronchi</b> g	1.936	0.342	20	1.935	0.258	20	1.928	0.266	20	1.994	0.222	19
Lung w/ bronchi/BWt %	0.3696	0.0507	20	0.3649	0.0327	20	0.3717	0.0496	20	0.3867	0.0428	19
Lung w/ bronchi/BrWt ratio	0.8908	0.1629	20	0.9036	0.1416	20	0.8868	0.0997	20	0.9196	0.0932	19
<b>Pituitary gl</b> g	0.0177	0.0046	20	0.0158	0.0016	20	0.0163	0.0015	20	0.0157	0.0022	20
Pituitary gl/BWt %	0.0034	0.0009	20	0.0030	0.0004	20	0.0031	0.0003	20	0.0030	0.0003	20
Pituitary gl/BrWt ratio	0.0081	0.0020	20	0.0074	0.0008	20	0.0075	0.0006	20	0.0073	0.0010	20

N - Number of measures used to calculate mean  
SD - Standard Deviation

**Table 32-1. Summary of Organ Weight Values – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Prostate gl</b> g	1.664	0.399	20	1.710	0.346	20	1.753	0.319	20	1.817	0.445	20
Prostate gl/BWt %	0.3193	0.0765	20	0.3252	0.0695	20	0.3403	0.0748	20	0.3492	0.0686	20
Prostate gl/BrWt ratio	0.7666	0.1895	20	0.7985	0.1770	20	0.8096	0.1553	20	0.8405	0.2086	20
<b>Sem. ves.</b> g	2.064	0.328	20	1.800 <sup>a</sup>	0.275	20	1.895	0.380	20	1.840	0.359	20
Sem. ves./BWt %	0.3952	0.0582	20	0.3416 <sup>a</sup>	0.0559	20	0.3665	0.0755	20	0.3572	0.0700	20
Sem. ves./BrWt ratio	0.9477	0.1391	20	0.8393	0.1312	20	0.8777	0.1966	20	0.8498	0.1591	20

N - Number of measures used to calculate mean

SD - Standard Deviation

<sup>a</sup>. Significantly different from control; (p< 0.05)



**Table 32-1. Summary of Organ Weight Values – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Spleen</b>												
g	0.893	0.231	20	0.852	0.159	20	0.839	0.153	20	0.859	0.175	20
Spleen/BWt %	0.1701	0.0392	20	0.1609	0.0263	20	0.1607	0.0225	20	0.1656	0.0260	20
Spleen/BrWt ratio	0.4103	0.1030	20	0.3967	0.0730	20	0.3862	0.0660	20	0.3961	0.0724	20
<b>Testes</b>												
g	3.853	0.320	20	3.761	0.301	20	3.734	0.279	19	3.808	0.394	20
Testes/BWt %	0.7402	0.0809	20	0.7144	0.0754	20	0.7275	0.0830	19	0.7415	0.0758	20
Testes/BrWt ratio	1.7740	0.1703	20	1.7542	0.1762	20	1.7212	0.1116	19	1.7633	0.1778	20

N - Number of measures used to calculate mean  
SD - Standard Deviation

**Table 32-1. Summary of Organ Weight Values – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Thymus</b>												
g	0.299	0.077	20	0.357	0.068	20	0.353	0.110	20	0.352	0.106	20
Thymus/BWt %	0.0572	0.0136	20	0.0670	0.0094	20	0.0675	0.0201	20	0.0675	0.0158	20
Thymus/BrWt ratio	0.1378	0.0369	20	0.1659	0.0312	20	0.1627	0.0509	20	0.1628	0.0495	20
<b>Thyroid/parathyroid gl</b>												
g	0.029	0.005	20	0.029	0.006	20	0.027	0.004	20	0.028	0.003	20
Thyroid/parathyroid gl/BWt %	0.0056	0.0008	20	0.0056	0.0012	20	0.0052	0.0007	20	0.0055	0.0008	20
Thyroid/parathyroid gl/BrWt ratio	0.0134	0.0022	20	0.0137	0.0028	20	0.0124	0.0016	20	0.0131	0.0017	20

N - Number of measures used to calculate mean  
SD - Standard Deviation

**Table 32-2. Summary of Organ Weight Values – Female**  
 MPI Research Study No. 1646-014  
 S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Body weight</b>												
g	271	24	20	270	22	20	270	22	20	253 <sup>a</sup>	18	20
<b>Brain</b>												
g	1.979	0.108	20	1.995	0.099	20	1.988	0.093	20	1.944	0.099	20
Brain/BWt												
%	0.7343	0.0643	20	0.7428	0.0568	20	0.7408	0.0502	20	0.7723	0.0584	20
<b>Adrenal gl</b>												
g	0.069	0.015	20	0.070	0.012	20	0.076	0.016	20	0.062	0.013	20
Adrenal gl/BWt												
%	0.0256	0.0047	20	0.0262	0.0048	20	0.0281	0.0061	20	0.0245	0.0052	20
Adrenal gl/BrWt												
ratio	0.0352	0.0083	20	0.0352	0.0058	20	0.0380	0.0080	20	0.0319	0.0069	20

N - Number of measures used to calculate mean  
 SD - Standard Deviation  
<sup>a</sup>. Significantly different from control; (p< 0.05)

**Table 32-2. Summary of Organ Weight Values – Female (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Heart</b>												
g	1.045	0.128	20	1.044	0.071	20	1.032	0.118	20	0.967	0.091	20
Heart/BWt %	0.3854	0.0333	20	0.3885	0.0311	20	0.3841	0.0437	20	0.3833	0.0300	20
Heart/BrWt ratio	0.5287	0.0652	20	0.5243	0.0398	20	0.5195	0.0576	20	0.4979	0.0415	20
<b>Kidneys</b>												
g	2.008	0.207	20	2.094	0.173	19	2.130	0.254	20	2.029	0.226	19
Kidneys/BWt %	0.7417	0.0559	20	0.7696	0.0427	19	0.7887 <sup>a</sup>	0.0463	20	0.8008 <sup>b</sup>	0.0642	19
Kidneys/BrWt ratio	1.0160	0.1055	20	1.0476	0.0905	19	1.0708	0.1138	20	1.0456	0.1270	19

N - Number of measures used to calculate mean

SD - Standard Deviation

<sup>a</sup>. Significantly different from control; (p< 0.05)<sup>b</sup>. Significantly different from control; (p< 0.01)

**Table 32-2. Summary of Organ Weight Values – Female (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Liver</b>												
g	7.851	1.053	20	7.818	0.987	20	8.162	1.054	20	7.872	0.794	20
Liver/BWt %	2.8891	0.2021	20	2.9022	0.3216	20	3.0274	0.3010	20	3.1153 <sup>a</sup>	0.2120	20
Liver/BrWt ratio	3.9759	0.5667	20	3.9225	0.4749	20	4.1059	0.4997	20	4.0581	0.4349	20
<b>Lung w/ bronchi</b>												
g	1.411	0.237	20	1.383	0.216	20	1.434	0.271	20	1.448	0.250	20
Lung w/ bronchi/BWt %	0.5200	0.0737	20	0.5124	0.0656	20	0.5329	0.1012	20	0.5718	0.0762	20
Lung w/ bronchi/BrWt ratio	0.7156	0.1381	20	0.6939	0.1062	20	0.7215	0.1370	20	0.7448	0.1193	20

N - Number of measures used to calculate mean

SD - Standard Deviation

<sup>a</sup>. Significantly different from control; (p< 0.05)

**Table 32-2. Summary of Organ Weight Values – Female (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Ovaries w/ oviducts</b>												
g	0.121	0.028	20	0.131	0.022	20	0.124	0.027	20	0.125	0.031	20
Ovaries w/ oviducts/BWt %	0.0449	0.0094	20	0.0489	0.0084	20	0.0460	0.0097	20	0.0494	0.0101	20
Ovaries w/ oviducts/BrWt ratio	0.0614	0.0144	20	0.0659	0.0105	20	0.0622	0.0122	20	0.0646	0.0163	20
<b>Pituitary gl</b>												
g	0.0206	0.0034	20	0.0199	0.0026	20	0.0198	0.0035	20	0.0191	0.0030	20
Pituitary gl/BWt %	0.0076	0.0009	20	0.0074	0.0010	20	0.0073	0.0010	20	0.0076	0.0010	20
Pituitary gl/BrWt ratio	0.0104	0.0016	20	0.0100	0.0011	20	0.0099	0.0016	20	0.0098	0.0017	20

N - Number of measures used to calculate mean

SD - Standard Deviation

**Table 32-2. Summary of Organ Weight Values – Female (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Spleen</b> g	0.493	0.053	20	0.534	0.063	20	0.536	0.093	20	0.531	0.085	20
Spleen/BWt %	0.1822	0.0179	20	0.1985	0.0235	20	0.1981	0.0244	20	0.2105 <sup>b</sup>	0.0326	20
Spleen/BrWt ratio	0.2495	0.0287	20	0.2677	0.0279	20	0.2691	0.0418	20	0.2738	0.0456	20
<b>Thymus</b> g	0.252	0.062	20	0.249	0.049	20	0.283	0.074	20	0.204 <sup>a</sup>	0.041	20
Thymus/BWt %	0.0931	0.0221	20	0.0926	0.0196	20	0.1047	0.0252	20	0.0804	0.0141	20
Thymus/BrWt ratio	0.1277	0.0322	20	0.1249	0.0259	20	0.1417	0.0339	20	0.1045 <sup>a</sup>	0.0191	20

N - Number of measures used to calculate mean

SD - Standard Deviation

<sup>a</sup>. Significantly different from control; (p< 0.05)<sup>b</sup>. Significantly different from control; (p< 0.01)

**Table 32-2. Summary of Organ Weight Values – Female (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
<b>Thyroid/parathyroid gl</b>												
g	0.021	0.003	20	0.022	0.004	20	0.021	0.004	19	0.020	0.003	20
Thyroid/parathyroid gl/BWt												
%	0.0078	0.0014	20	0.0081	0.0017	20	0.0079	0.0012	19	0.0078	0.0013	20
Thyroid/parathyroid gl/BrWt												
ratio	0.0106	0.0018	20	0.0109	0.0020	20	0.0107	0.0018	19	0.0101	0.0017	20
<b>Uterus w/ cervix</b>												
g	0.653	0.249	20	0.601	0.168	19	0.670	0.198	20	0.541	0.137	19
Uterus w/ cervix/BWt												
%	0.2416	0.0906	20	0.2219	0.0629	19	0.2486	0.0724	20	0.2131	0.0492	19
Uterus w/ cervix/BrWt												
ratio	0.3315	0.1303	20	0.3004	0.0806	19	0.3353	0.0909	20	0.2791	0.0731	19

N - Number of measures used to calculate mean  
SD - Standard Deviation



**Table 33-1. Summary of Microscopic Observations – Male**  
 MPI Research Study No. 1646-014  
 S3643: A 13 Week Dietary Administration Toxicity Study in Rats

<b>Tissue</b>		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Observation	Severity				
Number of Animals Examined		20	20	20	20
<b>adrenal glands</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>aorta</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>bone marrow, femur</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>bone marrow, sternum</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>bone, femur</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>bone, sternum</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>brain</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20

( ) – Number observed

**Table 33-1. Summary of Microscopic Observations – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

<b>Tissue</b>		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Observation	Severity				
Number of Animals Examined		20	20	20	20
<b>epididymides</b>		(20)	(0)	(1)	(20)
anomaly, developmental	- no grade	0	0	1	0
within normal limits		20	0	0	20
<b>esophagus</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>eyes</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>eyes, optic nerves</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>galt</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>heart</b>		(20)	(0)	(0)	(20)
cardiomyopathy		7	0	0	5
	- minimal	6	0	0	3
	- mild	1	0	0	2
within normal limits		13	0	0	15
<b>joint, tibiofemoral</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20

( ) – Number observed

**Table 33-1. Summary of Microscopic Observations – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

<b>Tissue</b>		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Observation	Severity				
Number of Animals Examined		20	20	20	20
<b>kidneys</b>		(20)	(0)	(0)	(20)
cyst	- mild	1	0	0	0
inflammation, perivascular	- mild	1	0	0	0
nephropathy, chronic progressive	- minimal	7	0	0	7
within normal limits		13	0	0	13
<b>lacrimal glands, exorbital</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>large intestine, cecum</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>large intestine, colon</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>large intestine, rectum</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>larynx</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>liver</b>		(20)	(20)	(20)	(20)
hematopoiesis, extramedullary	- mild	1	0	0	0

( ) – Number observed

**Table 33-1. Summary of Microscopic Observations – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

<b>Tissue</b>		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Observation	Severity				
Number of Animals Examined		20	20	20	20
<b>liver</b>		(20)	(20)	(20)	(20)
hypertrophy, hepatocyte, centrilobular	- minimal	0	0	0	3
infiltration, mononuclear cell	- minimal	20	19	20	16
necrosis, focal	- minimal	0	1	0	0
within normal limits		0	1	0	4
<b>lung</b>		(20)	(0)	(0)	(20)
hemorrhage		3	0	0	1
	- minimal	2	0	0	0
	- mild	1	0	0	1
histiocytosis, alveolar	- minimal	5	0	0	5
inflammation, subacute	- minimal	1	0	0	2
within normal limits		12	0	0	12
<b>lymph node, mandibular</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>lymph node, mesenteric</b>		(20)	(0)	(0)	(20)
inflammation, perivascular	- minimal	1	0	0	0
within normal limits		19	0	0	20
<b>nerve, sciatic</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20

( ) – Number observed

**Table 33-1. Summary of Microscopic Observations – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

<b>Tissue</b>		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Observation	Severity				
Number of Animals Examined		20	20	20	20
<b>pancreas</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>parathyroid glands</b>		(16)	(0)	(0)	(16)
within normal limits		16	0	0	16
<b>pituitary gland</b>		(20)	(0)	(0)	(20)
cyst		3	0	0	0
	- minimal	1	0	0	0
	- mild	2	0	0	0
within normal limits		17	0	0	20
<b>prostate gland</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>salivary gland, mandibular</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>salivary gland, parotid</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>salivary gland, sublingual</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20

( ) – Number observed

**Table 33-1. Summary of Microscopic Observations – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

<b>Tissue</b>		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Observation	Severity				
Number of Animals Examined		20	20	20	20
<b>seminal vesicles</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>skeletal muscle, biceps femoris</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>skin</b>		(20)	(0)	(0)	(20)
exudate, epidermal surface	- minimal	0	0	0	1
within normal limits		20	0	0	19
<b>small intestine, duodenum</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>small intestine, ileum</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>small intestine, jejunum</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>spinal cord, cervical</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>spinal cord, lumbar</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20

( ) – Number observed

**Table 33-1. Summary of Microscopic Observations – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

<b>Tissue</b>		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Observation	Severity				
Number of Animals Examined		20	20	20	20
<b>spinal cord, thoracic</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>spleen</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>stomach, glandular</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>stomach, nonglandular</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>testes</b>		(20)	(0)	(1)	(20)
anomaly, developmental	- no grade	0	0	1	0
within normal limits		20	0	0	20
<b>thymus</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>thyroid gland</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20

( ) – Number observed

**Table 33-1. Summary of Microscopic Observations – Male (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

<b>Tissue</b>		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Observation	Severity				
Number of Animals Examined		20	20	20	20
<b>tongue</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>trachea</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>ureters</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>urinary bladder</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20

( ) – Number observed



**Table 33-2. Summary of Microscopic Observations – Female**  
 MPI Research Study No. 1646-014  
 S3643: A 13 Week Dietary Administration Toxicity Study in Rats

<b>Tissue</b>		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Observation	Severity				
Number of Animals Examined		20	20	20	20
<b>adrenal glands</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>aorta</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>bone marrow, femur</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>bone marrow, sternum</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>bone, femur</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>bone, sternum</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>brain</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20

( ) – Number observed

**Table 33-2. Summary of Microscopic Observations – Female (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

<b>Tissue</b>		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Observation	Severity				
Number of Animals Examined		20	20	20	20
<b>clitoral glands</b>		(0)	(1)	(0)	(0)
dilatation	- mild	0	1	0	0
hyperplasia	- mild	0	1	0	0
<b>esophagus</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>eyes</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>eyes, optic nerves</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>galt</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>heart</b>		(20)	(0)	(0)	(20)
cardiomyopathy	- minimal	2	0	0	2
within normal limits		18	0	0	18
<b>joint, tibiofemoral</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20

( ) – Number observed

**Table 33-2. Summary of Microscopic Observations – Female (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

<b>Tissue</b>		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Observation	Severity				
Number of Animals Examined		20	20	20	20
<b>kidneys</b>		(20)	(2)	(0)	(20)
carcinoma, renal tubule, amphophilic-vacuolar (av) type, malignant, primary		0	1	0	0
hydronephrosis, bilateral	- minimal	0	0	0	1
hydronephrosis, unilateral	- minimal	1	0	0	0
mineralization	- minimal	3	0	0	0
nephropathy, chronic progressive	- minimal	1	0	0	0
pyelitis	- minimal	1	0	0	0
within normal limits		15	1	0	19
<b>lacrimal glands, exorbital</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>large intestine, cecum</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>large intestine, colon</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>large intestine, rectum</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>larynx</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20

( ) – Number observed

**Table 33-2. Summary of Microscopic Observations – Female (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

<b>Tissue</b>		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Observation	Severity				
Number of Animals Examined		20	20	20	20
<b>liver</b>		(20)	(20)	(20)	(20)
infiltration, mononuclear cell within normal limits	- minimal	18 2	17 3	18 2	17 3
<b>lung</b>		(20)	(0)	(0)	(20)
hemorrhage	- minimal	1	0	0	0
histiocytosis, alveolar	- minimal	5	0	0	2
inflammation, subacute within normal limits	- minimal	1 14	0 0	0 0	1 17
<b>lymph node, mandibular</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>lymph node, mesenteric</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>mammary gland</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>nerve, sciatic</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20

( ) – Number observed

**Table 33-2. Summary of Microscopic Observations – Female (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

<b>Tissue</b>		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Observation	Severity				
Number of Animals Examined		20	20	20	20
<b>ovaries</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>oviducts</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>pancreas</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>parathyroid glands</b>		(17)	(0)	(0)	(15)
within normal limits		17	0	0	15
<b>pituitary gland</b>		(20)	(0)	(0)	(20)
cyst		1	0	0	1
	- minimal	1	0	0	0
	- mild	0	0	0	1
within normal limits		19	0	0	19
<b>salivary gland, mandibular</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>salivary gland, parotid</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20

( ) – Number observed

**Table 33-2. Summary of Microscopic Observations – Female (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

<b>Tissue</b>		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Observation	Severity				
Number of Animals Examined		20	20	20	20
<b>salivary gland, sublingual</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>skeletal muscle, biceps femoris</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>skin</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>small intestine, duodenum</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>small intestine, ileum</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>small intestine, jejunum</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>spinal cord, cervical</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>spinal cord, lumbar</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20

( ) – Number observed

**Table 33-2. Summary of Microscopic Observations – Female (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

<b>Tissue</b>		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Observation	Severity				
Number of Animals Examined		20	20	20	20
<b>spinal cord, thoracic</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>spleen</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>stomach, glandular</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>stomach, nonglandular</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>thymus</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>thyroid gland</b>		(20)	(0)	(1)	(20)
hyperplasia, c-cell, focal	- mild	0	0	0	1
within normal limits		20	0	1	19
<b>tongue</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20
<b>trachea</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20

( ) – Number observed

**Table 33-2. Summary of Microscopic Observations – Female (continued)**

MPI Research Study No. 1646-014

S3643: A 13 Week Dietary Administration Toxicity Study in Rats

<b>Tissue</b>		0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Observation	Severity				
Number of Animals Examined		20	20	20	20
<b>ureters</b>		(20)	(1)	(0)	(20)
dilatation		1	1	0	0
	- minimal	1	0	0	0
	- moderate	0	1	0	0
hyperplasia, transitional cell within normal limits	- moderate	0	1	0	0
		19	0	0	20
<b>urinary bladder</b>		(20)	(1)	(0)	(20)
hyperplasia, papillary/nodular transitional cell within normal limits	- moderate	0	1	0	0
		20	0	0	20
<b>uterus with cervix</b>		(20)	(1)	(0)	(20)
leiomyoma, benign, primary within normal limits		0	1	0	0
		20	0	0	20
<b>vagina</b>		(20)	(0)	(0)	(20)
within normal limits		20	0	0	20

( ) – Number observed