Toxicological Evaluation of the Flavour Ingredient *N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)-2,6-dimethylisonicotinamide (S2218)

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Supplemental Material

Supplemental Material

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Qualitative Metabolic Profiling of S2218 Using Human and Rat Mixed Gender Pooled Hepatic Microsomes

Rat and Human Liver Microsome Preparation

Liver microsomes were purchased as 20.0 mg/mL stocks. Human liver microsomes (HLMs) were received as mixed gender stocks. The rat liver microsomes were received as individual sexes and were pooled to form mixed gender stocks. Using 100 mM potassium phosphate buffer (pH 7.4, containing 3.3 mM $MgCl_2$), microsomes of both species were diluted to 0.556 mg/mL.

Microsome Incubations of S2218, Buspirone, and Loperamide

A stock solution of a mixture of buspirone (10.0 mM) and loperamide (10.0 mM) was prepared in dimethyl sulfoxide. Stock solutions of S2218 were prepared at 10.0 mM in dimethyl sulfoxide. NADPH at 10 mM was prepared by adding 3.5 mL of water into the pre-packaged NADPH reagent vial. Exactly 3.3 µL of each 10.0 mM stock was added to 3.00 mL of human and rat microsomes (0.556 mg/mL in phosphate buffer). Two hundred and fifty µL of microsomes containing the compound was aliquoted to 1-mL glass inserts in 2-mL 96-well Grenier plate. At this point, 0 minute incubation samples received 500 µL of acetonitrile. Samples then received 25 µL of either water (minus NADPH control) or 10 mM NADPH. Samples with NADPH were then incubated at 37 ºC for 20, 60, and 120 minutes and samples without NADPH for 120 minutes. (The final microsome concentration for each species was 0.50 mg/mL; the final concentration of each compound was 10 µM). At the end of incubation, 500 µL of cold acetonitrile was added to samples to quench all microsomal activity. Samples were then centrifuged at 6,000 rpm for 30 minutes at 4 ºC to separate the precipitated microsomes from the supernatant containing the parent compound and its potential metabolites. Portions of the supernatant were transferred to autosampler vials for analysis, while the remainder of the samples were stored at -80 ºC.

LC-QTOF/MS Analysis

The prepared plasma samples and samples from the microsomal incubations were analyzed using an LC-QTOF/MS (Agilent iFunnel 6550 Accurate Mass Q-TOF with iFunnel Technology) equipped with an Agilent 1290 Infinity Binary pump and an Agilent 1290 Infinity autosampler. The HPLC and MS conditions are described in the Tables shown below.

Chromatographic Conditions

HPLC pump	Agilent 1290 Infinity Binary pump
Autosampler	Agilent 1290 Infinity Autosampler
Column	Waters Acquity HSS T3, 2.1 x 50 mm, 1.8 µm
Mobile Phase A	0.1 % formic acid in water
Mobile Phase B	Acetonitrile
Flow Rate	0.75 mL/min
Injection Volume	2.0 µL

Gradient	0.0 – 4.0 min, linear gradient 1-20% B 4.0 – 8.0 min, linear gradient 20 – 100% B 8.0 – 10.75 min, isocratic at 100% B 10.75 – 11.0 min, linear gradient 100-1% B
Post time	2.0 min

Mass Spectrometric Conditions

Instrument	Agilent iFunnel 6550 UHD Accurate Mass Q-TOF with iFunnel Technology
Ionization	ESI
Polarity	Positive
Gas Temp (◦C)	235
Gas Flow (L/min)	18
Nebulizer (psig)	45
SheathGasTemp (◦C)	350
SheathGasFlow (L/min)	10
VCap (V)	3500
Nozzle Voltage (V)	1000
Fragmentor (V)	400
OCT 1 RF Vpp (V)	750
Ref Mass Enabled	Enabled (121.05087, 922.00980)
Mode	MS or Targeted MS/MS
Acquisition Rate (spectra/s)	2

Table 1. EIC Peak Areas for Buspirone and Loperamide in Rat and Human Microsomal Incubations

Compound	EIC Peak Area Measured[a]	m/z (M+H)	RT (min)	% MS (EIC) Peak Area[b]					
				Rat (min)			Human (min)		
				20	60	120	20	60	120
Buspirone	A+1 isotoplogue	387.2584	4.66	78	41	21	64	15	2
Loperamide	A+3 isotoplogue	480.2307	5.57	88	65	47	87	55	30

a. EICs for buspirone and loperamide isotoplogues were used for evaluation of parent compound concentration change to mitigate signal saturation

b. % MS peak area relative to time = 0

Table 2. Major Metabolites of S2218 in Rat and Human Microsomal Incubations

Metabolite	m/z (M+H)	Formula	RT (min)	% MS (EIC) Peak Area[a]						Observed Parent and Fragment Ions (positive mode)
				Rat (min)			Human (min)			
				20	60	120	20	60	120	
S2218	418.1544	$C_{19}H_{24}N_5O_4S^+$	3.43	103.7	100.6	96.5	100.5	98.0	98.4	418.1541 (M+H), 214.0288, 205.1329, 177.1395, 151.0879, 134.0615
M222	223.1441	$C_{12}H_{19}N_2O_2^+$	1.48	0.3	0.5	2.0	--	--	0.3	223.1439 (M+H), 205.1362, 151.0873, 108.0827
M220	221.1285	$C_{12}H_{17}N_2O_2^+$	1.60	--	0.1	0.2	--	--	--	221.1254 (M+H), 203.1180
M433A	434.1487	$C_{19}H_{24}N_5O_5S^+$	2.80	0.2	1.4	1.1	--	0.2	0.1	433.1487 (M+H), 229.0156, 205.1340, 151.0851, 134.0615
M433B	434.1487	$C_{19}H_{24}N_5O_5S^+$	2.90	0.3	1.4	2.2	0.1	0.4	0.5	433.1487 (M+H), 205.1340, 177.1346, 151.0851, 134.0615

a. % MS peak area relative to S2218 at time = 0

Figure 1. Mass Spectral Fragmentation Pathway of S2218

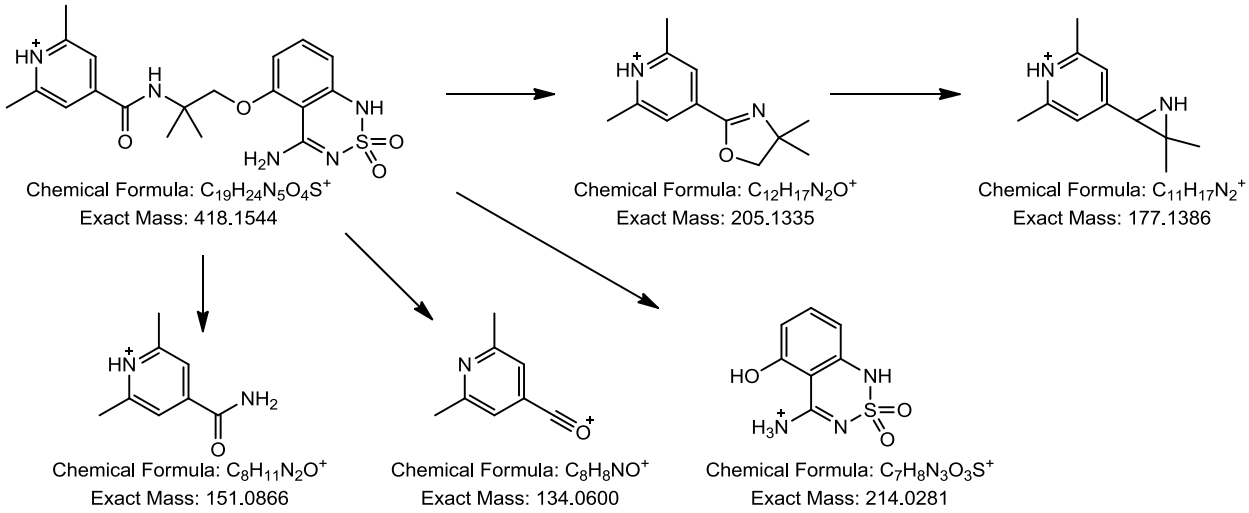
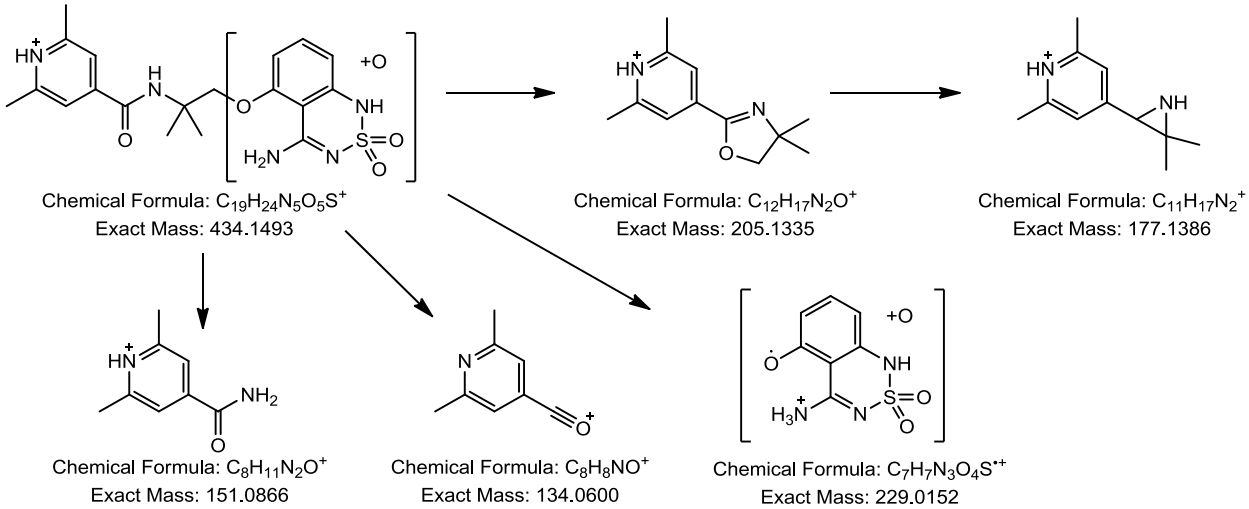


Figure 2. Mass Spectral Fragmentation Pathway of 433A/B



<u>Note</u>: Not all fragments were observed with both M433A and M433B (see Table 4)

Figure 3. Mass Spectral Fragmentation Pathway of M222

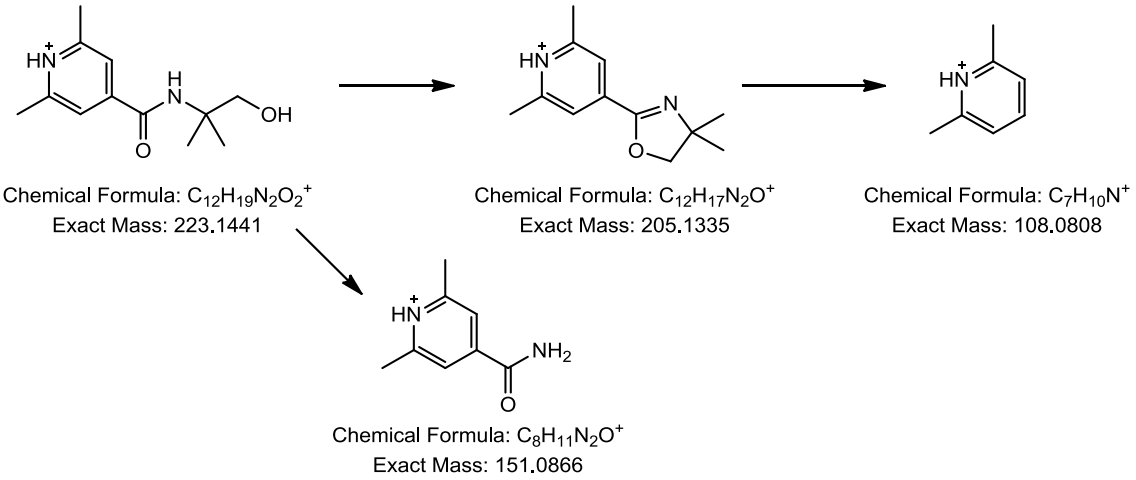
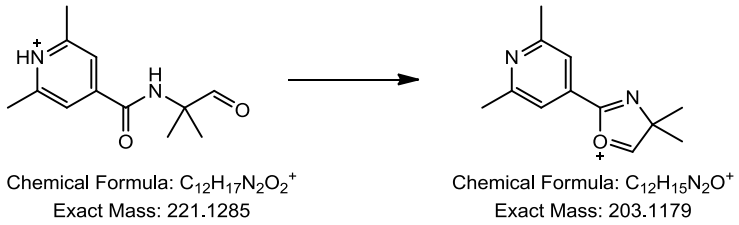


Figure 4. Mass Spectral Fragmentation Pathway of M220



Pharmacokinetics and Oral Bioavailability of S2218 and its Sulfate Salt (S8069) in Sprague-Dawley Rats

Sample Collection, Handling, Storage

For intravenous administration, 4 male and 4 female Sprague-Dawley rats (Charles River Laboratories, Hollister, CA) were bolus injected with S2218 at 1 mg/kg bw in 10% DMSO in 50 mM phosphate buffer (pH 7.4). Blood samples were collected from an implanted jugular cannulae of each rat at pre-dose and at approximately 2, 5, 10, 30 min, 1, 2, 4, and 8 hours post-dose. For oral administration, 4 male and 4 female Sprague-Dawley rats per group were given a single dose of either S2218 at 10, 30, or 100 mg/kg bw, or S8069 at 10 or 100 mg/kg bw, in 1% methyl cellulose (MC) in deionized water by oral gavage. Blood samples were taken from an implanted jugular cannulae of each rat at approximately 15, 30 min, 1, 2, 4, 8, and 24 hours post-dose. The blood samples were collected into tubes containing K_2EDTA as the anticoagulant. 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.

Plasma Sample Preparation

On the day of analysis, the plasma samples were thawed at room temperature (RT). Proteins from plasma samples (25 µL) were precipitated by addition of 75 µL of acetonitrile containing 10 ng/mL internal standard [*N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)-2-(1*H*-imidazol-1-yl)isonicotinamide; S9284]. 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. S2218 and S9284 (internal standard = IS) were detected using the ion transitions (418.1/205.1 for S2218 and 456.1/243.2 for IS). The calibration curve, obtained by spiking known concentrations of S2218 into blank rat plasma, ranged from 0.2 to 200 ng/mL for both IV and oral dose. The lower limit of quantitation (LLOQ) for S2218 was 0.2 ng/mL. The HPLC and MS conditions were described in the tables below.

Chromatographic Conditions

Column	Waters XSelect™ CSH C18 column, 2.1 mm x 50 mm, 3.5 µm		
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	Waste
	1.0		MS
	1.5	95	

	2.5 2.51 3.0 4.0	95 5 5 5	 Waste
Acquisition Time	2.0 min		
S2218 Retention Time	~ 1.59 min		
S9284 Retention Time	~ 1.63 min		

Mass Spectrometric Conditions

Instrument	API 3200 Q Trap
Ionization Mode	TurboIonspray
Polarity	Positive

Scan Function		Multiple Reaction Monitoring (MRM)	
Parameters		S2218	S9284 (IS)
	Precursor Ion	418.1	456.1
	Product Ion	205.1	243.2
	Dwell Time (ms)	150	150
	DP - Declustering Potential (V)	71	80
	CE - Collision Energy (eV)	31	37
	CXP – Collision Cell Exit Potential (V)	4	4
	EP-Entrance Potential (V)	10	8
	IS – Ionspray Voltage (V)	4500	
	TEM – Turbo Gas Temperature (°C)	650	
	GS1 – Ion Source Gas 1	60.0	
	GS2 – Ion Source Gas 2	50.0	
	CUR – Curtain Gas	40.0	
	CAD – Collision Gas	Medium	
	Resolution	Unit	
Software		Analyst 1.6.1	

Pharmacokinetic Analysis

The plasma concentration-time data were analyzed by non-compartmental methods using Phoenix WinNonlin version 1.2 (Pharsight/Certara company). The area under the curve (AUC_{last}) was determined by the trapezoidal rule from time zero to the last time point. The maximum plasma concentration (C_{max}) and the corresponding peak time (T_{max}) were observed values. The terminal half-life ($t_{½}$) was calculated by the first order rate constant associated with the terminal log-linear portion of the curve as defined by at least three data points.

Table 3. Concentrations and Pharmacokinetic Parameters of S2218 in Plasma Following Single Intravenous Administration to SD Rats (n = 4)

			Time (hr)								PK Parameters					
			0.033	**0.083**	**0.167**	**0.5**	**1.0**	**2.0**	**4.0**	**8.0**						
Gender	**Dose (mg/kg)**	**Subject**	**Concentration**								**AUC_{last} (hr*ng/mL)**	**C_{max} (ng/mL)**	**T_{max} (hr)**	**$t_{1/2}$ (hr)**	**Cl_obs (mL/hr/kg)**	**Vz_obs (mL/kg)**
Male	1	Rat_25	2830	1160	791	81.9	9.96	5.78	0.451	0.32	496	2830	0.033	0.223	2010	647
		Rat_26	3370	1070	626	86.2	8.15	1.06	0.312	0.3	506	3370	0.033	0.177	1980	504
		Rat_27	2700	1000	652	80.1	8.75	0.509	LLOQ	LLOQ	441	2700	0.033	0.165	2270	539
		Rat_28	3020	1650	916	110	13.8	1.19	LLOQ	LLOQ	558	3020	0.033	0.176	1790	455
		N	4	4	4	4	4	4	2	2	4	4	4	4	4	4
		Mean	**2980**	**1220**	**746**	**89.6**	**10.2**	**2.13**	**0.382**	**0.31**	**500**	**2980**	**0.033**	**0.185**	**2010**	**536**
		SD	291	294	134	13.9	2.54	2.45	0.0983	0.0141	47.9	291	0	0.0257	196	81.4
Female	1	Rat_29	3580	1120	594	62.2	8.94	1.14	LLOQ	LLOQ	508	3580	0.033	0.179	1970	508
		Rat_30	3340	1310	431	51.8	5.96	0.772	LLOQ	LLOQ	445	3340	0.033	0.17	2250	552
		Rat_31	3020	1400	528	46.5	7.77	0.928	LLOQ	LLOQ	438	3020	0.033	0.175	2280	576
		Rat_32	2660	1160	419	31.9	4.23	0.662	LLOQ	LLOQ	368	2660	0.033	0.17	2720	664
		N	4	4	4	4	4	4	0	0	4	4	4	4	4	4
		Mean	**3150**	**1250**	**493**	**48.1**	**6.73**	**0.876**			**440**	**3150**	**0.033**	**0.173**	**2300**	**575**
		SD	399	130	83.2	12.6	2.07	0.207			57.1	399	0	0.00428	308	65.8

LLOQ: 0.2 ng/mL

Table 4. Concentrations and Pharmacokinetic Parameters of S2218 in Plasma Following Single Oral Administration of S2218 to SD Rats (n = 4)

			Time (hr)							PK Parameters			
			0.25	**0.5**	**1**	**2**	**4**	**8**	**24**				
Gender	**Dose (mg/kg)**	**Subject**	**Concentration (ng/mL)**							**AUC_{last} (hr*ng/mL)**	**C_{max} (ng/mL)**	**T_{max} (hr)**	**$t_{1/2}$ (hr)**
Male	10	Rat_1	6.72	10.3	7.26	2.04	0.619	0.335	LLOQ	16.6	10.3	0.5	0.849
		Rat_2	19.9	15.6	5.77	2.12	0.368	0.216	LLOQ	19.9	19.9	0.25	0.679
		Rat_3	23.5	19.9	5.62	2.16	0.699	0.353	LLOQ	23.6	23.5	0.25	0.792
		Rat_4	13.3	11.3	3.1	1.35	0.308	LLOQ	LLOQ	12.2	13.3	0.25	0.734
		N	4	4	4	4	4	3	0	4	4	4	4
		Mean	**15.9**	**14.3**	**5.44**	**1.92**	**0.499**	**0.301**		**18.1**	**16.8**	**0.313**	**0.763**
		SD	7.41	4.4	1.73	0.382	0.19	0.0744		4.84	6.03	0.125	0.0734
Male	30	Rat_5	15.8	10	2.76	1.53	LLOQ	LLOQ	LLOQ	10.5	15.8	0.25	0.599
		Rat_6	32	37	16.1	5.68	1.13	0.63	LLOQ	47.1	37	0.5	0.72
		Rat_7	48.7	30.1	15.7	9.1	1.19	0.797	LLOQ	54.1	48.7	0.25	0.773
		Rat_8	19.1	23.1	4.19	2.31	0.237	0.226	LLOQ	21.2	23.1	0.5	0.584
		N	4	4	4	4	3	3	0	4	4	4	4
		Mean	**28.9**	**25.1**	**9.69**	**4.66**	**0.852**	**0.551**		**33.2**	**31.2**	**0.375**	**0.669**
		SD	14.9	11.5	7.2	3.47	0.534	0.294		20.7	14.6	0.144	0.0921
Male	100	Rat_9	39.6	88.2	42.7	21.2	2.1	1.53	0.392	132	88.2	0.5	0.666
		Rat_10	97.2	36.4	17.9	6.58	2.37	1.24	LLOQ	70.8	97.2	0.25	0.923
		Rat_11	43.4	31.7	36.7	11.5	2.94	5.58	LLOQ	87.5	43.4	0.25	0.939
		N	3	3	3	3	3	3	1	3	3	3	3
		Mean	**60.1**	**52.1**	**32.4**	**13.1**	**2.47**	**2.78**	**0.392**	**96.6**	**76.3**	**0.333**	**0.842**
		SD	32.2	31.4	12.9	7.44	0.429	2.43		31.4	28.8	0.144	0.153
Female	10	Rat_13	12	9.5	2.24	1.03	0.411	LLOQ	LLOQ	10.2	12	0.25	0.876
		Rat_14	25.5	20.5	4.53	2.34	0.897	0.333	0.226	28.8	25.5	0.25	0.89
		Rat_15	20.6	31.9	4.69	2.35	0.814	0.432	LLOQ	27.5	31.9	0.5	0.773
		Rat_16	19	4.59	1.56	0.442	LLOQ	0.216	LLOQ	9.84	19	0.25	0.457
		N	4	4	4	4	3	3	1	4	4	4	4
		Mean	**19.3**	**16.6**	**3.26**	**1.54**	**0.707**	**0.327**	**0.226**	**19.1**	**22.1**	**0.313**	**0.749**
		SD	5.58	12.2	1.59	0.959	0.26	0.108		10.5	8.55	0.125	0.202
Female	30	Rat_17	58.7	44.7	13.5	4.52	1.33	0.836	LLOQ	54	58.7	0.25	0.743
		Rat_18	28.6	24.2	7.05	3.84	0.412	0.551	LLOQ	29.6	28.6	0.25	0.638
		Rat_19	23.2	33.1	11.5	5.72	2.3	0.918	LLOQ	44.2	33.1	0.5	1
		Rat_20	26.9	22.6	6.02	1.96	0.29	LLOQ	LLOQ	22.9	26.9	0.25	0.593
		N	4	4	4	4	4	3	0	4	4	4	4
		Mean	**34.4**	**31.2**	**9.52**	**4.01**	**1.08**	**0.768**		**37.7**	**36.8**	**0.313**	**0.744**
		SD	16.4	10.1	3.56	1.57	0.935	0.193		14	14.8	0.125	0.184
Female	100	Rat_21	68.7	43.6	28.6	8.22	1.54	3.73	0.749	115	68.7	0.25	0.717
		Rat_22	32	24.1	5.78	2.3	4.03	1.08	1.52	59.9	32	0.25	1.75
		Rat_23	23.5	20	17.2	4.58	5.49	1.99	LLOQ	53.6	23.5	0.25	1.78
		Rat_24	30.4	21.2	17.1	1.51	0.937	0.704	N/A	34.9	30.4	0.25	0.736
		N	4	4	4	4	4	4	2	4	4	4	4
		Mean	**38.7**	**27.2**	**17.2**	**4.15**	**3**	**1.88**	**1.13**	**65.9**	**38.7**	**0.25**	**1.25**
		SD	20.4	11.1	9.32	3.01	2.13	1.35	0.545	34.6	20.4	0	0.6

LLOQ: 0.2 ng/mL

Table 5. Concentrations and Pharmacokinetic Parameters of S2218 in Plasma Following Single Oral Administration of S8069 to SD Rats

S8069			Time (hr)							PK Parameters			
			0.2	**0.5**	**1**	**2**	**4**	**8**	**24**				
Gender	**Dose (mg/kg)**	**Subject**	**Concentration (ng/mL)**							**AUC_{last} (hr*ng/mL)**	**C_{max} (ng/mL)**	**T_{max} (hr)**	**$t_{1/2}$ (hr)**
Male	10	Rat_1	22.2	17	4.96	1.95	0.832	LLOQ	LLOQ	19.4	22.2	0.25	0.889
		Rat_2	16.3	19.6	7.87	5.11	0.484	0.957	LLOQ	28.4	19.6	0.5	0.689
		Rat_3	20.8	12.2	4.6	1.6	0.629	0.607	LLOQ	18.7	20.8	0.25	0.874
		Rat_4	23.1	21.2	7.82	3.24	0.531	0.963	LLOQ	28	23.1	0.25	0.692
		N	4	4	4	4	4	3	0	4	4	4	4
		Mean	**20.**	**17.**	**6.3**	**2.98**	**0.61**	**0.84**		**23.6**	**21.4**	**0.31**	**0.78**
		SD	3.02	3.93	1.78	1.59	0.154	0.204		5.26	1.54	0.125	0.11
Male	100	Rat_5	63	29.2	13.9	4.39	2.44	1.01	LLOQ	53.1	63	0.25	1.02
		Rat_6	51.8	32.4	10.5	1.72	LLOQ	LLOQ	LLOQ	33.8	51.8	0.25	0.358
		Rat_7	83	46.7	22.2	4.94	3.37	2.39	LLOQ	77.2	83	0.25	0.955
		Rat_8	44.1	25.5	9.97	3.47	2.33	1.29	0.659	58.4	44.1	0.25	1.1
		N	4	4	4	4	3	3	1	4	4	4	4
		Mean	**60.**	**33.**	**14.**	**3.63**	**2.71**	**1.56**	**0.65**	**55.6**	**60.5**	**0.25**	**0.86**
		SD	16.9	9.27	5.65	1.41	0.571	0.729		17.8	16.9	0	0.34
Female	10	Rat_13	12	4.24	1.35	0.83	0.709	0.32	LLOQ	9.62	12	0.25	1.66
		Rat_14	25.5	11.8	5.07	4.11	0.682	0.732	LLOQ	24.3	25.5	0.25	0.914
		Rat_15	23.3	13.6	5.81	3.48	1.26	1.5	LLOQ	27.3	23.3	0.25	1.11
		Rat_16	36.6	21.7	12.9	7.17	1.42	1.27	LLOQ	44.5	36.6	0.25	0.91
		N	4	4	4	4	4	4	0	4	4	4	4
		Mean	**24.**	**12.**	**6.2**	**3.9**	**1.02**	**0.95**		**26.4**	**24.4**	**0.25**	**1.15**
		SD	10.1	7.17	4.82	2.6	0.378	0.532		14.3	10.1	0	0.353
Female	100	Rat_17	97.3	42.4	25.3	18.4	4.07	3.08	LLOQ	105	97.3	0.25	1.08
		Rat_18	57.7	39	20.2	9.82	2.91	1.09	LLOQ	69.8	57.7	0.25	0.975
		Rat_19	153	85.3	19.1	5.28	0.697	0.468	LLOQ	95.5	153	0.25	0.538
		Rat_20	117	52.5	16.9	8.66	5.92	3.16	0.222	126	117	0.25	1.29
		N	4	4	4	4	4	4	1	4	4	4	4
		Mean	**106**	**54.**	**20.**	**10.5**	**3.4**	**1.95**	**0.22**	**99.1**	**106**	**0.25**	**0.96**
		SD	39.7	21.1	3.56	5.58	2.19	1.38		23.2	39.7	0	0.315

LLOQ: 0.2 ng/mL

Table 6. Comparison of S2218 Exposure (AUC_{last} and C_{max}) in Plasma Between Female and Male Following Single IV and Oral Administration of S2218 or S8069 to SD Rats

Test Article	Route	PK Parameter	Dose (mg/kg)	Ratio of Mean (Female/Male)	SD
S2218 (1%MC)	IV	AUC_{last}	1	0.88	0.14
		C_{max}	1	1.06	0.17
	PO	AUC_{last}	10	1.06	0.65
		AUC_{last}	30	1.13	0.82
		AUC_{last}	100	0.68	0.42
		C_{max}	10	1.32	0.7
		C_{max}	30	1.18	0.73
		C_{max}	100	0.51	0.33
S8069 (1%MC)	PO	AUC_{last}	10	1.12	0.66
		AUC_{last}	100	1.78	0.71
		C_{max}	10	1.14	0.48
		C_{max}	100	1.76	0.82

Table 7. Absolute Bioavailability of S2218 in Plasma Following Single IV and Oral Administration of S2218 or S8069 to SD Rats

Test Article	Route	S2218 Dose Equivalent (mg/kg)	Gender	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{0\text{-last}}$ (ng.hr/mL)	$AUC_{0\text{-last}}$/dose (ng.hr/mL/mg/kg)	%F
S2218	PO	10	M	16.8	0.313	0.76	18.1	1.81	0.36
			F	22.1	0.313	0.75	19.1	1.91	0.43
		30	M	31.2	0.375	0.67	33.2	1.11	0.22
			F	36.8	0.313	0.74	37.7	1.26	0.29
		100	M	76.3	0.333	0.84	96.6	0.97	0.19
			F	38.7	0.25	1.25	65.9	0.66	0.15
S8069	PO	7.82	M	21.4	0.313	0.79	23.6	3.02	0.60
			F	24.4	0.25	1.15	26.4	3.37	0.77
		78.25	M	60.5	0.25	0.86	55.6	0.71	0.14
			F	106	0.25	0.97	99.1	1.27	0.29
S2218	IV	1	M	2980	0.033	0.185	500	500	N/A
		1	F	3150	0.033	0.173	440	440	

Table 8. Relative Bioavailability of S2218 in Plasma Following Oral Administration of S2218 or S8069 to SD Rats

Test Article	Route	S2218 Dose Equivalent (mg/kg)	Sex	$AUC_{0\text{-last}}$ (ng.hr/mL)	$AUC_{0\text{-last/dose}}$ (ng.hr/mL/mg/kg)	Relative F (S8069/S2218)
S2218 (1%MC)	PO	10	M	18.1	1.81	1.67
			F	19.1	1.91	1.77
		100	M	96.6	0.97	0.74
			F	65.9	0.66	1.92
S8069 (1%MC)	PO	7.82	M	23.6	3.02	N/A
			F	26.4	3.37	
		78.25	M	55.6	0.71	
			F	99.1	1.27	

In Vivo Metabolism of S2218 in Rats

Sample Collection, Handling, Storage

A group of 4 male and 4 female Sprague-Dawley rats were given a single dose of S8069 (S2218 sulfate salt) at 100 mg/kg bw in 1% methyl cellulose (MC) in deionized water (10 mL) by oral gavage. Blood samples were taken from an implanted jugular cannulae of each rat at pre-dose and at approximately 0, 15, 30 min, 1, 2, 4, 8, and 24 hours post-dose. The blood samples were collected into tubes containing K_2EDTA as the anticoagulant. 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.

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), 260 µL of the resulting supernatant was concentrated under a stream of nitrogen to ~40 µl. 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 shown below.

Chromatographic Conditions

HPLC pump	Agilent 1290 Infinity Binary pump		
Autosampler	Agilent 1290 Infinity Autosampler		
Column	Acquity UPLC HSS T3 C18, 2.1 x 50 mm, 1.8 µm		
Mobile Phase A	0.1 % formic acid in Optima water		
Mobile Phase B	Acetonitrile		
Flow Rate	0.75 mL/min		
Injection Volume	10 µL		
Column Temperature	30 °C		
Gradient	Time (min)	%B	Valve Position
	0.0	1	1 => 6
	5.0	15	
	7.0	100	
	11.9	100	
	12.0	1	
Acquisition Time	12.0 min		
Post Time	3.0 min		
S2218 Retention Time	~ 4.96 min		

Mass Spectrometric Conditions

Instrument	Agilent iFunnel 6550A MS Q-TOF
Ionization Source	Dual AJS ESI
Polarity	Positive
Gas Temp (◦C)	235
Gas Flow (L/min)	18
Nebulizer (psig)	45
SheathGasTemp (◦C)	350
SheathGasFlow (L/min)	10
VCap (V)	3500
Nozzle Voltage (V)	1000
Ref Mass Enabled	Enabled (121,05087, 922.00980)

Table 9. Summary of Metabolites of S2218 Observed in Rat Plasma from a Sample at 0.25 Hour Post Dose (100 mg/kg bw)

Metabolite	m/z (M+H)	Formula	RT (min)	MS (EIC) Peak Area (cps)	% MS Peak Area	Observed Parent and Fragment Ions (positive mode)
S2218	418.1544	$C_{19}H_{24}N_5O_4S^+$	4.96	6,940,000	95.98	418.1491 (M+H), 214.0318, 205.1347, 151.0869, 134.0599, 106.0652, 55.0547
M222	223.1441	$C_{12}H_{19}N_2O_2^+$	1.83	189,000	2.61	223.1406 (M+H), 151.0847, 108.0829
M236	237.1234	$C_{12}H_{17}N_2O_3^+$	1.70	76,100	1.05	227.1198 (M+H), 191.1212, 122.0918, 94.0657
M433B	434.1493	$C_{19}H_{24}N_5O_5S^+$	4.17	26,200	0.36	433.1523 (M+H), 205.1341, 151.0859, 134.0595, 106.0637

Figure 5. Mass Spectral Fragmentation Pathway of M236

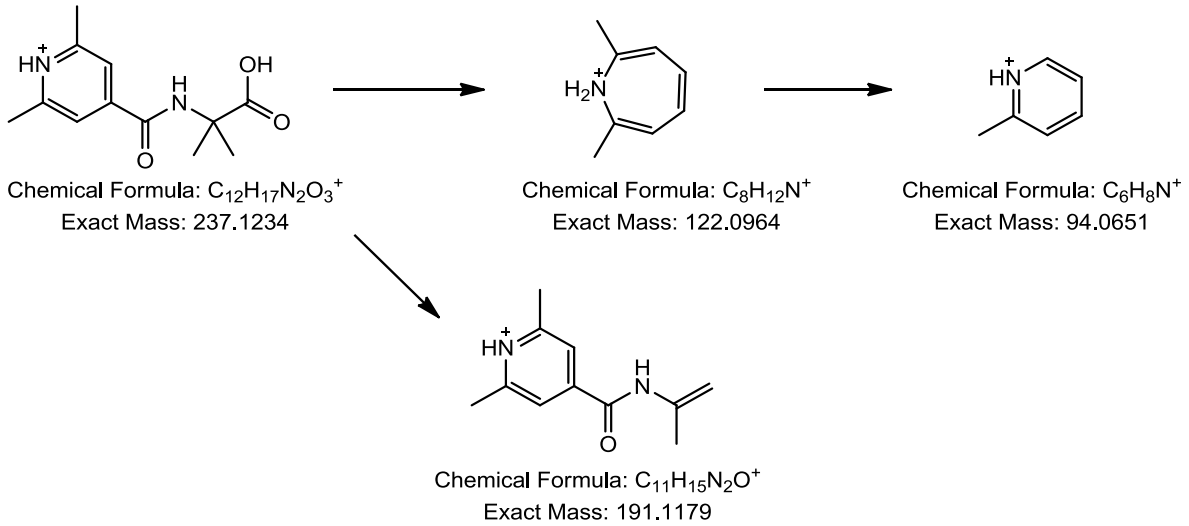
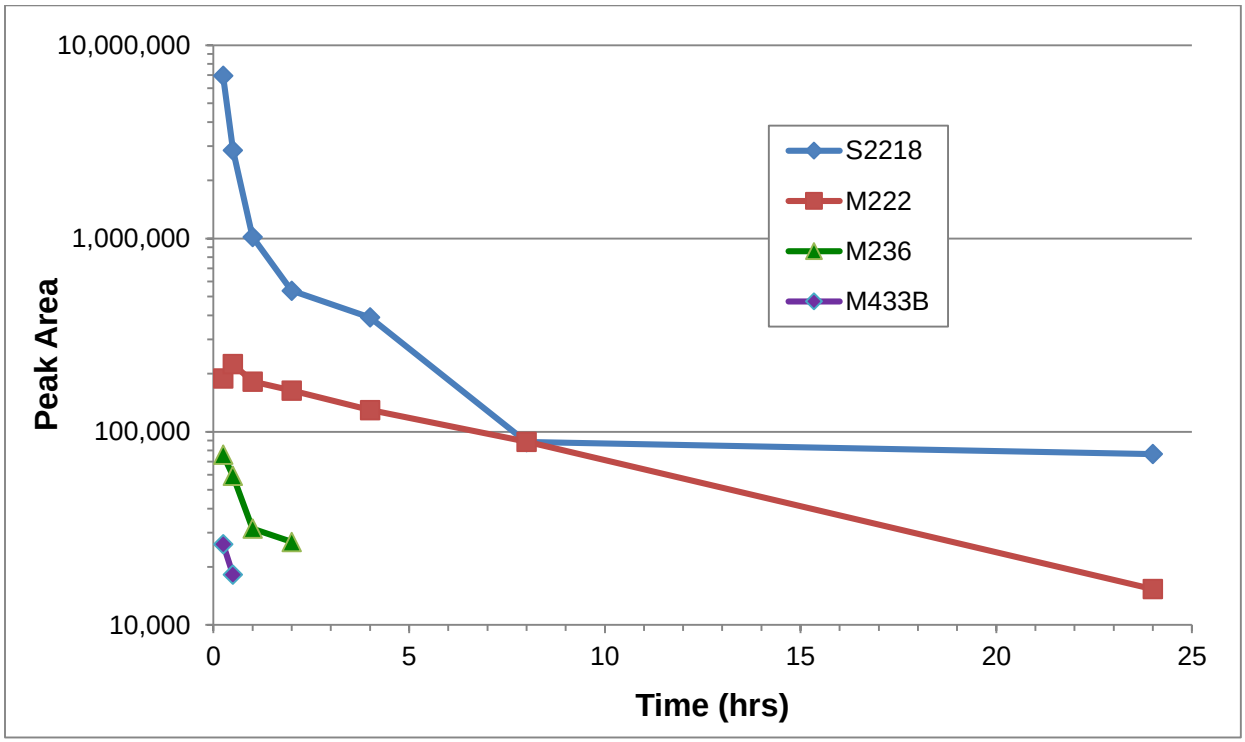


Table 10. S2218 and Major Metabolites Observed from 0.25-24 Hours in Rat Plasma

	Time (hr)						
	0.25	0.5	1	2	4	8	24
Compound	Peak Area (counts)						
S2218	6.94E+06	2.86E+06	1.02E+06	5.36E+05	3.91E+05	8.84E+04	7.67E+04
M222	1.89E+05	2.24E+05	1.82E+05	1.63E+05	1.30E+05	8.88E+04	1.53E+04
M236	7.61E+04	5.92E+04	3.15E+04	2.69E+04	LOD	LOD	LOD
M433B	2.62E+04	1.82E+04	LOD	LOD	LOD	LOD	LOD

LOD = 1.50E+04

Figure 6. Mean plasma concentrations of S2218, M222, M236 and M433B after oral administration of S8069 (100 mg/kg) to Sprague-Dawley rats



Excretion of S2218 in Rats

Sample Collection, Handling, and Storage

A group of 4 male and 4 female Sprague-Dawley rats were given a single dose of S8069 (S2218 sulfate salt) at 10 mg/kg bw in 1% methyl cellulose (MC) in deionized water (10 mL) by oral gavage. Feces and urine were collected from metabolic cages into separate pre-weighed 50 mL centrifuge tubes at room temperature over 0-24, 24-48, and 48-72 hours post-dose. The samples were stored at -20 °C prior to analysis.

Preparation of Calibration Standards

For fecal samples, blank feces (0.5 – 0.7 g) were extracted with 4 volumes (by feces weight) of 0.2 % formic acid in methanol containing 4 µg/mL of internal standard [*N*-(1-((4-amino-2,2-dioxido-1*H*-benzo[*c*][1,2,6]thiadiazin-5-yl)oxy)-2-methylpropan-2-yl)-2-(1*H*-imidazol-1-yl)isonicotinamide; S9284] for 3 hours. A Tissue Homogenizer OMNI TH_Q (OMNI International) with a disposable probe (Omini Tip Plastic 30007HT) was used to homogenize feces with a motor speed at 12,000 rpm. Twelve working standards (0.625 – 2500 µg/mL) of S8069 were prepared in 0.1% formic acid in water and spiked into blank feces. This set of calibration standards in feces were capped tightly to prevent solvent evaporation and were orbital shaking at 200 rpm for 120 hours. For urine samples, nine working standards (0.5 – 250 µg/mL) of S8069 were prepared in methanol and 10 µL of working standards were spiked into 490 µL of blank urine.

Fecal Sample Extraction

Each fecal sample was extracted with 1.6 – 4 volumes (by feces weight) of 0.2% formic acid in methanol containing 4 µg/mL of internal standard (S9284) and blank 0.1% formic acid in water (4% of methanol volume) for 3 hours. A Tissue Homogenizer OMNI TH_Q (OMNI International) with a disposable probe (Omini Tip Plastic 30007HT) was used to homogenize feces with a motor speed at 12,000 rpm. The fecal homogenates were capped tightly to prevent solvent evaporation and were orbital shaking at 200 rpm for 120 hours. Both fecal samples and calibration standards were vortexed, then centrifuged for 3 minutes (Sorvall Legend XTR, 3,000 rpm, room temperature), 10 µL of the resulting supernatant was mixed with 490 µL of 40% acetonitrile in water for the first dilution (D1). Then 20 µL of solution D1 was further diluted with 180 µL of 40% acetonitrile in water (D2). The solution D2 was analyzed by LC-MS/MS.

Urine Sample Preparation

On the day of analysis, the urine samples were thawed at room temperature (RT). Urine samples and calibration standards (20 µL) were extracted by addition of 180 µL of 0.1% formic acid in water containing 50 ng/mL of the internal standard (S9284). After 10 minutes of centrifugation (Sorvall Legend XTR, 6,000 rpm, 20 °C), 10 µL of the resulting supernatant was mixed with 190 µL 0.1% formic acid in deionized water. The solution was analyzed by LC-MS/MS.

LC-MS/MS Analysis

The prepared feces and urine samples were analyzed using an LC-MS/MS (Applied Biosystems) equipped with an Agilent 1100 binary pump and a CTC PAL injector. S2218 and S9284 (internal standard = IS) were detected using the ion transitions 418.1/205.1 for S2218 and 456.1/243.2 for IS. The HPLC and MS conditions are described in the tables below.

Chromatographic Conditions

Column	XSELECT ™ CSH 130 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 Waste 1.0 MS 1.5 95 2.5 95 2.51 5 3.0 5 Waste 4.0 5
Acquisition Time	2.0 min
S2218 Retention Time	~ 1.59 min
S9284 Retention Time	~ 1.63 min

Mass Spectrometric Conditions

Instrument	API 3200 Q Trap
Ionization Mode	TurboIonspray
Polarity	Positive

Scan Function	Multiple Reaction Monitoring (MRM)	
Parameters	S2218	S9284 (IS)
Precursor Ion	418.1	456.1
Product Ion	205.1	243.2
Dwell Time (ms)	150	150
DP - Declustering Potential (V)	71	80
CE - Collision Energy (eV)	31	37
CXP – Collision Cell Exit Potential (V)	4	4
EP-Entrance Potential (V)	10	8
IS – Ionspray Voltage (V)	4500	
TEM – Turbo Gas Temperature (°C)	650	
GS1 – Ion Source Gas 1	60.0	
GS2 – Ion Source Gas 2	50.0	
CUR – Curtain Gas	40.0	
CAD – Collision Gas	Medium	
Resolution	Unit	
Software	Analyst 1.6.1	

Table 11. Total Percentage Recovery of S2218 in Rat Feces and Urine over 72 Hours Following a Single Oral Dose of its Sulfate Salt (S8069) to SD Rats

Gender	Rat	Amount of S8069 Dose (µg)	Total Recovery in Urine (0 - 72 hours)		Total Recovery in Feces (0 - 72 hours)		Total Recovery in Feces and Urine (0 - 72 hours)	
			S8069* Amount (µg)	S8069* Recovery (%)	S8069* Amount (µg)	S8069* Recovery (%)	S8069* Amount (µg)	S8069* Recovery (%)
Male	1	2361	1.124	0.048	2142	90.69	2143	90.7
	2	3423	1.90	0.056	2864	83.68	2866	83.7
	3	3289	1.966	0.060	3091	93.99	3093	94.0
	4	3455	0.43	0.012	2072	59.98	2072	60.0
	Mean			0.044		82.08		82.1
	SD			0.022		15.35		15.4
Female	5	2085	12.59	0.604	1693	81.21	1706	81.8
	6	2264	1.59	0.070	2133	94.20	2134	94.3
	7	2219	3.34	0.151	2172	97.91	2176	98.1
	8	2245	2.13	0.095	1927	85.84	1929	85.9
	Mean			0.230		89.79		90.0
	SD			0.252		7.63		7.5
Overall	**Mean**			0.137		85.94		86.07
	SD			0.193		11.95		11.95

* Amount of S8069 and percent S8069 recovery (% S8069 administered dose) calculated from the S2218 LC-MS peak areas in comparison to those of the S8069 calibration standards

Table 12. Concentration, Amount, and Percent Recovery of S2218 in Feces and Urine Following a Single Oral Administration of its Sulfate Salt (S8069) to SD Rat

Matrix	Gender	Rat	Amount of S8069 Dose (µg)	0 - 24 hours				24 - 48 hours				48 - 72 hours			
				Amount of Feces Collected (g)	Determined S8069* Concentration (µg/g)	S8069* Amount (µg)	S8069* Recovery (%)	Amount of Feces Collected (g)	Determined S8069* Concentration (µg/g)	S8069* Amount (µg)	S8069* Recovery (%)	Amount of Feces Collected (g)	Determined S8069* Concentration (µg/g)	S8069* Amount (µg)	S8069* Recovery (%)
Feces	Male	1	2361	13.2113	148.25	1959	82.94	13.6463	12.63	172.28	7.296	13.0213	0.829	10.788	0.457
		2	3423	10.3832	241.00	2502	73.11	10.6116	33.65	357.08	10.432	9.6504	0.494	4.764	0.139
		3	3289	9.5913	313.50	3007	91.43	12.9919	6.44	83.70	2.545	7.5739	LLOQ	N/A	N/A
		4	3455	20.1972	101.35	2047	59.25	20.2672	1.22	24.73	0.716	17.9247	LLOQ	N/A	N/A
		Mean					76.68				5.247				0.298
		SD					13.82				4.432				0.225
	Female	5	2085	7.7284	184.50	1426	68.37	9.7100	27.25	264.60	12.688	9.0265	0.332	2.992	0.143
		6	2264	8.5677	213.25	1827	80.70	11.5488	26.43	305.18	13.479	11.4512	LLOQ	N/A	N/A
		7	2219	6.9068	304.00	2100	94.63	3.5127	19.33	67.88	3.059	8.1111	0.601	4.873	0.220
		8	2245	8.6192	221.50	1909	85.05	3.8431	4.61	17.71	0.789	7.7362	0.272	2.107	0.094
		Mean					82.19				7.504				0.152
		SD					10.89				6.517				0.063
Urine	Male	1	2361	12.8090	0.08	1.00	0.042	6.3405	0.019	0.123	0.005	5.4230	LLOQ	N/A	N/A
		2	3423	10.6029	0.15	1.57	0.046	6.4910	0.036	0.236	0.007	8.0472	0.012	0.098	0.003
		3	3289	9.5004	0.19	1.82	0.055	6.5395	0.022	0.142	0.004	4.9946	LLOQ	N/A	N/A
		4	3455	0.0000	0.00	0.00	0.000	0.3255	1.315	0.428	0.012	0.0000	0.000	0.000	0.000
		Mean					0.036				0.007				0.001
		SD					0.025				0.004				0.001
	Female	5	2085	6.1717	1.77	10.89	0.522	5.8169	0.214	1.245	0.060	7.5544	0.060	0.453	0.022
		6	2264	16.2877	0.09	1.45	0.064	8.4232	0.017	0.140	0.006	3.3501	LLOQ	N/A	N/A
		7	2219	8.5733	0.37	3.13	0.141	7.9524	0.020	0.157	0.007	4.4612	0.013	0.056	0.003
		8	2245	8.0495	0.22	1.81	0.081	7.9340	0.019	0.147	0.007	8.9657	0.020	0.176	0.008
		Mean					0.202				0.020				0.008
		SD					0.216				0.027				0.010

* Amount of S8069 and percent S8069 recovery (% S8069 administered dose) calculated from the S2218 LC-MS peak areas in comparison to those of the S8069 calibration standards

Reverse Bacterial Mutation Assay: S2218

TABLE 13
Initial Toxicity-Mutation Assay without S9 activation

Study Number: AE51TS.503.BTL — Study Code: AE51TS
Experiment: B1 — Date Plated: 3/8/2016
Exposure Method: Plate incorporation assay — Evaluation Period: 3/14/2016

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	**S2218**	5000 µg	*15*	*1*	*1.3*	14[A] 1 NP, 16[A] 1 NP
		1500 µg	*13*	*4*	*1.1*	16[A], 10[A]
		500 µg	*15*	*3*	*1.3*	13[A], 17[A]
		150 µg	*16*	*2*	*1.3*	17[A], 14[A]
		50.0 µg	*13*	*6*	*1.1*	8[A], 17[A]
		15.0 µg	*13*	*6*	*1.1*	8[A], 17[A]
		5.00 µg	*14*	*6*	*1.2*	10[A], 18[A]
		1.50 µg	*16*	*10*	*1.3*	9[A], 23[A]
	DMSO	50.0 µL	*12*	*3*		14[A], 10[A]
TA100	**S2218**	5000 µg	*127*	*5*	*1.2*	130[A] 1 NP, 123[A] 1 NP
		1500 µg	*102*	*14*	*1.0*	92[A], 112[A]
		500 µg	*122*	*7*	*1.2*	127[A], 117[A]
		150 µg	*129*	*9*	*1.2*	122[A], 135[A]
		50.0 µg	*117*	*8*	*1.1*	111[A], 122[A]
		15.0 µg	*116*	*9*	*1.1*	122[A], 109[A]
		5.00 µg	*114*	*7*	*1.1*	109[A], 119[A]
		1.50 µg	*103*	*5*	*1.0*	106[A], 99[A]
	DMSO	50.0 µL	*105*	*5*		108[A], 101[A]
TA1535	**S2218**	5000 µg	*12*	*2*	*1.3*	10[A] 1 NP, 13[A] 1 NP
		1500 µg	*9*	*1*	*1.0*	8[A], 10[A]
		500 µg	*13*	*2*	*1.4*	11[A], 14[A]
		150 µg	*10*	*6*	*1.1*	14[A], 6[A]
		50.0 µg	*13*	*4*	*1.4*	15[A], 10[A]
		15.0 µg	*10*	*1*	*1.1*	9[A], 10[A]
		5.00 µg	*9*	*1*	*1.0*	8[A], 10[A]
		1.50 µg	*12*	*3*	*1.3*	14[A], 10[A]
	DMSO	50.0 µL	*9*	*1*		8[A], 9[A]
TA1537	**S2218**	5000 µg	*7*	*2*	*1.2*	8[A] 1 NP, 5[A] 1 NP
		1500 µg	*7*	*6*	*1.2*	2[A], 11[A]
		500 µg	*7*	*0*	*1.2*	7[A], 7[A]
		150 µg	*7*	*0*	*1.2*	7[A], 7[A]
		50.0 µg	*7*	*0*	*1.2*	7[A], 7[A]
		15.0 µg	*6*	*1*	*1.0*	5[A], 7[A]
		5.00 µg	*6*	*1*	*1.0*	6[A], 5[A]
		1.50 µg	*5*	*3*	*0.8*	3[A], 7[A]
	DMSO	50.0 µL	*6*	*4*		3[A], 9[A]

Key to Automatic Count Flags	Key to Plate Postfix Codes	
[A]: Automatic count	1	Normal background
	NP	Non-interfering particulate

TABLE 13 (CONT.)
Initial Toxicity-Mutation Assay without S9 activation

Study Number: AE51TS.503.BTL
Experiment: B1
Exposure Method: Plate incorporation assay

Study Code: AE51TS
Date Plated: 3/8/2016
Evaluation Period: 3/14/2016

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
WP2uvrA	**S2218**	5000 µg	*26*	*6*	*1.4*	30[A] 1 NP, 22[A] 1 NP
		1500 µg	*22*	*4*	*1.2*	25[A], 19[A]
		500 µg	*21*	*4*	*1.1*	18[A], 24[A]
		150 µg	*23*	*5*	*1.2*	19[A], 26[A]
		50.0 µg	*17*	*1*	*0.9*	17[A], 16[A]
		15.0 µg	*17*	*1*	*0.9*	17[A], 16[A]
		5.00 µg	*21*	*7*	*1.1*	26[A], 16[A]
		1.50 µg	*21*	*3*	*1.1*	23[A], 19[A]
	DMSO	50.0 µL	*19*	*6*		14[A], 23[A]
TA98	**2NF**	1.0 µg	*84*	*8*	*7.0*	90[A], 78[A]
TA100	**SA**	1.0 µg	*568*	*81*	*5.4*	625[A], 510[A]
TA1535	**SA**	1.0 µg	*573*	*4*	*63.7*	570[A], 576[A]
TA1537	**9AAD**	75 µg	*343*	*34*	*57.2*	319[A], 367[A]
WP2uvrA	**MMS**	1000 µg	*243*	*74*	*12.8*	295[A], 190[A]

Key to Positive Controls

2NF	2-nitrofluorene
SA	sodium azide
9AAD	9-Aminoacridine
MMS	methyl methanesulfonate

Key to Plate Postfix Codes

1	Normal background
NP	Non-interfering particulate

Key to Automatic Count Flags

[A]: Automatic count

TABLE 14
Initial Toxicity-Mutation Assay with S9 activation

Study Number: AE51TS.503.BTL
Study Code: AE51TS
Experiment: B1
Date Plated: 3/8/2016
Exposure Method: Plate incorporation assay
Evaluation Period: 3/14/2016

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	**S2218**	5000 µg	*25*	*2*	*1.4*	23[A] 1 NP, 26[A] 1 NP
		1500 µg	*20*	*6*	*1.1*	24[A], 15[A]
		500 µg	*18*	*5*	*1.0*	21[A], 14[A]
		150 µg	*22*	*1*	*1.2*	21[A], 23[A]
		50.0 µg	*16*	*1*	*0.9*	15[A], 16[A]
		15.0 µg	*18*	*7*	*1.0*	23[A], 13[A]
		5.00 µg	*16*	*8*	*0.9*	21[A], 10[A]
		1.50 µg	*14*	*1*	*0.8*	15[A], 13[A]
	DMSO	50.0 µL	*18*	*10*		25[A], 11[A]
TA100	**S2218**	5000 µg	*116*	*13*	*1.3*	107[A] 1 NP, 125[A] 1 NP
		1500 µg	*113*	*3*	*1.3*	111[A], 115[A]
		500 µg	*97*	*10*	*1.1*	90[A], 104[A]
		150 µg	*105*	*1*	*1.2*	104[A], 105[A]
		50.0 µg	*95*	*6*	*1.1*	99[A], 90[A]
		15.0 µg	*102*	*21*	*1.1*	116[A], 87[A]
		5.00 µg	*124*	*1*	*1.4*	125[A], 123[A]
		1.50 µg	*83*	*7*	*0.9*	88[A], 78[A]
	DMSO	50.0 µL	*89*	*11*		96[A], 81[A]
TA1535	**S2218**	5000 µg	*14*	*1*	*1.2*	15[A] 1 NP, 13[A] 1 NP
		1500 µg	*14*	*1*	*1.2*	14[A], 13[A]
		500 µg	*15*	*3*	*1.3*	13[A], 17[A]
		150 µg	*14*	*4*	*1.2*	16[A], 11[A]
		50.0 µg	*10*	*1*	*0.8*	11[A], 9[A]
		15.0 µg	*12*	*6*	*1.0*	7[A], 16[A]
		5.00 µg	*12*	*2*	*1.0*	13[A], 10[A]
		1.50 µg	*9*	*1*	*0.8*	10[A], 8[A]
	DMSO	50.0 µL	*12*	*5*		15[A], 8[A]
TA1537	**S2218**	5000 µg	*11*	*4*	*1.2*	14[A] 1 NP, 8[A] 1 NP
		1500 µg	*10*	*0*	*1.1*	10[A], 10[A]
		500 µg	*7*	*1*	*0.8*	8[A], 6[A]
		150 µg	*12*	*3*	*1.3*	14[A], 10[A]
		50.0 µg	*8*	*3*	*0.9*	6[A], 10[A]
		15.0 µg	*8*	*3*	*0.9*	6[A], 10[A]
		5.00 µg	*7*	*0*	*0.8*	7[A], 7[A]
		1.50 µg	*7*	*6*	*0.8*	3[A], 11[A]
	DMSO	50.0 µL	*9*	*4*		6[A], 11[A]

Key to Plate Postfix Codes

1	Normal background
NP	Non-interfering particulate

Key to Automatic Count Flags

[A]: Automatic count

TABLE 14 (CONT.)
Initial Toxicity-Mutation Assay with S9 activation

Study Number: AE51TS.503.BTL | Study Code: AE51TS
Experiment: B1 | Date Plated: 3/8/2016
Exposure Method: Plate incorporation assay | Evaluation Period: 3/14/2016

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
WP2uvrA	**S2218**	5000 µg	*31*	*1*	*1.0*	32[A] 1 NP, 30[A] 1 NP
		1500 µg	*34*	*11*	*1.1*	41[A], 26[A]
		500 µg	*22*	*0*	*0.7*	22[A], 22[A]
		150 µg	*30*	*4*	*1.0*	27[A], 33[A]
		50.0 µg	*23*	*6*	*0.7*	19[A], 27[A]
		15.0 µg	*27*	*8*	*0.9*	21[A], 32[A]
		5.00 µg	*31*	*7*	*1.0*	36[A], 26[A]
		1.50 µg	*24*	*8*	*0.8*	29[A], 18[A]
	DMSO	50.0 µL	*31*	*0*		31[A], 31[A]
TA98	**2AA**	1.0 µg	*256*	*16*	*14.2*	245[A], 267[A]
TA100	**2AA**	2.0 µg	*422*	*11*	*4.7*	430[A], 414[A]
TA1535	**2AA**	1.0 µg	*84*	*4*	*7.0*	87[A], 81[A]
TA1537	**2AA**	2.0 µg	*48*	*3*	*5.3*	50[A], 46[A]
WP2uvrA	**2AA**	15 µg	*296*	*25*	*9.5*	314[A], 278[A]

Key to Positive Controls

2AA 2-aminoanthracene

Key to Plate Postfix Codes

1 Normal background
NP Non-interfering particulate

Key to Automatic Count Flags

[A]: Automatic count

TABLE 15
Confirmatory Mutagenicity Assay without S9 activation

Study Number: AE51TS.503.BTL
Experiment: B2
Exposure Method: Plate incorporation assay

Study Code: AE51TS
Date Plated: 3/22/2016
Evaluation Period: 3/28/2016

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	**S2218**	5000 µg	*17*	*4*	*1.1*	15[A] 1 NP, 22[A] 1 NP, 15[A] 1 NP
		3333 µg	*12*	*4*	*0.8*	17[A] 1 NP, 10[A] 1 NP, 10[A] 1 NP
		1000 µg	*13*	*3*	*0.9*	15[A], 15[A], 10[A]
		333 µg	*11*	*5*	*0.7*	8[A], 17[A], 9[A]
		100 µg	*16*	*7*	*1.1*	10[A], 23[A], 15[A]
	DMSO	50.0 µL	*15*	*3*		15[A], 18[A], 13[A]
TA100	**S2218**	5000 µg	*73*	*9*	*0.8*	83[A] 1 NP, 68[A] 1 NP, 67[A] 1 NP
		3333 µg	*77*	*10*	*0.9*	81[A] 1 NP, 66[A] 1 NP, 84[A] 1 NP
		1000 µg	*79*	*8*	*0.9*	82[A], 70[A], 86[A]
		333 µg	*76*	*3*	*0.9*	73[A], 78[A], 76[A]
		100 µg	*78*	*3*	*0.9*	75[A], 80[A], 80[A]
	DMSO	50.0 µL	*86*	*24*		66[A], 112[A], 80[A]
TA1535	**S2218**	5000 µg	*14*	*3*	*1.0*	17[A] 1 NP, 11[A] 1 NP, 13[A] 1 NP
		3333 µg	*11*	*2*	*0.8*	13[A] 1 NP, 9[A] 1 NP, 11[A] 1 NP
		1000 µg	*15*	*3*	*1.1*	13[A], 13[A], 19[A]
		333 µg	*12*	*3*	*0.9*	15[A], 9[A], 13[A]
		100 µg	*13*	*5*	*0.9*	19[A], 9[A], 11[A]
	DMSO	50.0 µL	*14*	*2*		13[A], 16[A], 14[A]
TA1537	**S2218**	5000 µg	*3*	*0*	*0.5*	3[A] 1 NP, 3[A] 1 NP, 3[A] 1 NP
		3333 µg	*4*	*2*	*0.7*	3[A] 1 NP, 6[A] 1 NP, 3[A] 1 NP
		1000 µg	*8*	*2*	*1.3*	7[A], 10[A], 7[A]
		333 µg	*7*	*1*	*1.2*	6[A], 8[A], 7[A]
		100 µg	*6*	*0*	*1.0*	6[A], 6[A], 6[A]
	DMSO	50.0 µL	*6*	*3*		7[A], 3[A], 8[A]

Key to Plate Postfix Codes

1	Normal background
NP	Non-interfering particulate

Key to Automatic Count Flags

[A]: Automatic count

TABLE 15 (CONT.)
Confirmatory Mutagenicity Assay without S9 activation

Study Number: AE51TS.503.BTL
Experiment: B2
Exposure Method: Plate incorporation assay

Study Code: AE51TS
Date Plated: 3/22/2016
Evaluation Period: 3/28/2016

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
WP2uvrA	**S2218**	5000 µg	*20*	*5*	*0.7*	25[A] 1 NP, 16[A] 1 NP, 18[A] 1 NP
		3333 µg	*22*	*4*	*0.8*	18[A] 1 NP, 25[A] 1 NP, 23[A] 1 NP
		1000 µg	*23*	*2*	*0.9*	24[A], 25[A], 21[A]
		333 µg	*31*	*2*	*1.1*	32[A], 29[A], 31[A]
		100 µg	*28*	*3*	*1.0*	32[A], 26[A], 26[A]
	DMSO	50.0 µL	*27*	*5*		31[A], 29[A], 22[A]
TA98	**2NF**	1.0 µg	*104*	*2*	*6.9*	107[A], 103[A], 103[A]
TA100	**SA**	1.0 µg	*577*	*57*	*6.7*	635[A], 575[A], 521[A]
TA1535	**SA**	1.0 µg	*515*	*29*	*36.8*	514[A], 545[A], 487[A]
TA1537	**9AAD**	75 µg	*375*	*104*	*62.5*	337[A], 492[A], 295[A]
WP2uvrA	**MMS**	1000 µg	*288*	*21*	*10.7*	308[A], 288[A], 267[A]

Key to Positive Controls

2NF	2-nitrofluorene
SA	sodium azide
9AAD	9-Aminoacridine
MMS	methyl methanesulfonate

Key to Plate Postfix Codes

1	Normal background
NP	Non-interfering particulate

Key to Automatic Count Flags

[A]: Automatic count

TABLE 16
Confirmatory Mutagenicity Assay with S9 activation

Study Number: AE51TS.503.BTL | Study Code: AE51TS
Experiment: B2 | Date Plated: 3/22/2016
Exposure Method: Plate incorporation assay | Evaluation Period: 3/28/2016

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
TA98	**S2218**	5000 µg	*16*	*1*	*0.8*	16[A] 1 NP, 15[A] 1 NP, 17[A] 1 NP
		3333 µg	*27*	*5*	*1.4*	24[A] 1 NP, 24[A] 1 NP, 33[A] 1 NP
		1000 µg	*20*	*5*	*1.0*	22[A], 14[A], 23[A]
		333 µg	*19*	*3*	*1.0*	18[A], 17[A], 22[A]
		100 µg	*17*	*4*	*0.9*	17[A], 21[A], 14[A]
	DMSO	50.0 µL	*20*	*2*		19[A], 22[A], 19[A]
TA100	**S2218**	5000 µg	*107*	*22*	*1.0*	84[A] 1 NP, 128[A] 1 NP, 109[A] 1 NP
		3333 µg	*83*	*8*	*0.8*	81[A] 1 NP, 91[A] 1 NP, 76[A] 1 NP
		1000 µg	*107*	*18*	*1.0*	121[A], 87[A], 114[A]
		333 µg	*94*	*11*	*0.9*	97[A], 82[A], 104[A]
		100 µg	*109*	*12*	*1.1*	96[A], 113[A], 119[A]
	DMSO	50.0 µL	*103*	*5*		107[A], 103[A], 98[A]
TA1535	**S2218**	5000 µg	*13*	*3*	*0.8*	14[A] 1 NP, 9[A] 1 NP, 15[A] 1 NP
		3333 µg	*15*	*4*	*0.9*	16[A] 1 NP, 18[A] 1 NP, 10[A] 1 NP
		1000 µg	*15*	*5*	*0.9*	15[A], 10[A], 19[A]
		333 µg	*12*	*2*	*0.7*	11[A], 10[A], 14[A]
		100 µg	*14*	*3*	*0.8*	16[A], 14[A], 11[A]
	DMSO	50.0 µL	*17*	*6*		17[A], 11[A], 22[A]
TA1537	**S2218**	5000 µg	*11*	*7*	*1.2*	6[A] 1 NP, 7[A] 1 NP, 19[A] 1 NP
		3333 µg	*8*	*1*	*0.9*	8[A] 1 NP, 8[A] 1 NP, 9[A] 1 NP
		1000 µg	*9*	*1*	*1.0*	8[A], 10[A], 8[A]
		333 µg	*10*	*4*	*1.1*	11[A], 13[A], 6[A]
		100 µg	*8*	*1*	*0.9*	8[A], 8[A], 7[A]
	DMSO	50.0 µL	*9*	*7*		2[A], 9[A], 15[A]

Key to Plate Postfix Codes

1	Normal background
NP	Non-interfering particulate

Key to Automatic Count Flags

[A]: Automatic count

TABLE 16 (CONT.)
Confirmatory Mutagenicity Assay with S9 activation

Study Number: AE51TS.503.BTL | Study Code: AE51TS
Experiment: B2 | Date Plated: 3/22/2016
Exposure Method: Plate incorporation assay | Evaluation Period: 3/28/2016

Strain	Article	Dose level per plate	Mean revertants per plate	Standard Deviation	Ratio treated / solvent	Individual revertant colony counts and background codes
WP2uvrA	**S2218**	5000 µg	*23*	*2*	*1.0*	22[A] 1 NP, 22[A] 1 NP, 26[A] 1 NP
		3333 µg	*24*	*4*	*1.0*	22[A] 1 NP, 29[A] 1 NP, 22[A] 1 NP
		1000 µg	*27*	*6*	*1.1*	21[A], 30[A], 31[A]
		333 µg	*27*	*7*	*1.1*	31[A], 19[A], 31[A]
		100 µg	*29*	*5*	*1.2*	34[A], 26[A], 26[A]
	DMSO	50.0 µL	*24*	*3*		25[A], 27[A], 21[A]
TA98	**2AA**	1.0 µg	*211*	*8*	*10.6*	217[A], 214[A], 202[A]
TA100	**2AA**	2.0 µg	*407*	*58*	*4.0*	473[A], 383[A], 364[A]
TA1535	**2AA**	1.0 µg	*89*	*10*	*5.2*	92[A], 78[A], 97[A]
TA1537	**2AA**	2.0 µg	*37*	*3*	*4.1*	40[A], 34[A], 38[A]
WP2uvrA	**2AA**	15 µg	*332*	*54*	*13.8*	351[A], 373[A], 271[A]

Key to Positive Controls

2AA 2-aminoanthracene

Key to Plate Postfix Codes

1 Normal background
NP Non-interfering particulate

Key to Automatic Count Flags

[A]: Automatic count

In Vitro Micronucleus Assay in Human Perpherial Blood Lymphocytes: S2218

TABLE 17

PRELIMINARY TOXICITY ASSAY USING S2218
IN THE ABSENCE OF EXOGENOUS METABOLIC ACTIVATION
4-HOUR TREATMENT, 24-HOUR HARVEST

Treatment Condition µg/mL	Total # of Cells Counted	Count per total cells Cells with # of nuclei 1	2	>2	CBPI[1]	Cytotoxicity[2]
DMSO	500	242	252	6	1.528	
S2218						
0.2	500	249	246	5	1.512	3%
0.6	500	237	255	8	1.542	-3%
2	500	238	251	11	1.546	-3%
6	500	251	246	3	1.504	5%
20	500	252	234	14	1.524	1%
60	500	257	238	5	1.496	6%
200	500	251	239	10	1.518	2%
600	500	254	240	6	1.504	5%
2000 p	500	248	242	10	1.524	1%

[1]CBPI = Cytokinesis-Block Proliferation Index

[2]Relative to vehicle control

p: Visible precipitate was observed in the treatment medium at the conclusion of the treatment period.

TABLE 18

PRELIMINARY TOXICITY ASSAY USING S2218
IN THE PRESENCE OF EXOGENOUS METABOLIC ACTIVATION
4-HOUR TREATMENT, 24-HOUR HARVEST

Treatment Condition µg/mL	Total # of Cells Counted	Count per total cells Cells with # of nuclei 1	2	>2	CBPI[1]	Cytotoxicity[2]
DMSO	500	197	300	3	1.612	
S2218						
0.2	500	220	274	6	1.572	7%
0.6	500	224	272	4	1.560	8%
2	500	240	255	5	1.530	13%
6	500	234	262	4	1.540	12%
20	500	232	261	7	1.550	10%
60	500	231	260	9	1.556	9%
200	500	268	226	6	1.476	22%
600	500	230	265	5	1.550	10%
2000 p	500	232	260	8	1.552	10%

[1]CBPI = Cytokinesis-Block Proliferation Index

[2]Relative to vehicle control

p: Visible precipitate was observed in the treatment medium at the conclusion of the treatment period.

TABLE 19

PRELIMINARY TOXICITY ASSAY USING S2218
IN THE ABSENCE OF EXOGENOUS METABOLIC ACTIVATION
24-HOUR TREATMENT, 24-HOUR HARVEST

Treatment Condition µg/mL	Total # of Cells Counted	Count per total cells Cells with # of nuclei 1	2	>2	CBPI[1]	Cytotoxicity[2]
DMSO	500	232	246	22	1.580	
S2218						
0.2	500	198	284	18	1.640	-10%
0.6	500	252	233	15	1.526	9%
2	500	260	225	15	1.510	12%
6	500	254	234	12	1.516	11%
20	500	226	257	17	1.582	0%
60	500	246	234	20	1.548	6%
200	500	236	235	29	1.586	-1%
600	500	234	250	16	1.564	3%
2000 p	500	226	255	19	1.586	-1%

[1]CBPI = Cytokinesis-Block Proliferation Index

[2]Relative to vehicle control

p: Visible precipitate was observed in the treatment medium at the conclusion of the treatment period.

TABLE 20

CONCURRENT CYTOTOXICITY TEST USING S2218
IN THE ABSENCE OF EXOGENOUS METABOLIC ACTIVATION
4-HOUR TREATMENT, 24-HOUR HARVEST

Treatment Condition µg/mL	Replicate Culture	Total # of Cells Counted	Count per total cells Cells with # of nuclei 1	2	>2	CBPI[1]	Cytotoxicity[2]
DMSO	A	500	181	299	20	1.668	
	B	500	186	299	15		
S2218							
100	A	500	181	301	18	1.652	2%
	B	500	199	287	14		
250	A	500	185	295	20	1.679	-2%
	B	508	179	309	20		
500	A	500	176	305	19	1.678	-1%
	B	500	180	305	15		
1000	A	500	163	316	21	1.705	-6%
	B	500	173	307	20		
1500	A	500	206	277	17	1.628	6%
	B	500	198	287	15		
2000 p	A	500	166	316	18	1.698	-4%
	B	500	170	314	16		

[1]CBPI = Cytokinesis-Block Proliferation Index

[2]Relative to vehicle control

p: Visible precipitate was observed in the treatment medium at the conclusion of the treatment period.

TABLE 21

CONCURRENT CYTOTOXICITY TEST USING S2218
IN THE PRESENCE OF EXOGENOUS METABOLIC ACTIVATION
4-HOUR TREATMENT, 24-HOUR HARVEST

Treatment Condition µg/mL	Replicate Culture	Total # of Cells Counted	Count per total cells Cells with # of nuclei 1	2	>2	CBPI[1]	Cytotoxicity[2]
DMSO	A	500	180	311	9	1.667	
	B	500	172	318	10		
S2218							
100	A	500	188	297	15	1.642	4%
	B	500	196	293	11		
250	A	500	184	308	8	1.663	1%
	B	500	173	315	12		
500	A	500	169	317	14	1.701	-5%
	B	500	154	336	10		
1000	A	500	159	322	19	1.702	-5%
	B	500	166	326	8		
1500	A	500	162	326	12	1.696	-4%
	B	500	165	324	11		
2000 p	A	500	169	316	15	1.697	-4%
	B	500	162	325	13		
CP, 2.5	A	500	276	223	1	1.445	33%
	B	500	281	218	1		
CP, 5	A	500	325	175	0	1.346	48%
	B	500	330	169	1		
CP, 7.5	A	500	361	138	1	1.267	60%
	B	500	374	125	1		

[1]CBPI = Cytokinesis-Block Proliferation Index

[2]Relative to vehicle control

p: Visible precipitate was observed in the treatment medium at the conclusion of the treatment period.

TABLE 22

CONCURRENT CYTOTOXICITY TEST USING S2218
IN THE ABSENCE OF EXOGENOUS METABOLIC ACTIVATION
24-HOUR TREATMENT, 24-HOUR HARVEST

Treatment Condition µg/mL	Replicate Culture	Total # of Cells Counted	Count per total cells Cells with # of nuclei 1	2	>2	CBPI[1]	Cytotoxicity[2]
DMSO	A	500	162	281	57	1.788	
	B	500	157	293	50		
S2218							
100	A	500	162	290	48	1.773	2%
	B	500	156	301	43		
250	A	500	150	310	40	1.770	2%
	B	500	161	298	41		
500	A	500	154	301	45	1.784	1%
	B	500	155	297	48		
1000 p	A	500	168	290	42	1.755	4%
	B	500	163	293	44		
1500 p	A	500	171	290	39	1.747	5%
	B	500	166	289	45		
2000 p	A	500	167	290	43	1.748	5%
	B	500	170	288	42		
VB, 5 ng/mL	A	500	180	270	50	1.750	5%
	B	500	173	274	53		
VB, 7.5 ng/mL	A	500	181	277	42	1.699	11%
	B	500	201	260	39		
VB, 10 ng/mL	A	500	413	75	12	1.186	76%
	B	500	421	71	8		

[1]CBPI = Cytokinesis-Block Proliferation Index

[2]Relative to vehicle control

p: Visible precipitate was observed in the treatment medium at the conclusion of the treatment period.

TABLE 23

MICRONUCLEUS ANALYSIS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES TREATED WITH S2218 IN THE ABSENCE OF EXOGENOUS METABOLIC ACTIVATION

DEFINITIVE ASSAY: 4-HOUR TREATMENT, 24-HOUR HARVEST

Treatment µg/mL	Replicate Culture	Total # of Cells Counted	Percentage of Micronucleated Binucleated Cells per culture	Average Percent Micronucleated Binucleated Cells per Dose
DMSO	A	1000	0.4%	0.4%
	B	1000	0.3%	
S2218				
500	A	1000	0.2%	0.2%
	B	1000	0.1%	
1000	A	1000	0.2%	0.2%
	B	1000	0.2%	
2000 p	A	1000	0.3%	0.3%
	B	1000	0.3%	

p: Visible precipitate was observed in the treatment medium at the conclusion of the treatment period.

TABLE 24

MICRONUCLEUS ANALYSIS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES TREATED WITH S2218 IN THE PRESENCE OF EXOGENOUS METABOLIC ACTIVATION

DEFINITIVE ASSAY: 4-HOUR TREATMENT, 24-HOUR HARVEST

Treatment µg/mL	Replicate Culture	Total # of Cells Counted	Percentage of Micronucleated Binucleated Cells per culture	Average Percent Micronucleated Binucleated Cells per Dose
DMSO	A	1000	0.3%	0.4%
	B	1000	0.4%	
S2218				
500	A	1000	0.3%	0.3%
	B	1000	0.2%	
1000	A	1000	0.1%	0.1%
	B	1000	0.1%	
2000 p	A	1000	0.4%	0.3%
	B	1000	0.2%	
CP, 5	A	1000	1.5%	1.3%**
	B	1000	1.1%	

p: Visible precipitate was observed in the treatment medium at the conclusion of the treatment period.

** $p \leq 0.01$, Fisher's exact test, relative to the solvent control.

TABLE 25

MICRONUCLEUS ANALYSIS OF HUMAN PERIPHERAL BLOOD LYMPHOCYTES TREATED WITH S2218 IN THE ABSENCE OF EXOGENOUS METABOLIC ACTIVATION

DEFINITIVE ASSAY: 24-HOUR TREATMENT, 24-HOUR HARVEST

Treatment µg/mL	Replicate Culture	Total # of Cells Counted	Percentage of Micronucleated Binucleated Cells per culture	Average Percent Micronucleated Binucleated Cells per Dose
DMSO	A	1000	0.1%	0.2%
	B	1000	0.2%	
S2218				
250	A	1000	0.4%	0.3%
	B	1000	0.2%	
500	A	1000	0.1%	0.2%
	B	1000	0.2%	
1000 p	A	1000	0.4%	0.3%
	B	1000	0.2%	
VB, 7.5 ng/mL	A	1000	0.9%	1.0%**
	B	1000	1.1%	

p: Visible precipitate was observed in the treatment medium at the conclusion of the treatment period.

** $p \leq 0.01$, Fisher's exact test, relative to the solvent control.

28-Day Dose Range-Finding Toxicology Study of S2218 in Sprague-Dawley Rats

Study Design

Three treatment groups of eight male and eight female CD® [Crl:CD®(SD)] rats were administered the test article in the diet at dose levels of 10, 30, and 100 mg/kg/day. One additional group of eight 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 twice weekly during Weeks 1 and 2and weekly during Weeks 3 and 4 during the study. Compound consumption was calculated at the same intervals as food consumption. Ophthalmoscopic examinations were conducted pre-test 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/day.

Table 26. Group Assignments

Group Number	Dose Level (mg/kg/day)	Number of Animals	
		Male	Female
1/2	0	8	8
3/4	10	8	8
5/6	30	8	8
7/8	100	8	8

[a]Odd group numbers apply to males and even group numbers apply to females.

Table 27. Organs or Tissues Weighed, Preserved, and Microscopically Examined

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination 1,2,7,8	Microscopic Examination 3,4,5,6
Adrenal glands	X	X		
Aorta		X		
Bone with bone marrow, femur		X		
Bone with bone marrow, sternum		X		
Bone marrow smear		X		
Brain	X	X		
Epididymides	X	X		
Esophagus		X		
Eye (with optic nerve)		X		
GALT (Gut-Associated Lymphoid Tissue)		X		
Heart	X	X		
Gross lesions (including tissue masses)		X	X	X
Joint, tibiofemoral		X		
Kidneys	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		
Lymph node, mesenteric		X		
Mammary gland (process females only)		X		
Nerve, sciatic		X		
Ovaries	X	X		
Oviducts		X		
Pancreas		X		
Pituitary	X	X		
Potential Target Organs		X	X	X
Prostate gland	X	X		
Salivary gland, mandibular		X		
Salivary gland, parotid		X		
Salivary gland, sublingual		X		
Seminal vesicles with coagulating glands		X		
Skeletal muscle, biceps femoris		X		

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination	
			1,2,7,8	3,4,5,6
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		
Testes	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		

Table 28-1. Summary of Body Weights - Male
MPI Research Study No. 1646-028
S2218: A 28 Day Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Day)	0 mg/kg/day Mean	SD	N	10 mg/kg/day Mean	SD	N	30 mg/kg/day Mean	SD	N	100 mg/kg/day Mean	SD	N
Body Weight g													
	1	227.1	12.06	8	228.0	12.96	8	227.4	10.58	8	229.1	13.03	8
	4	253.5	10.73	8	257.9	14.41	8	258.1	11.92	8	257.3	13.36	8
	7	276.4	10.01	8	281.8	14.97	8	281.5	12.08	8	280.9	14.51	8
	11	303.1	12.52	8	312.4	18.20	8	309.6	13.23	8	308.3	17.40	8
	14	324.4	10.11	8	338.3	21.00	8	327.8	16.17	8	331.3	21.43	8
	21	359.4	14.36	8	377.0	25.94	8	371.8	18.48	8	366.6	27.19	8
	28	396.0	16.15	8	418.8	34.11	8	412.6	22.75	8	402.4	28.43	8

Table 28-2. Summary of Body Weights - Female
MPI Research Study No. 1646-028
S2218: A 28 Day Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Day)	0 mg/kg/day Mean	SD	N	10 mg/kg/day Mean	SD	N	30 mg/kg/day Mean	SD	N	100 mg/kg/day Mean	SD	N
Body Weight g													
	1	193.8	10.15	8	192.6	11.96	8	189.9	7.32	8	188.6	8.30	8
	4	202.3	10.51	8	205.0	15.35	8	203.8	7.67	8	201.6	10.10	8
	7	209.6	13.03	8	209.0	12.54	8	208.1	9.33	8	210.4	6.63	8
	11	221.0	12.80	8	218.1	13.94	8	217.4	8.57	8	219.0	8.30	8
	14	225.4	14.19	8	222.0	14.09	8	221.4	12.78	8	223.5	12.44	8
	21	237.1	12.26	8	229.6	15.19	8	232.0	11.34	8	236.3	13.80	8
	28	243.0	10.23	8	241.5	23.02	8	242.1	13.78	8	245.6	16.53	8

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

Table 29-1. Summary of Food Consumption Values - Male
MPI Research Study No. 1646-028
S2218: A 28 Day Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Day)	0 mg/kg/day Mean	SD	N	10 mg/kg/day Mean	SD	N	30 mg/kg/day Mean	SD	N	100 mg/kg/day Mean	SD	N
Food Consumption g/animal/day													
	1-4	21.04	0.950	8	23.04[a]	1.676	8	22.21	1.425	8	22.50	1.737	8
	4-7	22.79	1.284	8	24.96[a]	1.046	8	24.04	0.967	8	23.75	2.144	8
	7-11	22.78	1.198	8	24.91	1.793	8	24.31	1.100	8	24.06	2.570	8
	11-14	23.63	1.327	8	26.92[a]	2.335	8	24.33	2.594	8	25.04	2.264	8
	14-21	23.80	1.372	8	26.57[a]	1.997	8	25.21	1.613	8	24.66	2.713	8
	21-28	23.80	0.907	8	27.02[a]	2.972	8	25.63	1.913	8	24.91	2.261	8

Table 29-2. Summary of Food Consumption Values - Female
MPI Research Study No. 1646-028
S2218: A 28 Day Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Day)	0 mg/kg/day Mean	SD	N	10 mg/kg/day Mean	SD	N	30 mg/kg/day Mean	SD	N	100 mg/kg/day Mean	SD	N
Food Consumption g/animal/day													
	1-4	14.88	0.872	8	15.96	2.615	8	15.00	0.797	8	15.38	1.419	8
	4-7	16.33	1.447	8	16.08	2.045	8	15.58	1.109	8	17.50	2.316	8
	7-11	15.22	1.073	8	18.25	7.932	8	15.34	1.281	8	15.16	1.802	8
	11-14	16.00	0.797	8	17.50	2.462	8	17.21	1.708	8	18.29	1.201	8
	14-21	16.18	1.361	8	18.13	5.626	8	16.04	2.837	8	17.18	1.707	8
	21-28	15.63	1.821	8	18.38	4.918	8	15.73	1.541	8	17.45	2.342	8

N – Number of measures used to calculate mean [a] Significantly different from control ($p<0.05$)
SD – Standard Deviation

Table 30-1. Summary of Compound Consumption Values - Male
MPI Research Study No. 1646-028
S2218: A 28 Day Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Day)	0 mg/kg/day Mean	SD	N	10 mg/kg/day Mean	SD	N	30 mg/kg/day Mean	SD	N	100 mg/kg/day Mean	SD	N
Compound Consumption mg/kg/day													
	1-4	0.000	0.0000	8	14.071	1.3995	8	40.710	2.7646	8	136.464	10.5733	8
	4-7	0.000	0.0000	8	13.464	0.8748	8	38.804	1.2861	8	128.220	10.9326	8
	7-11	0.000	0.0000	8	13.067	1.1424	8	38.231	1.5385	8	126.308	11.2617	8
	11-14	0.000	0.0000	8	12.728	1.1559	8	34.798	3.6075	8	119.774	7.8038	8
	14-21	0.000	0.0000	8	10.703	0.8260	8	31.412	1.8983	8	101.103	6.6990	8
	21-28	0.000	0.0000	8	10.830	1.1197	8	33.071	1.4838	8	107.166	6.0108	8

Table 30-2. Summary of Compound Consumption Values - Female
MPI Research Study No. 1646-028
S2218: A 28 Day Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Day)	0 mg/kg/day Mean	SD	N	10 mg/kg/day Mean	SD	N	30 mg/kg/day Mean	SD	N	100 mg/kg/day Mean	SD	N
Compound Consumption mg/kg/day													
	1-4	0.000	0.0000	8	10.707	1.4959	8	30.666	0.9638	8	105.597	10.1018	8
	4-7	0.000	0.0000	8	10.128	0.6468	8	29.734	2.4768	8	112.582	16.3188	8
	7-11	0.000	0.0000	8	13.099	4.7429	8	33.729	3.0300	8	109.658	11.8316	8
	11-14	0.000	0.0000	8	12.177	1.0886	8	36.199	3.6003	8	127.342	9.2113	8
	14-21	0.000	0.0000	8	12.632	3.9406	8	33.590	4.9666	8	118.928	8.6043	8
	21-28	0.000	0.0000	8	10.429	2.4254	8	27.159	2.7634	8	96.614	10.3291	8

N – Number of measures used to calculate mean
SD – Standard Deviation
No statistical analysis performed

Table 31-1. Summary of Hematology Values - Male
MPI Research Study No. 1646-028
S2218: A 28 Day Dietary Administration Toxicity Study in Rats

	Study	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Interval	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Leukocytes $10^3/\mu L$	Terminal	11.39	2.040	8	12.94	1.275	8	11.94	3.335	8	11.34	2.508	8
Erythrocytes $10^6/\mu L$	Terminal	8.218	0.2406	8	8.241	0.4730	8	8.061	0.3959	8	8.143	0.6774	8
Hemoglobin g/dL	Terminal	16.13	0.362	8	16.10	0.769	8	16.24	0.573	8	16.03	1.283	8
Hematocrit %	Terminal	51.29	1.143	8	51.75	2.670	8	51.24	1.694	8	50.61	3.833	8
MCV fL	Terminal	62.43	1.449	8	62.86	2.861	8	63.64	2.404	8	62.19	0.934	8
MCH pg	Terminal	19.65	0.359	8	19.58	0.698	8	20.16	0.838	8	19.71	0.285	8
MCHC g/dL	Terminal	31.46	0.424	8	31.13	0.489	8	31.66	0.542	8	31.69	0.728	8
Platelets $10^3/\mu L$	Terminal	1167.9	164.58	8	1150.0	142.92	8	1056.5	116.17	8	1076.6	259.22	8
Absolute Reticulocytes $10^3/\mu L$	Terminal	209.70	24.362	8	208.40	41.995	8	244.44	26.968	8	209.99	38.156	8
Neutrophils $10^3/\mu L$	Terminal	1.045	0.3592	8	1.266	0.2580	8	1.176	0.6971	8	1.360	0.3901	8
Lymphocytes $10^3/\mu L$	Terminal	9.846	1.9521	8	11.095	1.1140	8	10.275	2.7209	8	9.559	2.5467	8

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

Table 31-1. Summary of Hematology Values – Male (continued)
MPI Research Study No. 1646-028
S2218: A 28 Day Dietary Administration Toxicity Study in Rats

	Study	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Interval	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Monocytes $10^3/\mu L$	Terminal	0.189	0.0620	8	0.255	0.0873	8	0.179	0.0692	8	0.185	0.0804	8
Eosinophils $10^3/\mu L$	Terminal	0.068	0.0231	8	0.080	0.0251	8	0.088	0.0373	8	0.078	0.0287	8
Basophils $10^3/\mu L$	Terminal	0.078	0.0427	8	0.069	0.0181	8	0.066	0.0233	8	0.060	0.0193	8
Other Cells $10^3/\mu L$	Terminal	0.135	0.0605	8	0.175	0.0682	8	0.139	0.0522	8	0.105	0.0220	8
RDW %	Terminal	11.20	0.200	8	11.25	0.330	8	11.41	0.383	8	11.39	0.426	8

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

Table 31-2. Summary of Hematology Values - Female
MPI Research Study No. 1646-028
S2218: A 28 Day Dietary Administration Toxicity Study in Rats

	Study	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Interval	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Leukocytes $10^3/\mu L$	Terminal	9.09	2.554	8	11.13	2.193	8	10.65	2.794	8	12.11	2.463	8
Erythrocytes $10^6/\mu L$	Terminal	7.869	0.3081	8	8.036	0.4430	8	8.168	0.3416	8	7.945	0.1822	8
Hemoglobin g/dL	Terminal	15.18	0.565	8	15.45	0.717	8	15.79	0.562	8	15.53	0.498	8
Hematocrit %	Terminal	47.04	2.023	8	48.13	2.097	8	49.03	1.497	8	47.48	1.094	8
MCV fL	Terminal	59.79	1.753	8	59.98	2.371	8	60.05	1.577	8	59.76	1.998	8
MCH pg	Terminal	19.31	0.617	8	19.25	0.791	8	19.30	0.507	8	19.54	0.534	8
MCHC g/dL	Terminal	32.33	0.528	8	32.13	0.592	8	32.15	0.400	8	32.70	0.713	8
Platelets $10^3/\mu L$	Terminal	1071.1	141.99	8	1100.9	173.85	8	1169.6	151.40	8	909.4	294.50	8
Absolute Reticulocytes $10^3/\mu L$	Terminal	186.19	44.192	8	199.31	37.972	8	197.81	29.666	8	194.28	40.315	8
Neutrophils $10^3/\mu L$	Terminal	1.061	0.2558	8	1.206	0.6128	8	1.051	0.3983	8	1.289	0.5909	8
Lymphocytes $10^3/\mu L$	Terminal	7.628	2.3150	8	9.374	1.5215	8	9.221	2.5315	8	10.333	2.4072	8

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

Table 31-2. Summary of Hematology Values – Female (continued)
MPI Research Study No. 1646-028
S2218: A 28 Day Dietary Administration Toxicity Study in Rats

	Study	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Interval	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Monocytes $10^3/\mu L$	Terminal	0.166	0.0616	8	0.201	0.0824	8	0.138	0.0590	8	0.179	0.0700	8
Eosinophils $10^3/\mu L$	Terminal	0.066	0.0130	8	0.074	0.0250	8	0.066	0.0169	8	0.074	0.0192	8
Basophils $10^3/\mu L$	Terminal	0.041	0.0136	8	0.061[a]	0.0173	8	0.058	0.0271	8	0.066[a]	0.0151	8
Other Cells $10^3/\mu L$	Terminal	0.123	0.0512	8	0.194	0.1412	8	0.120	0.0484	8	0.173	0.0542	8
RDW %	Terminal	11.03	0.365	8	11.08	0.276	8	10.85	0.278	8	11.25	0.438	8

N – Number of measures used to calculate mean [a] Significantly different from control ($p<0.05$)
SD – Standard Deviation

Table 32-1. Summary of Coagulation Values - Male
MPI Research Study No. 1646-028
S2218: A 28 Day Dietary Administration Toxicity Study in Rats

		0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Study Interval	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
APTT sec	Terminal	15.48	2.347	8	12.68[a]	2.614	8	15.19	1.671	8	15.00	1.773	7
Prothrombin Time sec	Terminal	17.21	0.751	8	16.76	0.964	8	17.10	0.609	8	16.94	0.629	7
Fibrinogen mg/dL	Terminal	290.3	23.83	8	316.5	33.44	8	288.0	25.64	8	304.0	24.30	7

N – Number of measures used to calculate mean [a] Significantly different from control ($p<0.05$)
SD – Standard Deviation

Table 32-2. Summary of Coagulation Values - Female
MPI Research Study No. 1646-028
S2218: A 28 Day Dietary Administration Toxicity Study in Rats

		0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Study Interval	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
APTT sec	Terminal	13.04	2.203	8	13.83	1.475	8	12.70	1.632	8	12.66	2.147	7
Prothrombin Time sec	Terminal	16.94	0.588	8	16.94	0.513	8	17.10	0.678	8	16.83	0.538	7
Fibrinogen mg/dL	Terminal	241.9	18.73	8	252.9	15.01	8	258.5	19.05	8	260.0	24.22	7

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

Table 33-1. Summary of Clinical Chemistry Values - Male
MPI Research Study No. 1646-028
S2218: A 28 Day Dietary Administration Toxicity Study in Rats

	Study	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Interval	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Sodium mEq/L	Terminal	147.1	2.90	8	146.6	1.06	8	146.6	2.07	8	147.0	1.53	7
Potassium mEq/L	Terminal	8.46	1.368	8	8.65	1.296	8	8.55	1.840	8	7.93	0.918	7
Chloride mEq/L	Terminal	99.0	1.77	8	99.1	1.64	8	99.9	2.03	8	98.6	1.13	7
Calcium mg/dL	Terminal	11.88	0.354	8	12.59[a]	0.587	8	11.63	0.512	8	12.23	0.528	7
Phosphorus mg/dL	Terminal	11.98	0.568	8	11.93	1.018	8	12.15	1.094	8	11.39	0.809	7
Alkaline Phosphatase U/L	Terminal	191.4	34.31	8	209.0	61.40	8	192.1	58.05	8	191.4	27.50	7
Total Bilirubin mg/dL	Terminal	0.10	0.000	8	0.10	0.000	8	0.11	0.035	8	0.10	0.000	7
AST U/L	Terminal	65.8	8.46	8	66.1	9.82	8	67.9	6.29	8	63.6	6.32	7
ALT U/L	Terminal	31.4	3.62	8	32.5	11.45	8	30.1	2.80	8	29.9	3.13	7
Urea Nitrogen mg/dL	Terminal	13.5	0.76	8	15.1	1.73	8	15.1	1.89	8	13.7	1.25	7
Creatinine mg/dL	Terminal	0.31	0.035	8	0.35	0.053	8	0.34	0.052	8	0.33	0.049	7

N – Number of measures used to calculate mean [a] Significantly different from control ($p<0.05$)
SD – Standard Deviation

Table 33-1. Summary of Clinical Chemistry Values – Male (continued)
MPI Research Study No. 1646-028
S2218: A 28 Day Dietary Administration Toxicity Study in Rats

	Study	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Interval	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Total Protein g/dL	Terminal	6.34	0.316	8	6.48	0.337	8	6.25	0.220	8	6.60	0.346	7
Albumin g/dL	Terminal	3.20	0.131	8	3.25	0.141	8	3.28	0.089	8	3.34	0.098	7
Globulin g/dL	Terminal	3.14	0.213	8	3.23	0.238	8	2.98	0.175	8	3.26	0.321	7
Albumin/Globulin Ratio	Terminal	1.01	0.035	8	1.00	0.076	8	1.11[a]	0.064	8	1.04	0.098	7
Triglyceride mg/dL	Terminal	54.3	17.66	8	69.5	21.78	8	52.0	20.65	8	52.9	15.05	7
Cholesterol mg/dL	Terminal	59.5	8.93	8	65.4	18.65	8	61.0	8.28	8	61.6	6.73	7
Glucose mg/dL	Terminal	212.9	37.82	8	310.8[b]	80.81	8	175.8	58.52	8	248.3	42.73	7

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

[a] Significantly different from control (p<0.05)
[b] Significantly different from control (p<0.01)

Table 33-2. Summary of Clinical Chemistry Values - Female
MPI Research Study No. 1646-028
S2218: A 28 Day Dietary Administration Toxicity Study in Rats

	Study	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Interval	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Sodium mEq/L	Terminal	144.1	1.81	8	144.0	2.78	8	143.1	2.90	8	144.5	1.60	8
Potassium mEq/L	Terminal	9.30	2.520	8	9.80	2.161	8	11.14	2.358	8	9.40	1.563	8
Chloride mEq/L	Terminal	100.9	1.73	8	101.1	1.36	8	101.9	2.03	8	101.1	2.23	8
Calcium mg/dL	Terminal	11.69	0.636	8	11.88	0.413	8	12.00	0.602	8	11.86	0.496	8
Phosphorus mg/dL	Terminal	10.76	1.733	8	10.65	1.666	8	11.99	1.218	8	10.80	1.228	8
Alkaline Phosphatase U/L	Terminal	105.1	37.70	8	115.4	21.90	8	109.6	34.21	8	115.6	26.26	8
Total Bilirubin mg/dL	Terminal	0.18	0.046	8	0.15	0.053	8	0.15	0.053	8	0.16	0.052	8
AST U/L	Terminal	85.0	46.94	8	88.1	34.08	8	78.4	21.63	8	91.6	54.46	8
ALT U/L	Terminal	34.8	16.54	8	36.8	23.17	8	30.5	7.63	8	41.3	28.59	8
Urea Nitrogen mg/dL	Terminal	17.0	3.70	8	15.5	1.69	8	16.1	2.23	8	15.4	2.13	8
Creatinine mg/dL	Terminal	0.39	0.035	8	0.38	0.046	8	0.38	0.089	8	0.39	0.035	8

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

Table 33-2. Summary of Clinical Chemistry Values – Female (continued)
MPI Research Study No. 1646-028
S2218: A 28 Day Dietary Administration Toxicity Study in Rats

	Study	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Interval	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Total Protein g/dL	Terminal	7.03	0.266	8	7.36	0.311	8	7.10	0.393	8	7.21	0.217	8
Albumin g/dL	Terminal	3.70	0.131	8	3.78	0.198	8	3.66	0.283	8	3.73	0.149	8
Globulin g/dL	Terminal	3.33	0.167	8	3.59[a]	0.203	8	3.44	0.151	8	3.49	0.136	8
Albumin/Globulin Ratio	Terminal	1.15	0.053	8	1.05[a]	0.076	8	1.08	0.071	8	1.08	0.071	8
Triglyceride mg/dL	Terminal	46.6	6.37	8	43.1	12.33	8	44.4	15.67	8	44.4	7.84	8
Cholesterol mg/dL	Terminal	64.4	8.40	8	77.5	17.04	8	71.0	11.43	8	63.9	12.65	8
Glucose mg/dL	Terminal	184.6	74.33	8	176.0	45.78	8	203.0	75.32	8	189.5	70.76	8

N – Number of measures used to calculate mean
SD – Standard Deviation
[a] Significantly different from control ($p<0.05$)

Table 34-1. Summary of Urinalysis Values – Male
MPI Research Study No. 1646-028
S2218: A 28 Day Dietary Administration Toxicity Study in Rats

		0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Study Interval	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Volume mL	Terminal	7.38	3.682	8	8.56	4.656	8	15.19	1.671	8	2.81	1.668	8
Specific Gravity	Terminal	1.0479*	0.02254*	8*	1.0523*	0.02493*	8*	1.0658*	0.02820*	8*	1.0808*	0.01734*	8*
pH	Terminal	7.56	0.821	8	7.31	0.530	8	6.81[a]	0.372	8	6.69[a]	0.530	8

N – Number of measures used to calculate mean * Calculation includes one or more individual value(s) out of linear range
SD – Standard Deviation [a] Significantly different from control (p<0.05)

Table 34-2. Summary of Urinalysis Values – Female
MPI Research Study No. 1646-028
S2218: A 28 Day Dietary Administration Toxicity Study in Rats

		0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Study Interval	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Volume mL	Terminal	4.06	2.705	8	5.75	5.113	8	3.99	3.207	7	2.88	2.311	8
Specific Gravity	Terminal	1.0538*	0.03399*	8*	1.0571*	0.03392*	8*	1.0587*	0.01936*	7	1.0769*	0.01956*	8*
pH	Terminal	6.81	0.530	8	6.94	0.776	8	7.08	0.376	6	6.63	0.443	8

N – Number of measures used to calculate mean * Calculation includes one or more individual value(s) out of linear range
SD – Standard Deviation [a] Significantly different from control (p<0.05)

Table 35-1. Summary of Macroscopic Observations – Male
MPI Research Study No. 1646-028
S2218: A 4-Week Dietary Administration Toxicity Study in Rats

Tissue Observation	Severity	0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Number of Animals Examined		8	8	8	8
all tissues					
within normal limits		8	8	7	7
epididymides					
small	- mild	0	0	0	1
small intestine, jejunum					
enlarged	- mild	0	0	1	0
testes					
small	- mild	0	0	0	1

Table 35-2. Summary of Macroscopic Observations – Female
MPI Research Study No. 1646-028
S2218: A 4-Week Dietary Administration Toxicity Study in Rats

Tissue Observation	Severity	0 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Number of Animals Examined		8	8	8	8
all tissues					
within normal limits		8	8	7	8
uterus with cervix					
enlarged	- mild	0	0	1	8

Table 36-1. Summary of Organ Weight Values – Male
MPI Research Study No. 1646-028
S2218: A 4-Week Dietary Administration Toxicity Study in Rats

	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body weight												
g	365	18	8	389	33	8	380	23	8	374	29	8
Brain												
g	2.010	0.055	8	1.942	0.178	8	2.038	0.041	8	1.973	0.094	8
Brain/BWt												
%	0.5515	0.0193	8	0.5020	0.0567	8	0.5386	0.0372	8	0.5313	0.0526	8
Adrenal gl												
g	0.069	0.016	8	0.067	0.013	8	0.064	0.008	8	0.061	0.010	8
Adrenal gl/BWt												
%	0.0190	0.0045	8	0.0175	0.0038	8	0.0168	0.0019	8	0.0164	0.0029	8
Adrenal gl/BrWt												
ratio	0.0345	0.0085	8	0.0347	0.0053	8	0.0313	0.0038	8	0.0309	0.0047	8
Epididymides												
g	1.053	0.113	8	1.058	0.049	8	1.017	0.114	8	1.075	0.142	7
Epididymides/BWt												
%	0.2889	0.0316	8	0.2736	0.0227	8	0.2686	0.0336	8	0.2857	0.0440	7
Epididymides/BrWt												
ratio	0.5246	0.0636	8	0.5476	0.0400	8	0.4993	0.0593	8	0.5475	0.0825	7

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

Table 36-1. Summary of Organ Weight Values – Male (continued)
MPI Research Study No. 1646-028
S2218: A 4-Week Dietary Administration Toxicity Study in Rats

	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Heart												
g	1.350	0.134	8	1.505	0.122	8	1.511	0.209	8	1.399	0.108	8
Heart/BWt												
%	0.3693	0.0206	8	0.3880	0.0212	8	0.3981	0.0503	8	0.3751	0.0260	8
Heart/BrWt												
ratio	0.6710	0.0542	8	0.7810[a]	0.0942	8	0.7423	0.1086	8	0.7107	0.0716	8
Kidneys												
g	2.984	0.137	8	3.089	0.189	8	3.168	0.230	8	3.147	0.161	8
Kidneys/BWt												
%	0.8180	0.0198	8	0.7975	0.0488	8	0.8351	0.0535	8	0.8444	0.0396	8
Kidneys/BrWt												
ratio	1.4846	0.0581	8	1.6072	0.2209	8	1.5555	0.1313	8	1.5999	0.1373	8
Liver												
g	12.735	1.361	8	13.776	1.525	8	13.822	1.351	8	13.676	1.490	8
Liver/BWt												
%	3.4856	0.2555	8	3.5422	0.1991	8	3.6384	0.2595	8	3.6651	0.3618	8
Liver/BrWt												
ratio	6.3339	0.6163	8	7.1719	1.2018	8	6.7858	0.6997	8	6.9683	1.0037	8

N – Number of measures used to calculate mean
SD – Standard Deviation
[a] Significantly different from control ($p<0.05$)

Table 36-1. Summary of Organ Weight Values – Male (continued)
MPI Research Study No. 1646-028
S2218: A 4-Week Dietary Administration Toxicity Study in Rats

	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Lung w/ bronchi												
g	1.746	0.256	8	1.963	0.159	8	1.715	0.224	7	1.857	0.354	8
Lung w/ bronchi/BWt												
%	0.4773	0.0542	8	0.5061	0.0293	8	0.4529	0.0458	7	0.4983	0.1000	8
Lung w/ bronchi/BrWt												
ratio	0.8669	0.1099	8	1.0183	0.1187	8	0.8384	0.1186	7	0.9437	0.1907	8
Pituitary gl												
g	0.0141	0.0013	8	0.0154	0.0012	8	0.0154	0.0021	8	0.0153	0.0028	8
Pituitary gl/BWt												
%	0.0039	0.0003	8	0.0040	0.0004	8	0.0041	0.0005	8	0.0041	0.0006	8
Pituitary gl/BrWt												
ratio	0.0070	0.0006	8	0.0080	0.0010	8	0.0076	0.0011	8	0.0078	0.0017	8
Prostate gl												
g	1.075	0.129	8	1.106	0.264	8	1.158	0.191	8	1.101	0.153	8
Prostate gl/BWt												
%	0.2941	0.0255	8	0.2874	0.0748	8	0.3066	0.0599	8	0.2952	0.0393	8
Prostate gl/BrWt												
ratio	0.5341	0.0558	8	0.5682	0.1111	8	0.5670	0.0863	8	0.5609	0.0948	8

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

Table 36-1. Summary of Organ Weight Values – Male (continued)
MPI Research Study No. 1646-028
S2218: A 4-Week Dietary Administration Toxicity Study in Rats

	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Pituitary gl												
g	0.0141	0.0013	8	0.0154	0.0012	8	0.0154	0.0021	8	0.0153	0.0028	8
Pituitary gl/BWt												
%	0.0039	0.0003	8	0.0040	0.0004	8	0.0041	0.0005	8	0.0041	0.0006	8
Pituitary gl/BrWt												
ratio	0.0070	0.0006	8	0.0080	0.0010	8	0.0076	0.0011	8	0.0078	0.0017	8
Prostate gl												
g	1.075	0.129	8	1.106	0.264	8	1.158	0.191	8	1.101	0.153	8
Prostate gl/BWt												
%	0.2941	0.0255	8	0.2874	0.0748	8	0.3066	0.0599	8	0.2952	0.0393	8
Prostate gl/BrWt												
ratio	0.5341	0.0558	8	0.5682	0.1111	8	0.5670	0.0863	8	0.5609	0.0948	8
Spleen												
g	0.766	0.109	8	0.807	0.137	8	0.812	0.105	8	0.738	0.140	8
Spleen/BWt												
%	0.2098	0.0259	8	0.2078	0.0324	8	0.2141	0.0262	8	0.1972	0.0316	8
Spleen/BrWt												
ratio	0.3810	0.0501	8	0.4230	0.1078	8	0.3986	0.0527	8	0.3751	0.0736	8

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

Table 36-1. Summary of Organ Weight Values – Male (continued)
MPI Research Study No. 1646-028
S2218: A 4-Week Dietary Administration Toxicity Study in Rats

	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Testes												
g	3.352	0.090	8	3.477	0.164	8	3.547	0.237	8	3.515	0.329	7
Testes/BWt												
%	0.9204	0.0464	8	0.8985	0.0579	8	0.9368	0.0814	8	0.9324	0.0972	7
Testes/BrWt												
ratio	1.6685	0.0550	8	1.8079	0.2243	8	1.7411	0.1256	8	1.7863	0.1708	7
Thymus												
g	0.517	0.134	8	0.586	0.090	8	0.608	0.100	8	0.599	0.133	8
Thymus/BWt												
%	0.1409	0.0312	8	0.1508	0.0200	8	0.1605	0.0266	8	0.1594	0.0276	8
Thymus/BrWt												
ratio	0.2563	0.0614	8	0.3051	0.0646	8	0.2979	0.0458	8	0.3034	0.0655	8
Thyroid/parathyroid gl												
g	0.022	0.006	8	0.022	0.006	8	0.024	0.004	8	0.021	0.004	8
Thyroid/parathyroid gl/BWt												
%	0.0059	0.0017	8	0.0056	0.0013	8	0.0063	0.0011	8	0.0055	0.0010	8
Thyroid/parathyroid gl/BrWt												
ratio	0.0108	0.0030	8	0.0112	0.0025	8	0.0118	0.0017	8	0.0105	0.0021	8

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

Table 36-2. Summary of Organ Weight Values – Female
MPI Research Study No. 1646-028
S2218: A 4-Week Dietary Administration Toxicity Study in Rats

	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body weight												
g	227	14	8	221	17	8	222	13	8	227	12	8
Brain												
g	1.820	0.058	8	1.870	0.086	8	1.846	0.052	8	1.841	0.070	8
Brain/BWt												
%	0.8045	0.0512	8	0.8501	0.0852	8	0.8317	0.0380	8	0.8122	0.0396	8
Adrenal gl												
g	0.067	0.013	8	0.072	0.008	8	0.075	0.010	8	0.071	0.015	8
Adrenal gl/BWt												
%	0.0299	0.0072	8	0.0326	0.0043	8	0.0338	0.0047	8	0.0311	0.0064	8
Adrenal gl/BrWt												
ratio	0.0370	0.0075	8	0.0386	0.0048	8	0.0406	0.0050	8	0.0385	0.0093	8
Heart												
g	0.909	0.089	8	0.896	0.067	8	0.865	0.077	8	0.927	0.069	8
Heart/BWt												
%	0.4020	0.0466	8	0.4054	0.0268	8	0.3890	0.0274	8	0.4082	0.0194	8
Heart/BrWt												
ratio	0.5003	0.0552	8	0.4802	0.0476	8	0.4689	0.0434	8	0.5039	0.0375	8

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

Table 36-2. Summary of Organ Weight Values – Female (continued)
MPI Research Study No. 1646-028
S2218: A 4-Week Dietary Administration Toxicity Study in Rats

	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Kidneys												
g	1.755	0.062	8	1.810	0.238	8	1.848	0.148	8	1.739	0.119	8
Kidneys/BWt %	0.7757	0.0461	8	0.8162	0.0666	8	0.8313	0.0512	8	0.7661	0.0329	8
Kidneys/BrWt ratio	0.9651	0.0399	8	0.9703	0.1445	8	1.0014	0.0762	8	0.9451	0.0599	8
Liver												
g	7.972	0.686	8	7.932	0.720	8	8.114	0.570	8	7.949	0.933	8
Liver/BWt %	3.5248	0.3719	8	3.5858	0.2311	8	3.6565	0.2914	8	3.4945	0.2806	8
Liver/BrWt ratio	4.3881	0.4403	8	4.2518	0.4621	8	4.3998	0.3440	8	4.3234	0.5387	8
Lung w/ bronchi												
g	1.225	0.167	8	1.183	0.104	8	1.167	0.136	8	1.197	0.105	7
Lung w/ bronchi/BWt %	0.5426	0.0894	8	0.5345	0.0303	8	0.5246	0.0527	8	0.5275	0.0389	7
Lung w/ bronchi/BrWt ratio	0.6727	0.0866	8	0.6341	0.0706	8	0.6317	0.0673	8	0.6491	0.0621	7

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

Table 36-2. Summary of Organ Weight Values – Female (continued)
MPI Research Study No. 1646-028
S2218: A 4-Week Dietary Administration Toxicity Study in Rats

	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Ovaries												
g	0.099	0.019	8	0.089	0.019	8	0.091	0.009	8	0.090	0.023	8
Ovaries/BWt %	0.0434	0.0071	8	0.0403	0.0086	8	0.0409	0.0057	8	0.0395	0.0098	8
Ovaries/BrWt ratio	0.0545	0.0114	8	0.0476	0.0098	8	0.0491	0.0054	8	0.0488	0.0126	8
Pituitary gl												
g	0.0172	0.0029	7	0.0176	0.0033	8	0.0172	0.0030	8	0.0171	0.0034	8
Pituitary gl/BWt %	0.0076	0.0012	7	0.0080	0.0016	8	0.0077	0.0013	8	0.0075	0.0014	8
Pituitary gl/BrWt ratio	0.0095	0.0017	7	0.0094	0.0017	8	0.0093	0.0018	8	0.0093	0.0019	8
Spleen												
g	0.518	0.088	8	0.580	0.062	8	0.556	0.100	8	0.543	0.067	8
Spleen/BWt %	0.2285	0.0350	8	0.2626	0.0259	8	0.2489	0.0333	8	0.2385	0.0218	8
Spleen/BrWt ratio	0.2855	0.0514	8	0.3112	0.0398	8	0.3005	0.0476	8	0.2950	0.0373	8

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

Table 36-2. Summary of Organ Weight Values – Female (continued)
MPI Research Study No. 1646-028
S2218: A 4-Week Dietary Administration Toxicity Study in Rats

	0 mg/kg/day			10 mg/kg/day			30 mg/kg/day			100 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Thymus												
g	0.460	0.127	8	0.479	0.102	8	0.463	0.069	8	0.381	0.044	8
Thymus/BWt												
%	0.2016	0.0495	8	0.2170	0.0495	8	0.2077	0.0241	8	0.1677	0.0168	8
Thymus/BrWt												
ratio	0.2530	0.0700	8	0.2566	0.0550	8	0.2508	0.0356	8	0.2073	0.0261	8
Thyroid/parathyroid gl												
g	0.023	0.007	7	0.018	0.003	8	0.019	0.005	8	0.020	0.004	8
Thyroid/parathyroid gl/BWt												
%	0.0100	0.0037	7	0.0081	0.0012	8	0.0085	0.0021	8	0.0089	0.0017	8
Thyroid/parathyroid gl/BrWt												
ratio	0.0125	0.0042	7	0.0097	0.0019	8	0.0102	0.0025	8	0.0109	0.0023	8
Uterus w/ cervix												
g	0.463	0.071	8	0.558	0.105	8	0.623	0.219	8	0.610	0.167	8
Uterus w/ cervix/BWt												
%	0.2055	0.0396	8	0.2506	0.0332	8	0.2801	0.0949	8	0.2691	0.0765	8
Uterus w/ cervix/BrWt												
ratio	0.2546	0.0406	8	0.3000	0.0643	8	0.3377	0.1195	8	0.3303	0.0858	8

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

Table 37-1. Summary of Microscopic Observations – Male
MPI Research Study No. 1646-028
S2218: A 4-Week Dietary Administration Toxicity Study in Rats

Tissue Observation	Severity	0 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Number of Animals Examined		8	1	8
epididymides		(0)	(0)	(1)
oligspermia/germ cell debris, unilateral	- severe	0	0	1
liver		(8)	(0)	(8)
hematopoiesis, extramedulally, increased	- minimal	1	0	4
infiltration, mononuclear cell	- minimal	6	0	7
necrosis, focal	- minimal	1	0	2
vacuolation, hepatocellular	- minimal	7	0	7
small intestine, jejunum		(0)	(1)	(0)
dilation	- mild	0	1	0
testes		(0)	(0)	(1)
degeneration/atrophy, seminiferous tubules, unilateral	- severe	0	0	1

Table 37-2. Summary of Microscopic Observations – Female
MPI Research Study No. 1646-028
S2218: A 4-Week Dietary Administration Toxicity Study in Rats

Tissue Observation	Severity	0 mg/kg/day	30 mg/kg/day	100 mg/kg/day
Number of Animals Examined		8	1	8
liver		(8)	(0)	(8)
hematopoiesis, extramedulally, increased	- minimal	1	0	1
infiltration, mononuclear cell	- minimal	8	0	7
vacuolation, hepatocellular	- minimal	6	0	8
uterus with cervix		(0)	(1)	(0)
dilation	- mild	0	1	0

13 Week Toxicology Study of S2218 Sulfate Salt (S8069) in Rats

Study Design

Compound was administered in the diet to four groups of twenty male and twenty female CD® [Crl:CD®(SD)] rats at dose levels of 0 (control), 30, 70, and 140 mg/kg/day. Additionally, one control group of four animals/sex and three treated groups of eight 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, 30, 70, and 140 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 46, and again prior to termination. Urinalysis and samples for coagulation evaluations were collected prior to termination only.

Table 38. Group Assignments

Group	Number of Animals		Treatment	Dose Level (mg/kg/day)*	Number of Animals	
					Necropsy Day 92	
	M	F			M	F
Main Study						
1	20	-	Vehicle	0	20	-
2	-	20	Vehicle	0	-	20
3	20	-	S2218†	30	20	-
4	-	20	S2218†	30	-	20
5	20	-	S2218†	70	20	-
6	-	20	S2218†	70	-	20
7	20	-	S2218†	140	20	-
8	-	20	S2218†	140	-	20
Toxicokinetics						
9	3+1**	-	Vehicle	0	-	-
10	-	3+1**	Vehicle	0	-	-
11	6+2**	-	S2218†	30	-	-
12	-	6+2**	S2218†	30	-	-
13	6+2**	-	S2218†	70	-	-
14	-	6+2**	S2218†	70	-	-
15	6+2**	-	S2218†	140	-	-
16	-	6+2**	S2218†	140	-	-

* Dose levels were maintained by estimating the mean body weight and food consumption per sex per group and adjusting the concentration of test article in the formulated diets weekly. Separate diet preparations will be made for each concentration and sex.

****** Additional animals/sex/group included as possible replacement TK animals.

† Administered as the corresponding sulfate salt (S8069)

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 S2218. 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 91. Samples were collected from 2 cohorts of 3 animals/sex (treated animals) at pre-dose 1, 3, 6, 12, and 24 hours post the start of the dark cycle (18:00) on Days 7 and 91. The pre-dose samples were collected from the treated TK animals between 17:00 and 18:00 hours on Days 7 and 91. The animals were not fasted prior to blood collection. Samples were placed in tubes containing K_2EDTA 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 -60 to -90°C until analyzed.

Sample Preparation for Toxicokinetic Analysis
A 50 µL aliquot of sample was mixed with 25 µL of working internal standard (IS, S9284) solution (100 ng/mL). The sample was vortexed and 300 µL of acetonitrile was added. The sample was vortexed, refrigerated, centrifuged, and a 200 µL aliquot of the resulting supernatant was transferred to a clean 96-well plate. The sample was evaporated and then reconstituted with 150 µL of water/acetonitrile (83/17, v/v), and an aliquot was injected onto an LC-MS/MS system for analysis.

Analytical Method
The liquid chromatography system used a Waters XBridge C18 column, 2.1 x 50 mm (2.5 µm particle size) with a gradient flow consisting of water/acetonitrile/formic acid (95/5/1, v/v/v) and acetonitrile/water/formic acid (95/5/1, v/v/v) at a flow rate of 750 µL/minute. The analyte and internal standard were detected using a SCIEX API 5000 triple quadrupole LC-MS/MS system equipped with an ESI (TurboIonSpray®) ionization source operated in the positive ion mode. The following MRM transitions of the respective $[M+H]^+$ ions were used to monitor S2218 and S9284.

Compound	Transition Monitored	Retention Time
S2218 (analyte)	*m/z* 418 → 205	0.3 – 0.8 min
S9284 (IS)	*m/z* 456 → 243	0.4 – 0.9 min

Data Collection and Analysis Software
Analyst® Version 1.4.2
Watson LIMS™ Version 7.4
ExyLIMS Version 3.0
NextDocs® v6.1

Regression type: linear $1/x^2$ weighting
Calibration range: 0.200 (LLOQ) to 200 (ULOQ) ng/mL

Table 39-1. Concentration Analysis of S2218 in Plasma on Days 7 and 91 Following Dietary Administration to Male and Female Rats

			Gender							
			Female				Male			
Dose (mg/kg)	Day	Time (hr)	N	Mean (ng/mL)	SD (ng/mL)	CV%	N	Mean (ng/mL)	SD (ng/mL)	CV%
30	7	0	3	2.84	0.622	21.9	3	1.73	0.779	45.0
		1	3	6.90	6.19	89.6	3	14.0	20.3	145
		3	3	20.1	12.9	64.3	3	2.15	0.590	27.5
		6	3	16.9	17.7	104	3	4.69	1.69	36.1
		12	3	10.5	4.54	43.2	3	6.37	4.18	65.7
		24	3	3.42	1.79	52.3	3	4.77	3.82	80.1
30	91	0	3	5.41	5.54	102	3	10.6	8.91	84.3
		1	3	2.03	0.405	20.0	3	0.776	0.339	43.7
		3	3	7.39	8.50	115	3	1.44	0.0850	5.92
		6	3	58.8	83.7	142	3	35.8	25.1	70.0
		12	3	7.86	3.14	40.0	3	24.0	21.7	90.2
		24	3	2.72	2.10	77.3	3	6.64	6.85	103
70	7	0	3	44.4	55.3	124	3	3.06	0.808	26.4
		1	3	15.3	16.6	108	3	7.88	2.00	25.4
		3	3	11.7	5.69	48.6	3	24.4	35.5	146
		6	3	23.8	20.3	85.2	3	32.8	35.2	107
		12	3	38.7	39.4	102	3	29.9	19.8	66.1
		24	3	13.5	7.31	54.3	3	24.9	16.0	64.0
70	91	0	3	27.8	10.1	36.4	3	10.3	8.87	85.9
		1	3	26.8	17.9	66.8	3	15.8	5.50	34.7
		3	3	19.6	12.5	64.0	3	60.4	87.4	145
		6	3	22.6	7.60	33.6	3	47.4	69.0	146
		12	3	23.9	10.7	44.6	3	25.1	20.9	83.2
		24	3	14.4	9.91	68.6	3	21.5	27.6	129
140	7	0	3	7.29	1.04	14.3	3	33.3	32.4	97.4
		1	3	17.4	12.3	70.6	3	18.6	4.80	25.9
		3	3	15.5	10.0	64.7	3	8.02	5.24	65.2
		6	3	116	120	103	3	57.0	38.0	66.7
		12	3	25.6	14.4	56.3	3	55.6	59.8	108
		24	3	137	190	139	3	32.5	24.0	73.9
140	91	0	3	15.2	6.19	40.8	3	38.8	40.2	104
		1	2	17.2	NA	NA	3	79.4	96.9	122
		3	3	41.6	42.7	103	3	105	90.6	86.2
		6	3	35.4	15.4	43.6	3	131	98.4	74.9
		12	3	85.0	66.8	78.6	3	358	296	82.6
		24	3	10.4	2.76	26.4	3	54.8	44.7	81.5

Table 39-2. Concentration Analysis of S2218 in Plasma on Days 7 and 91 Following Dietary Administration to Male and Female Rats (Males and Females Combined)

		Day							
		7				91			
Nominal Dose (mg/kg)	Time (hr)	N	Mean (ng/mL)	SD (ng/mL)	CV%	N	Mean (ng/mL)	SD (ng/mL)	CV%
30	0	6	2.28	0.874	38.3	6	7.98	7.21	90.3
	1	6	10.5	14.0	134	6	1.40	0.762	54.4
	3	6	11.1	12.8	115	6	4.41	6.29	142
	6	6	10.8	13.1	121	6	47.3	56.7	120
	12	6	8.43	4.51	53.5	6	15.9	16.4	103
	24	6	4.10	2.77	67.6	6	4.68	5.02	107
70	0	6	23.8	41.7	175	6	19.1	12.8	67.2
	1	6	11.6	11.3	97.7	6	21.3	13.3	62.2
	3	6	18.0	23.8	132	6	40.0	60.2	150
	6	6	28.3	26.1	92.4	6	35.0	45.9	131
	12	6	34.3	28.3	82.4	6	24.5	14.8	60.6
	24	6	19.2	12.8	66.5	6	18.0	19.0	106
140	0	6	20.3	25.0	123	6	27.0	28.8	107
	1	6	18.0	8.37	46.5	5	54.5	76.7	141
	3	6	11.7	8.22	70.0	6	73.3	72.3	98.5
	6	6	86.5	85.7	99.0	6	83.4	82.1	98.4
	12	6	40.6	42.3	104	6	222	243	110
	24	6	84.7	134	158	6	32.6	37.3	114

Table 40. Organs or Tissues Weighed, Preserved, and Microscopically Examined

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination Groups	
			1, 2, 7, 8	3, 4, 5, 6
Adrenal glands	X	X	X	
Aorta		X	X	
Bone marrow smear		X		
Bone with bone marrow, femur		X	X	
Bone with bone marrow, sternum		X	X	
Brain	X	X	X	
Epididymides	X	X	X	
Esophagus		X	X	
Eyes (with optic nerve)		X	X	
GALT (Gut-Associated Lymphoid Tissue)		X	X	
Gross lesions (including tissue masses)		X	X	X
Harderian gland		X	X	
Heart	X	X	X	
Joint, tibiofemoral		X	X	
Kidneys	X	X	X	
Lacrimal glands, 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	
Nose (4 Sections)		X	X	
Ovaries	X	X	X	
Oviducts		X	X	
Pancreas		X	X	
Pituitary gland	X	X	X	
Potential target organs		X	X	X
Prostate gland	X	X	X	
Salivary gland, mandibular		X	X	
Salivary gland, parotid		X		
Salivary gland, sublingual		X		

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination Groups	
			1, 2, 7, 8	3, 4, 5, 6
Seminal vesicles with coagulating glands	X	X	X	
Skeletal muscle, biceps femoris		X	X	
Skin		X	X	
Small intestine, duodenum		X	X	
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	
Testes	X	X	X	
Thymus	X	X	X	
Thyroid gland (with parathyroid)	X	X	X	
Tongue		X	X	
Trachea		X	X	
Ureters		X		
Urinary bladder		X	X	
Uterus (with cervix)	X	X	X	
Vagina		X	X	

Table 41-1. Summary of Body Weights - Male
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Day)	0 mg/kg/day Mean	SD	N	30 mg/kg/day Mean	SD	N	70 mg/kg/day Mean	SD	N	140 mg/kg/day Mean	SD	N
Body Weight													
g													
	-1	262.2	12.63	20	262.3	12.35	20	262.0	10.92	20	262.8	10.37	20
	7	309.6	17.68	20	311.1	19.14	20	312.9	16.93	20	315.7	15.66	20
	14	325.0	20.65	20	329.5	16.66	20	329.6	18.50	20	335.7	19.30	20
	21	376.6	25.28	20	384.5	19.15	20	382.2	20.79	20	391.1	25.77	20
	28	411.7	21.53	20	414.3	23.19	20	412.0	23.64	20	421.5	28.12	20
	35	437.9	24.42	20	444.3	25.52	20	437.6	25.21	20	453.5	35.63	20
	42	457.5	27.01	20	464.9	30.62	20	458.8	26.24	20	472.4	38.08	20
	49	469.3	26.99	20	478.5	33.30	20	470.4	27.92	20	485.3	43.09	20
	56	489.4	25.65	20	498.2	34.80	20	488.8	29.46	20	497.8	47.95	20
	63	511.9	31.66	20	517.2	37.52	20	506.8	31.77	20	516.0	50.54	20
	70	523.8	29.39	20	528.1	40.00	20	516.5	34.10	20	530.9	51.34	19
	77	543.8	32.25	20	547.0	40.29	20	536.4	33.41	20	548.5	55.36	19
	84	553.0	35.41	20	557.9	44.95	20	544.6	35.19	20	557.4	55.91	19
	91	566.3	39.00	20	569.5	46.30	20	555.9	35.06	20	572.1	56.66	19

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

Table 41-2. Summary of Body Weights – Female
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Day)	0 mg/kg/day Mean	SD	N	30 mg/kg/day Mean	SD	N	70 mg/kg/day Mean	SD	N	140 mg/kg/day Mean	SD	N
Body Weight g													
	-1	192.3	9.50	20	190.8	11.06	20	192.5	12.82	20	190.9	11.51	20
	7	216.7	19.19	20	215.4	13.83	20	216.8	15.99	20	218.0	15.05	20
	14	218.6	16.49	20	215.6	16.45	20	218.3	16.73	20	217.1	13.41	20
	21	246.8	15.19	20	242.9	19.30	20	249.8	23.13	20	248.3	17.34	20
	28	260.2	18.61	20	255.0	21.28	20	262.0	22.01	20	259.1	16.86	20
	35	269.3	18.05	20	264.1	23.74	20	272.5	21.35	20	269.0	20.64	20
	42	272.7	20.33	20	268.2	24.28	20	277.6	26.10	20	274.0	19.09	20
	49	278.3	17.45	20	274.5	25.30	20	280.2	23.04	20	279.3	19.34	20
	56	285.4	20.32	20	280.4	25.05	20	285.7	23.04	20	284.0	19.63	20
	63	290.4	20.20	20	282.1	26.28	20	290.5	22.59	20	287.2	21.48	20
	70	287.6	24.91	20	287.7	28.27	20	291.7	24.53	20	291.4	21.73	20
	77	294.2	25.78	20	295.4	27.85	20	301.0	26.75	20	301.5	21.88	20
	84	302.0	27.07	20	298.8	32.34	20	299.5	24.49	20	304.0	22.81	20
	91	304.5	22.43	20	301.4	32.98	20	300.9	22.64	20	303.6	22.71	20

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

Table 41-3. Summary of Toxicokinetic Body Weights - Male
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Day)	0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight g													
	-1	266.5	17.06	4	265.0	9.96	8	263.6	10.08	8	265.8	10.69	8
	7	322.5	19.87	4	314.0	29.02	8	316.5	12.24	8	323.4	14.69	8
	14	365.0	18.60	4	346.0	31.69	8	350.4	14.97	8	359.3	22.06	8
	21	402.8	20.61	4	390.6	22.53	8	384.4	14.43	8	398.8	24.97	8
	28	432.3	25.28	4	422.6	22.40	8	410.1	16.00	8	432.1	26.49	8
	35	462.0	29.11	4	451.4	19.64	8	438.3	16.82	8	454.6	42.21	8
	42	480.3	37.21	4	474.3	22.31	8	457.0	18.75	8	479.1	31.86	8
	49	504.3	30.38	4	495.8	25.41	8	467.1	34.99	8	502.3	30.07	8
	56	521.0	29.53	4	512.3	27.18	8	491.9	20.74	8	518.9	32.22	8
	63	536.5	27.09	4	529.3	28.65	8	506.3	20.82	8	537.4	33.89	8
	70	549.8	23.47	4	542.1	32.02	8	517.8	21.12	8	545.8	28.30	8
	77	567.5	23.87	4	560.3	34.00	8	532.5	19.76	8	564.1	35.46	8
	84	577.3	28.44	4	568.0	35.45	8	541.1	23.95	8	571.1	30.31	8
	91	594.3	27.75	4	585.0	38.30	8	554.4	23.81	8	578.6	36.22	8

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

No statistical analysis performed

Table 41-4. Summary of Toxicokinetic Body Weights - Female
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Day)	0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body Weight													
g													
	-1	201.3	14.48	4	199.1	10.74	8	193.1	8.82	8	192.5	11.88	8
	7	221.5	16.11	4	223.0	13.73	8	216.1	9.73	8	218.9	14.35	8
	14	228.0	16.71	4	238.3	12.75	8	231.5	8.99	8	231.5	15.48	8
	21	251.5	12.40	4	258.1	19.13	8	246.9	13.12	8	249.0	17.53	8
	28	264.5	16.34	4	274.3	21.00	8	257.8	15.05	8	251.9	25.48	8
	35	274.3	16.32	4	282.1	21.59	8	266.9	16.44	8	270.0	19.63	8
	42	280.0	20.61	4	286.9	20.49	8	274.5	15.25	8	279.8	25.12	8
	49	288.8	18.55	4	292.8	20.93	8	279.1	16.84	8	284.1	23.65	8
	56	296.0	20.94	4	301.5	20.94	8	277.4	23.97	8	286.4	22.87	8
	63	303.0	26.72	4	304.1	20.88	8	272.1	47.86	8	291.8	21.64	8
	70	301.5	28.90	4	309.1	24.71	8	278.8	44.42	8	296.0	26.93	8
	77	310.8	25.28	4	320.0	24.32	8	304.4	19.65	7	302.6	25.37	8
	84	314.5	26.81	4	317.0	33.70	8	306.7	19.18	7	307.6	23.04	8
	91	319.8	28.63	4	330.6	23.98	8	312.6	21.13	7	312.5	24.41	8

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

No statistical analysis performed

Table 42-1. Summary of Food Consumption Values - Male
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Week)	0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Consumption g/animal/day													
	1	23.56	3.053	20	23.26	3.745	20	24.32	2.116	20	24.48	2.165	20
	2	24.50	1.916	20	24.55	2.926	20	24.18	2.543	20	26.36	4.785	20
	3	25.90	3.012	20	27.04	2.422	20	26.74	2.101	20	27.39	2.473	20
	4	25.40	1.908	20	27.48[a]	2.965	20	25.34	2.265	20	26.39	2.118	20
	5	25.71	2.210	20	25.72	2.279	20	25.71	2.224	20	26.48	3.362	20
	6	25.19	1.893	20	26.75	2.528	20	25.61	2.372	20	26.69	2.296	20
	7	25.50	3.017	20	27.40	3.601	20	24.81	2.072	20	25.00	4.429	20
	8	26.74	2.430	20	27.83	2.574	20	26.42	2.742	20	28.44	3.559	20
	9	27.41	2.834	20	27.54	1.822	20	26.56	2.854	20	26.76	2.773	20
	10	27.26	1.668	20	27.47	1.965	20	26.56	2.166	18	25.98	3.376	20
	11	26.82	1.581	20	29.05	5.223	20	26.08	2.719	20	30.69[b]	4.401	19
	12	29.76	3.776	20	27.91	2.299	20	26.72[b]	2.536	20	27.11[a]	2.351	19
	13	27.10	3.867	20	27.63	3.354	20	25.04	2.687	20	25.92	1.659	19

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

[a] Significantly different from control; ($p<0.05$)
[b] Significantly different from control; ($p<0.01$)

Table 42-2. Summary of Food Consumption Values - Female
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Week)	0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Food Consumption g/animal/day													
	1	17.07	3.788	20	16.38	1.501	20	16.64	2.068	20	17.43	3.318	20
	2	17.98	2.115	20	16.95	1.835	20	18.10	2.408	20	18.08	4.272	20
	3	18.68	1.245	20	17.42	1.807	20	19.20	2.219	20	19.59	2.670	20
	4	19.06	3.689	20	20.74	4.391	20	17.99	2.349	20	18.35	2.641	20
	5	17.80	1.410	20	17.33	3.485	20	17.88	2.635	20	17.93	2.501	20
	6	17.24	2.660	20	16.86	3.625	20	17.66	2.246	20	17.55	2.006	20
	7	18.84	2.663	20	17.79	1.989	20	17.09[a]	1.473	20	17.31[a]	1.629	20
	8	17.92	1.676	20	17.48	1.608	20	18.27	2.921	20	18.64	2.768	20
	9	17.99	2.187	20	15.76[a]	3.486	20	18.10	2.942	20	17.66	2.012	20
	10	17.26	2.266	20	18.12	4.932	20	18.04	2.543	20	17.99	1.702	20
	11	16.74	3.708	20	19.40	4.743	20	16.96	2.720	20	19.84	4.891	20
	12	19.69	4.176	20	21.36	4.574	20	17.28	2.277	20	17.95	2.389	20
	13	20.06	6.653	20	19.04	4.142	20	15.86[a]	2.966	20	16.63	3.684	20

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

[a] Significantly different from control; ($p<0.05$)
[b] Significantly different from control; ($p<0.01$)

Table 43-1. Summary of Compound Consumption Values - Male
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Week)	30 mg/kg/day Mean	30 mg/kg/day SD	30 mg/kg/day N	70 mg/kg/day Mean	70 mg/kg/day SD	70 mg/kg/day N	140 mg/kg/day Mean	140 mg/kg/day SD	140 mg/kg/day N
Compound Consumption mg/kg/day										
	1	25.80	3.383	20	62.79	2.791	20	125.44	8.927	20
	2	32.00	4.303	20	73.20	4.266	20	157.61	32.464	20
	3	34.31	2.882	20	79.54	3.484	20	159.48	12.308	20
	4	31.05	3.019	20	67.09	3.343	20	136.95	10.150	20
	5	27.82	2.395	20	65.79	3.607	20	130.78	13.515	20
	6	30.31	2.323	20	68.51	3.702	20	139.13	10.938	20
	7	31.44	4.090	20	67.42	3.434	20	131.77	22.712	20
	8	31.06	2.891	20	71.89	4.765	20	151.17	15.926	20
	9	29.13	1.781	20	71.27	5.163	20	139.46	7.765	20
	10	28.76	2.479	20	68.99	3.873	18	125.76	14.986	19
	11	31.87	5.094	20	68.84	7.073	20	154.65	23.787	19
	12	28.67	2.046	20	67.96	5.353	20	137.30	8.324	19
	13	28.66	3.271	20	68.59	5.356	20	123.11	9.395	19

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

No statistical analysis performed

Table 43-2. Summary of Compound Consumption Values - Female
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval (Week)	30 mg/kg/day Mean	30 mg/kg/day SD	30 mg/kg/day N	70 mg/kg/day Mean	70 mg/kg/day SD	70 mg/kg/day N	140 mg/kg/day Mean	140 mg/kg/day SD	140 mg/kg/day N
Compound Consumption mg/kg/day										
	1	27.77	1.096	20	65.42	5.431	20	136.58	26.572	20
	2	32.11	1.630	20	79.06	7.338	20	159.53	40.296	20
	3	31.69	2.586	20	79.08	4.764	20	163.02	25.019	20
	4	33.15	6.071	20	65.29	4.970	20	135.42	21.530	20
	5	27.79	3.445	20	65.12	6.597	20	133.08	19.605	20
	6	27.09	4.114	20	64.35	3.916	20	130.41	18.059	20
	7	30.25	3.529	20	66.21	3.320	20	135.15	17.244	20
	8	29.95	1.525	20	74.19	10.533	20	149.73	19.599	20
	9	26.87	4.720	20	73.39	8.643	20	143.00	16.064	20
	10	31.07	6.968	20	70.90	8.334	20	135.80	12.814	20
	11	34.55	6.950	20	64.47	7.445	20	151.96	41.711	20
	12	35.57	7.810	20	67.12	5.481	20	136.65	19.461	20
	13	30.46	6.101	20	66.10	10.679	20	121.60	28.467	20

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

No statistical analysis performed

Table 44-1. Summary of Hematology Values - Male
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day Mean	SD	N	30 mg/kg/day Mean	SD	N	70 mg/kg/day Mean	SD	N	140 mg/kg/day Mean	SD	N
Leukocytes $10^3/\mu L$	Day 14	12.22	3.895	20	11.31	1.901	20	12.46	2.898	20	12.16	2.504	20
	Day 46	12.02	3.299	20	11.31	2.714	20	11.54	3.527	20	12.29	3.224	20
	Terminal	12.51	2.289	20	11.97	2.317	20	12.45	2.575	20	12.78	2.419	19
Erythrocytes $10^6/\mu L$	Day 14	8.623	0.5196	20	8.399	0.3061	20	8.411	0.3226	20	8.297[a]	0.4006	20
	Day 46	9.065	0.4167	20	9.022	0.3148	20	8.981	0.4469	20	8.889	0.3711	20
	Terminal	8.969	0.4977	20	9.020	0.3692	20	9.028	0.3671	20	8.773	0.3544	19
Hemoglobin g/dL	Day 14	16.56	0.615	20	16.10	0.667	20	16.32	0.522	20	15.92[b]	0.738	20
	Day 46	16.57	0.534	20	16.22	0.605	20	16.29	0.617	20	16.15	0.721	20
	Terminal	16.34	0.731	20	16.16	0.753	20	16.40	0.651	20	15.83	0.660	19
Hematocrit %	Day 14	53.03	2.383	20	51.29[a]	1.869	20	52.03	1.637	20	50.88[b]	2.563	20
	Day 46	52.49	1.812	20	51.76	2.026	20	51.98	2.400	20	51.18	2.387	20
	Terminal	53.82	2.637	20	53.80	2.717	20	54.43	1.976	20	52.26	1.777	19
MCV fL	Day 14	61.58	1.773	20	61.10	1.978	20	61.90	1.591	20	61.32	1.195	20
	Day 46	57.95	1.596	20	57.40	1.940	20	57.92	1.488	20	57.58	1.089	20
	Terminal	60.06	1.664	20	59.66	2.179	20	60.30	1.463	20	59.61	1.133	19
MCH pg	Day 14	19.25	0.783	20	19.16	0.701	20	19.43	0.623	20	19.18	0.516	20
	Day 46	18.30	0.578	20	18.00	0.619	20	18.15	0.439	20	18.18	0.396	20
	Terminal	18.22	0.608	20	17.93	0.565	20	18.17	0.500	20	18.06	0.407	19

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

[a] Significantly different from control; ($p<0.05$)
[b] Significantly different from control; ($p<0.01$)

Table 44-1. Summary of Hematology Values – Male (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day Mean	SD	N	30 mg/kg/day Mean	SD	N	70 mg/kg/day Mean	SD	N	140 mg/kg/day Mean	SD	N
MCHC													
g/dL	Day 14	31.25	0.544	20	31.36	0.519	20	31.36	0.580	20	31.30	0.714	20
	Day 46	31.59	0.679	20	31.34	0.472	20	31.37	0.572	20	31.57	0.493	20
	Terminal	30.34	0.598	20	30.06	0.516	20	30.13	0.422	20	30.30	0.523	19
Platelets													
$10^3/\mu L$	Day 14	1038.2	226.17	20	1034.8	243.41	20	983.7	204.78	20	952.6	266.54	20
	Day 46	1126.4	146.87	20	1078.8	158.84	20	1084.9	116.64	20	1078.7	124.81	20
	Terminal	1106.5	213.98	20	1020.4	148.53	20	1046.8	109.59	20	1063.8	148.57	19
Absolute Reticulocytes													
$10^3/\mu L$	Day 14	242.60	57.787	20	242.74	51.118	20	225.45	43.199	20	213.75	39.575	20
	Day 46	158.96	23.722	20	168.17	25.796	20	162.25	19.126	20	141.22	32.432	20
	Terminal	161.64	18.761	20	165.64	19.199	20	159.56	24.238	20	151.56	25.767	19
Neutrophils													
$10^3/\mu L$	Day 14	1.403	0.5038	20	1.294	0.3080	20	1.473	0.7277	20	1.366	0.4858	20
	Day 46	1.331	0.4558	20	1.334	0.4360	20	1.390	0.9156	20	1.225	0.3062	20
	Terminal	1.347	0.3544	20	1.182	0.3278	20	1.426	0.6277	20	1.322	0.4355	19
Lymphocytes													
$10^3/\mu L$	Day 14	10.345	3.5145	20	9.599	1.8977	20	10.493	2.5534	20	10.304	2.2933	20
	Day 46	10.207	3.1219	20	9.548	2.5514	20	9.681	2.7570	20	10.558	2.9435	20
	Terminal	10.577	2.1874	20	10.269	2.0423	20	10.488	2.0678	20	10.861	2.0820	19
Monocytes													
$10^3/\mu L$	Day 14	0.251	0.1152	20	0.224	0.1093	20	0.246	0.0657	20	0.248	0.0962	20
	Day 46	0.232	0.0992	20	0.191	0.0676	20	0.200	0.0765	20	0.236	0.0991	20
	Terminal	0.319	0.1177	20	0.256	0.0909	20	0.267	0.0764	20	0.283	0.1243	19

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

Table 44-1. Summary of Hematology Values – Male (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day Mean	SD	N	30 mg/kg/day Mean	SD	N	70 mg/kg/day Mean	SD	N	140 mg/kg/day Mean	SD	N
Eosinophils													
$10^3/\mu L$	Day 14	0.074	0.0341	20	0.069	0.0333	20	0.090	0.0403	20	0.074	0.0218	20
	Day 46	0.107	0.0264	20	0.100	0.0420	20	0.128	0.0546	20	0.120	0.0399	20
	Terminal	0.109	0.0258	20	0.101	0.0469	20	0.118	0.0358	20	0.129	0.0414	19
Basophils													
$10^3/\mu L$	Day 14	0.050	0.0292	20	0.041	0.0263	20	0.056	0.0314	20	0.054	0.0322	20
	Day 46	0.047	0.0347	20	0.044	0.0274	20	0.042	0.0307	20	0.048	0.0286	20
	Terminal	0.054	0.0147	20	0.054	0.0182	20	0.055	0.0209	20	0.057	0.0142	19
Other Cells													
$10^3/\mu L$	Day 14	0.103	0.0549	20	0.081	0.0361	20	0.100	0.0320	20	0.110	0.0527	20
	Day 46	0.095	0.0391	20	0.098	0.0445	20	0.098	0.0551	20	0.107	0.0436	20
	Terminal	0.101	0.0516	20	0.110	0.0236	20	0.101	0.0382	20	0.125	0.0613	19
RDW													
%	Day 14	11.64	0.408	20	11.93	0.475	20	11.77	0.303	20	11.81	0.384	20
	Day 46	11.24	0.428	20	11.50	0.407	20	11.26	0.385	20	11.37	0.507	20
	Terminal	11.87	0.429	20	12.28[a]	0.541	20	12.02	0.431	20	12.23	0.675	19

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

[a] Significantly different from control; ($p<0.05$)

Table 44-2. Summary of Hematology Values – Female
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day Mean	SD	N	30 mg/kg/day Mean	SD	N	70 mg/kg/day Mean	SD	N	140 mg/kg/day Mean	SD	N
Leukocytes													
10^3/µL	Day 14	8.61	2.419	20	10.16	2.240	20	8.70	2.560	20	9.43	3.056	20
	Day 46	7.41	1.924	20	8.46	2.283	20	8.46	2.169	20	9.45[a]	2.604	20
	Terminal	9.33	1.703	20	9.53	1.316	20	10.15	2.390	20	9.79	2.601	17
Erythrocytes													
10^6/µL	Day 14	8.382	0.3768	20	8.609	0.3955	20	8.516	0.2832	20	8.478	0.3340	20
	Day 46	8.528	0.2825	20	8.765	0.3702	20	8.773	0.5035	20	8.712	0.2873	20
	Terminal	8.294	0.4079	20	8.464	0.4742	20	8.289	0.6421	20	8.549	0.4012	17
Hemoglobin													
g/dL	Day 14	15.88	0.458	20	16.20	0.552	20	16.04	0.353	20	15.95	0.654	20
	Day 46	15.86	0.555	20	16.02	0.511	20	16.11	0.641	20	16.06	0.540	20
	Terminal	15.72	0.804	20	15.88	0.793	20	15.56	1.179	20	16.00	0.857	17
Hematocrit													
%	Day 14	49.47	1.295	20	50.14	1.767	20	49.80	1.148	20	49.49	1.729	20
	Day 46	49.61	1.850	20	50.57	1.807	20	50.68	1.940	20	50.30	1.475	20
	Terminal	51.11	2.289	20	51.71	2.525	20	50.69	3.887	20	52.16	2.355	17
MCV													
fL	Day 14	59.10	1.997	20	58.29	1.444	20	58.52	1.649	20	58.40	1.480	20
	Day 46	58.19	1.601	20	57.73	1.516	20	57.85	1.716	20	57.75	1.052	20
	Terminal	61.66	1.306	20	61.14	1.667	20	61.16	1.677	20	61.04	1.603	17
MCH													
pg	Day 14	18.98	0.787	20	18.83	0.590	20	18.84	0.586	20	18.80	0.701	20
	Day 46	18.60	0.603	20	18.29	0.531	20	18.39	0.569	20	18.44	0.437	20
	Terminal	18.95	0.517	20	18.77	0.501	20	18.80	0.591	20	18.72	0.554	17

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

[a] Significantly different from control; ($p<0.05$)

Table 44-2. Summary of Hematology Values – Female (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day Mean	SD	N	30 mg/kg/day Mean	SD	N	70 mg/kg/day Mean	SD	N	140 mg/kg/day Mean	SD	N
MCHC													
g/dL	Day 14	32.09	0.659	20	32.31	0.582	20	32.20	0.577	20	32.19	0.609	20
	Day 46	31.96	0.452	20	31.70	0.536	20	31.77	0.413	20	31.92	0.425	20
	Terminal	30.75	0.628	20	30.70	0.453	20	30.73	0.568	20	30.66	0.551	17
Platelets													
$10^3/\mu L$	Day 14	1011.4	230.53	20	1071.5	212.83	20	1029.3	271.01	20	1043.2	265.98	20
	Day 46	1114.0	110.49	20	1119.1	174.20	20	1124.9	122.24	20	1116.5	168.00	20
	Terminal	1014.1	143.21	20	960.2	144.63	20	1045.5	176.77	20	1031.1	90.86	17
Absolute Reticulocytes													
$10^3/\mu L$	Day 14	181.42	51.720	20	157.16	29.444	20	164.63	37.890	20	160.05	36.084	20
	Day 46	152.18	36.325	20	141.55	27.146	20	136.05	32.355	20	128.21	31.865	20
	Terminal	138.04	23.902	20	124.17	29.016	20	152.45	103.615	20	116.62	27.169	17
Neutrophils													
$10^3/\mu L$	Day 14	1.107	0.3987	20	0.900	0.3715	20	0.993	0.3584	20	1.170	0.7985	20
	Day 46	0.968	0.2732	20	0.986	0.5301	20	0.980	0.2722	20	1.114	0.5060	20
	Terminal	0.917	0.4883	20	0.789	0.3800	20	0.962	0.4548	20	0.998	0.7147	17
Lymphocytes													
$10^3/\mu L$	Day 14	7.181	2.0482	20	8.906[a]	2.0505	20	7.408	2.4777	20	7.915	2.3459	20
	Day 46	6.175	1.7440	20	7.166	1.9957	20	7.160	2.1152	20	7.977[a]	2.2369	20
	Terminal	7.947	1.3220	20	8.319	1.2418	20	8.706	2.3432	20	8.326	2.1297	17
Monocytes													
$10^3/\mu L$	Day 14	0.141	0.0725	20	0.131	0.0442	20	0.128	0.0577	20	0.154	0.0769	20
	Day 46	0.103	0.0408	20	0.114	0.0412	20	0.133	0.0566	20	0.137[a]	0.0415	20
	Terminal	0.249	0.1459	20	0.197	0.0739	20	0.236	0.0873	20	0.231	0.1075	17

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

[a] Significantly different from control; ($p<0.05$)

Table 44-2. Summary of Hematology Values – Female (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rats

Endpoint	Study Interval	0 mg/kg/day Mean	SD	N	30 mg/kg/day Mean	SD	N	70 mg/kg/day Mean	SD	N	140 mg/kg/day Mean	SD	N
Eosinophils													
$10^3/\mu L$	Day 14	0.089	0.0451	20	0.098	0.1072	20	0.069	0.0221	20	0.088	0.0383	20
	Day 46	0.093	0.0519	20	0.086	0.0399	20	0.091	0.0351	20	0.096	0.0256	20
	Terminal	0.094	0.0365	20	0.085	0.0328	20	0.086	0.0327	20	0.094	0.0367	17
Basophils													
$10^3/\mu L$	Day 14	0.031	0.0206	20	0.048	0.0261	20	0.030	0.0182	20	0.039	0.0283	20
	Day 46	0.020	0.0126	20	0.039	0.0419	20	0.030	0.0203	20	0.040	0.0298	20
	Terminal	0.043	0.0165	20	0.043	0.0138	20	0.051	0.0190	20	0.042	0.0130	17
Other Cells													
$10^3/\mu L$	Day 14	0.060	0.0255	20	0.077	0.0308	20	0.070	0.0313	20	0.069	0.0395	20
	Day 46	0.051	0.0213	20	0.067	0.0268	20	0.065	0.0314	20	0.084[b]	0.0390	20
	Terminal	0.084	0.0216	20	0.093	0.0315	20	0.112	0.0442	20	0.098	0.0338	17
RDW													
%	Day 14	10.73	0.431	20	10.61	0.327	20	10.47	0.316	20	10.62	0.283	20
	Day 46	11.31	0.412	20	11.26	0.309	20	11.08	0.277	20	11.24	0.345	20
	Terminal	11.18	0.720	20	11.04	0.338	20	11.14	1.051	20	11.02	0.340	17

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

[b] Significantly different from control; ($p<0.01$)

Table 45-1. Summary of Coagulation Values – Male
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

Endpoint	Study Interval	0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
APTT sec	Terminal	17.37	1.884	19	16.71	2.400	17	17.52	1.721	19	17.38	1.138	18
Prothrombin Time sec	Terminal	16.43	0.818	19	16.24	0.968	17	16.41	0.717	19	16.47	0.826	18
Fibrinogen mg/dL	Terminal	306.3	27.81	19	304.2	22.57	17	307.8	23.77	19	302.8	18.84	18

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

Table 45-2. Summary of Coagulation Values – Female
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

Endpoint	Study Interval	0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
APTT sec	Terminal	14.69	1.476	15	14.54	1.845	16	13.89	2.443	19	13.28	2.493	13
Prothrombin Time sec	Terminal	15.93	0.860	15	15.89	0.946	16	15.96	0.774	19	15.71	0.804	13
Fibrinogen mg/dL	Terminal	232.8	75.66	15	220.8	22.24	16	225.1	25.19	19	237.5	24.94	13

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

Table 46-1. Summary of Clinical Chemistry Values – Male
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

		0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
Endpoint	Study Interval	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Sodium mEq/L	Day 14	143.5	1.83	20	142.4[a]	1.70	20	142.7	1.15	20	142.3[a]	1.08	20
	Day 46	142.5	1.10	20	142.3	1.25	20	142.7	1.68	20	142.0	1.45	20
	Terminal	143.6	1.65	20	143.1	2.35	20	143.2	1.90	20	143.2	1.64	19
Potassium mEq/L	Day 14	5.16	0.458	20	5.18	0.426	20	5.08	0.509	20	5.05	0.369	20
	Day 46	5.68	0.535	20	5.60	0.509	20	5.43	0.429	20	5.63	0.445	20
	Terminal	8.13	1.567	20	8.22	1.681	20	8.41	1.496	20	7.97	1.371	19
Chloride mEq/L	Day 14	101.6	1.59	20	101.1	1.17	20	101.6	1.70	20	101.1	1.58	20
	Day 46	102.0	1.31	20	102.2	1.22	20	102.4	0.97	20	101.9	1.40	20
	Terminal	101.0	1.24	20	100.5	1.29	20	100.6	1.57	20	100.7	1.36	19
Calcium mg/dL	Day 14	10.74	0.328	20	10.80	0.239	20	10.81	0.305	20	10.70	0.298	20
	Day 46	10.51	0.274	20	10.52	0.249	20	10.50	0.330	20	10.54	0.287	20
	Terminal	11.66	0.488	20	11.83	0.576	20	11.93	0.406	20	11.59	0.426	19
Phosphorus mg/dL	Day 14	9.03	0.619	20	9.17	0.666	20	8.72	0.509	20	8.78	0.661	20
	Day 46	7.62	0.647	20	7.73	0.752	20	7.26	0.440	20	7.63	0.571	20
	Terminal	10.09	0.987	20	10.20	0.980	20	10.28	1.139	20	9.88	0.945	19
Alkaline Phosphatase U/L	Day 14	244.1	42.38	20	261.7	59.35	20	264.5	62.57	20	273.9	56.74	20
	Day 46	183.8	43.80	20	200.4	54.92	20	192.1	48.68	20	212.3	56.51	20
	Terminal	78.7	11.84	20	88.8	22.68	20	87.7	20.47	20	96.9[a]	23.10	19

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

[a] Significantly different from control; ($p<0.05$)

Table 46-1. Summary of Clinical Chemistry Values – Male (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

Endpoint	Study Interval	0 mg/kg/day Mean	SD	N	30 mg/kg/day Mean	SD	N	70 mg/kg/day Mean	SD	N	140 mg/kg/day Mean	SD	N
Total Bilirubin mg/dL	Day 14	0.14	0.021	20	0.14	0.016	20	0.14	0.026	20	0.13	0.018	20
	Day 46	0.17	0.030	20	0.17	0.026	20	0.16	0.018	20	0.17	0.022	20
	Terminal	0.12	0.015	20	0.12	0.016	20	0.11	0.016	20	0.12	0.014	19
AST U/L	Day 14	107.8	24.55	20	104.6	15.59	20	102.6	21.23	20	95.4	15.68	20
	Day 46	98.2	26.32	20	97.0	16.57	20	91.7	14.96	20	84.5	11.86	20
	Terminal	70.7	12.98	20	71.7	9.21	20	66.0	8.70	20	66.4	8.45	19
ALT U/L	Day 14	34.9	5.42	20	36.8	5.82	20	35.4	5.32	20	34.2	5.53	20
	Day 46	42.7	5.15	20	44.1	4.75	20	42.6	5.24	20	42.1	6.06	20
	Terminal	29.3	8.66	20	29.4	6.83	20	27.5	5.18	20	27.3	4.45	19
Urea Nitrogen mg/dL	Day 14	13.6	2.46	20	13.4	2.38	20	12.8	1.61	20	13.7	1.99	20
	Day 46	14.3	2.35	20	15.4	2.73	20	14.5	2.07	20	15.2	2.11	20
	Terminal	14.1	2.29	20	14.2	2.21	20	13.8	1.34	20	13.3	1.17	19
Creatinine mg/dL	Day 14	0.27	0.044	20	0.25*	0.036*	20*	0.25	0.036	20	0.24*,a	0.035*	20*
	Day 46	0.34	0.056	20	0.34	0.039	20	0.34	0.040	20	0.32	0.040	20
	Terminal	0.40	0.042	20	0.41	0.054	20	0.40	0.028	20	0.38	0.027	19
Total Protein g/dL	Day 14	6.56	0.278	20	6.38	0.330	20	6.50	0.254	20	6.37	0.250	20
	Day 46	6.81	0.193	20	6.72	0.315	20	6.78	0.310	20	6.70	0.305	20
	Terminal	6.48	0.219	20	6.46	0.322	20	6.56	0.346	20	6.41	0.359	19

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

[a] Significantly different from control; ($p<0.05$)
* Calculation includes one or more individual value(s) out of linear range

Table 46-1. Summary of Clinical Chemistry Values – Male (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

		0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
Endpoint	Study Interval	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Albumin g/dL	Day 14	3.53	0.157	20	3.41[a]	0.149	20	3.48	0.111	20	3.39[b]	0.124	20
	Day 46	3.47	0.087	20	3.41	0.141	20	3.46	0.129	20	3.41	0.112	20
	Terminal	3.25	0.133	20	3.24	0.124	20	3.27	0.153	20	3.22	0.114	19
Triglyceride mg/dL	Day 14	49.6	13.86	20	59.4	17.23	20	55.5	13.72	20	58.1	14.42	20
	Day 46	59.3	11.61	20	69.0	20.21	20	62.5	19.96	20	66.6	23.66	20
	Terminal	52.9	15.24	20	59.2	22.11	20	58.2	19.60	20	58.6	17.93	19
Cholesterol mg/dL	Day 14	71.1	12.08	20	70.6	10.70	20	71.1	11.42	20	69.7	10.35	20
	Day 46	75.6	13.12	20	73.8	12.90	20	75.3	9.54	20	74.2	10.12	20
	Terminal	65.4	12.78	20	62.7	14.05	20	68.1	12.33	20	63.6	8.40	19
Glucose mg/dL	Day 14	90.4	9.50	20	91.2	8.49	20	90.5	10.12	20	90.6	9.65	20
	Day 46	99.4	11.38	20	99.1	5.47	20	99.4	9.30	20	98.0	8.95	20
	Terminal	221.6	69.58	20	267.1	77.63	20	248.9	59.30	20	216.5	45.14	19
Globulin g/dL	Day 14	3.03	0.194	20	2.97	0.230	20	3.02	0.175	20	2.98	0.163	20
	Day 46	3.34	0.148	20	3.31	0.198	20	3.32	0.201	20	3.29	0.233	20
	Terminal	3.23	0.122	20	3.21	0.223	20	3.29	0.217	20	3.20	0.275	19
Albumin/Globulin Ratio	Day 14	1.17	0.081	20	1.15	0.078	20	1.15	0.056	20	1.14	0.053	20
	Day 46	1.04	0.046	20	1.03	0.044	20	1.04	0.041	20	1.04	0.061	20
	Terminal	1.01	0.041	20	1.01	0.051	20	1.00	0.043	20	1.01	0.072	19

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

[a] Significantly different from control; ($p<0.05$)
[b] Significantly different from control; ($p<0.01$)

Table 46-2. Summary of Clinical Chemistry Values – Female
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

Endpoint	Study Interval	0 mg/kg/day Mean	SD	N	30 mg/kg/day Mean	SD	N	70 mg/kg/day Mean	SD	N	140 mg/kg/day Mean	SD	N
Sodium mEq/L	Day 14	141.8	1.42	20	141.1	1.30	20	141.4	1.46	20	141.6	1.56	20
	Day 46	141.4	1.63	20	141.6	1.85	20	141.3	1.55	20	141.8	1.57	20
	Terminal	141.0	2.28	20	141.2	1.76	20	142.3	1.45	20	141.9	2.07	20
Potassium mEq/L	Day 14	4.93	0.562	20	5.06	0.519	20	4.90	0.481	20	5.15	0.667	20
	Day 46	5.00	0.624	20	5.16	0.503	20	5.25	0.493	20	5.32	0.800	20
	Terminal	8.66	1.746	20	8.40	1.322	20	7.97	0.994	20	8.34	1.771	20
Chloride mEq/L	Day 14	102.6	1.77	20	102.0	1.55	20	101.8	1.96	20	102.5	1.58	20
	Day 46	102.3	1.68	20	103.0	1.66	20	102.7	1.79	20	103.0	1.30	20
	Terminal	99.7	2.33	20	99.3	1.97	20	100.3	1.54	20	100.8	1.77	20
Calcium mg/dL	Day 14	10.70	0.369	20	10.86	0.400	20	10.74	0.313	20	10.85	0.483	20
	Day 46	10.74	0.531	20	10.79	0.406	20	10.82	0.365	20	10.89	0.421	20
	Terminal	12.57	0.662	20	12.67	0.829	20	12.42	0.556	20	12.32	0.575	20
Phosphorus mg/dL	Day 14	7.51	0.970	20	7.83	0.770	20	7.51	0.825	20	8.08	1.579	20
	Day 46	5.78	0.825	20	6.21	0.917	20	6.35	0.951	20	6.55[a]	0.956	20
	Terminal	9.31	0.829	20	9.47	0.825	20	9.33	0.756	20	9.60	0.883	20
Alkaline Phosphatase U/L	Day 14	154.0	45.11	20	148.3	28.84	20	165.4	36.87	20	167.1	35.31	20
	Day 46	112.5	33.72	20	108.0	22.58	20	126.5	36.97	20	139.7[a]	38.54	20
	Terminal	53.4	21.18	20	45.2	14.85	20	54.3	15.41	20	58.1	22.18	20

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

[a] Significantly different from control; ($p<0.05$)

Table 46-2. Summary of Clinical Chemistry Values – Female (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

		0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
Endpoint	Study Interval	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Total Bilirubin mg/dL	Day 14	0.15	0.021	20	0.15	0.021	20	0.13[a]	0.018	20	0.14	0.022	20
	Day 46	0.17	0.033	20	0.16	0.024	20	0.16	0.017	20	0.16	0.020	20
	Terminal	0.15	0.022	20	0.15	0.022	20	0.14	0.022	20	0.14	0.020	20
AST U/L	Day 14	98.3	15.87	20	93.0	17.61	20	91.1	10.50	20	97.7	15.74	20
	Day 46	93.4	17.92	20	88.1	14.56	20	89.0	15.64	20	92.6	28.68	20
	Terminal	109.0	104.30	20	114.7	110.31	20	82.5	26.04	20	95.7	82.56	20
ALT U/L	Day 14	30.8	4.69	20	30.1	5.46	20	30.8	4.48	20	31.3	5.40	20
	Day 46	42.8	11.92	20	38.5	7.36	20	42.6	9.63	20	42.3	12.82	20
	Terminal	59.1	70.17	20	45.8	25.57	20	36.5	15.28	20	43.3	42.92	20
Urea Nitrogen mg/dL	Day 14	15.1	1.78	20	14.5	2.23	20	15.6	2.38	20	14.5	2.31	20
	Day 46	16.5	2.36	20	15.8	2.48	20	16.2	1.72	20	16.2	3.75	20
	Terminal	13.8	2.66	20	15.0	2.65	20	15.3	2.32	20	14.9	2.79	20
Creatinine mg/dL	Day 14	0.32	0.035	20	0.34	0.120	20	0.32	0.070	20	0.32	0.040	20
	Day 46	0.44	0.047	20	0.44	0.052	20	0.44	0.062	20	0.41	0.050	20
	Terminal	0.44	0.040	20	0.44	0.041	20	0.46	0.031	20	0.42	0.033	20
Total Protein g/dL	Day 14	6.97	0.401	20	6.94	0.345	20	6.94	0.399	20	6.97	0.343	20
	Day 46	7.70	0.651	20	7.51	0.361	20	7.46	0.432	20	7.50	0.507	20
	Terminal	7.68	0.704	20	7.76	0.827	20	7.39	0.453	20	7.38	0.521	20

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

[a] Significantly different from control; ($p<0.05$)

Table 46-2. Summary of Clinical Chemistry Values – Female (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

		0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
Endpoint	Study Interval	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Albumin g/dL	Day 14	3.82	0.214	20	3.81	0.177	20	3.76	0.164	20	3.78	0.193	20
	Day 46	4.11	0.385	20	4.04	0.204	20	3.94	0.215	20	3.93	0.292	20
	Terminal	4.14	0.341	20	4.22	0.449	20	3.97	0.247	20	3.93	0.312	20
Triglyceride mg/dL	Day 14	40.6	16.92	20	42.4	12.97	20	38.3	9.51	20	40.2	7.68	20
	Day 46	56.2	49.13	20	48.0	13.47	20	55.3	34.54	20	62.1	29.00	20
	Terminal	47.0	17.85	20	45.2	15.32	20	45.6	11.68	20	43.2	10.12	20
Cholesterol mg/dL	Day 14	79.0	16.41	20	81.8	11.53	20	74.5	11.98	20	76.7	9.38	20
	Day 46	87.7	17.84	20	81.7	13.39	20	79.1	10.73	20	78.6	8.70	20
	Terminal	94.1	29.01	20	89.2	18.38	20	77.1[a]	17.96	20	78.9	15.98	20
Glucose mg/dL	Day 14	90.0	9.16	20	94.1	13.43	20	90.6	9.78	20	90.6	13.04	20
	Day 46	100.5	9.76	20	98.0	11.29	20	97.6	10.43	20	95.7	7.85	20
	Terminal	224.7	70.68	20	224.2	59.37	20	219.8	49.60	20	201.8	52.88	20
Globulin g/dL	Day 14	3.15	0.253	20	3.12	0.209	20	3.17	0.284	20	3.19	0.205	20
	Day 46	3.59	0.310	20	3.47	0.192	20	3.52	0.263	20	3.56	0.244	20
	Terminal	3.55	0.403	20	3.53	0.404	20	3.42	0.261	20	3.46	0.245	20
Albumin/Globulin Ratio	Day 14	1.22	0.090	20	1.22	0.069	20	1.19	0.090	20	1.19	0.075	20
	Day 46	1.15	0.073	20	1.17	0.052	20	1.12	0.064	20	1.10	0.053	20
	Terminal	1.17	0.081	20	1.20	0.069	20	1.16	0.074	20	1.14	0.061	20

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

[a] Significantly different from control; ($p<0.05$)

Table 47-1. Summary of Urinalysis Values – Male
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

Endpoint	Study Interval	0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Volume mL	Terminal	5.64	4.302	20	5.55	3.448	20	6.13	4.356	20	5.16	2.882	19
Specific Gravity	Terminal	1.0593*	0.02363*	20*	1.0630*	0.01914*	20*	1.0650*	0.02915*	20*	1.0642*	0.02166*	19*
pH	Terminal	7.72	0.548	18	7.55	0.583	20	7.30	0.677	20	7.50	0.527	19

N - Number of measures used to calculate mean
SD - Standard Deviation
* Calculation includes one or more individual value(s) out of linear range

Table 47-2. Summary of Urinalysis Values – Female
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

Endpoint	Study Interval	0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
		Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Volume mL	Terminal	2.92	2.021	20	4.20	2.567	20	2.49	1.852	19	3.92	3.051	20
Specific Gravity	Terminal	1.0705*	0.02029*	20*	1.0572*	0.02209*	20*	1.0671*	0.01771*	19*	1.0628*	0.02641*	20*
pH	Terminal	7.03	0.456	19	7.08	0.584	19	7.00	0.500	15	6.97	0.456	19

N - Number of measures used to calculate mean
SD - Standard Deviation
* Calculation includes one or more individual value(s) out of linear range

Table 48-1. Summary of Macroscopic Observations – Male
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

Tissue Observation	Severity	0 mg/kg/day DOS	 SNC	30 mg/kg/day DOS	 SNC	70 mg/kg/day DOS	 SNC	140 mg/kg/day DOS	 SNC
Number of Animals Examined		0	20	0	20	0	20	1	19
all tissues									
within normal limits		0	19	0	20	0	18	0	19
small intestine, jejunum									
deformity/malformation	- no grade	0	1	0	0	0	0	0	0
thymus									
discoloration, red	- mild	0	0	0	0	0	1	0	0
focus/foci, red	- mild	0	0	0	0	0	1	0	0
tooth/teeth									
absent/broken/malocclusion/overgrown	- no grade	0	0	0	0	0	0	1	0

DOD – Died or euthanized on study
SNC – Scheduled necropsy

Table 48-2. Summary of Macroscopic Observations – Female
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

Tissue Observation	Severity	0 mg/kg/day DOS	 SNC	30 mg/kg/day DOS	 SNC	70 mg/kg/day DOS	 SNC	140 mg/kg/day DOS	 SNC
Number of Animals Examined		0	20	0	20	0	20	0	20
all tissues									
within normal limits		0	20	0	20	0	18	0	19
eyes									
Laceration/perforation	- moderate	0	0	0	0	0	1	0	0
lung with bronchi									
focus/foci, red	- mild	0	0	0	0	0	0	0	1
Stomach, nonglandular									
Swollen/thickened	- mild	0	0	0	0	0	1	0	0

DOD – Died or euthanized on study
SNC – Scheduled necropsy

Table 49-1. Summary of Organ Weight Values – Male
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

	0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body weight												
g	533	37	20	537	44	20	524	37	20	542	57	18
Brain												
g	2.147	0.072	20	2.148	0.099	20	2.187	0.076	20	2.133	0.070	19
Brain/BWt												
%	0.4045	0.0298	20	0.4016	0.0307	20	0.4190	0.0320	20	0.3981	0.0391	18
Adrenal gl												
g	0.076	0.031	20	0.072	0.014	20	0.067	0.010	20	0.072	0.018	19
Adrenal gl/BWt												
%	0.0142	0.0060	20	0.0134	0.0026	20	0.0129	0.0019	20	0.0139	0.0037	18
Adrenal gl/BrWt												
ratio	0.0350	0.0129	20	0.0337	0.0075	20	0.0308	0.0044	20	0.0339	0.0084	19
Epididymides												
g	1.490	0.337	20	1.546	0.172	20	1.535	0.150	20	1.551	0.179	19
Epididymides/BWt												
%	0.2802	0.0649	20	0.2882	0.0272	20	0.2936	0.0315	20	0.2907	0.0373	18
Epididymides/BrWt												
ratio	0.6942	0.1547	20	0.7193	0.0656	20	0.7019	0.0655	20	0.7280	0.0893	19

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

Table 49-1. Summary of Organ Weight Values – Male (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

	0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Heart g	1.761	0.195	20	1.826	0.219	20	1.750	0.228	20	1.774	0.226	19
Heart/BWt %	0.3307	0.0325	20	0.3405	0.0376	20	0.3338	0.0374	20	0.3280	0.0382	18
Heart/BrWt ratio	0.8204	0.0868	20	0.8516	0.1088	20	0.8002	0.1001	20	0.8329	0.1142	19
Kidneys g	3.691	0.366	20	3.837	0.351	20	3.865	0.438	20	3.824	0.509	19
Kidneys/BWt %	0.6934	0.0584	20	0.7173	0.0761	20	0.7374	0.0681	20	0.7037	0.0744	18
Kidneys/BrWt ratio	1.7204	0.1674	20	1.7869	0.1470	20	1.7662	0.1804	20	1.7935	0.2364	19
Liver g	14.445	1.884	20	14.809	1.585	20	14.878	1.627	20	14.700	1.654	19
Liver/BWt %	2.7042	0.2366	20	2.7579	0.2177	20	2.8354	0.2051	20	2.7121	0.1244	18
Liver/BrWt ratio	6.7348	0.8980	20	6.9026	0.7580	20	6.8052	0.7220	20	6.8959	0.7790	19

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

Table 49-1. Summary of Organ Weight Values – Male (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

	0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Lung w/ bronchi												
g	2.046	0.326	20	2.062	0.225	20	1.937	0.228	20	2.106	0.274	19
Lung w/ bronchi/BWt												
%	0.3843	0.0597	20	0.3849	0.0415	20	0.3692	0.0320	20	0.3896	0.0399	18
Lung w/ bronchi/BrWt												
ratio	0.9517	0.1402	20	0.9617	0.1127	20	0.8874	0.1150	20	0.9885	0.1382	19
Pituitary gl												
g	0.0169	0.0022	20	0.0166	0.0021	20	0.0175	0.0024	20	0.0169	0.0022	19
Pituitary gl/BWt												
%	0.0032	0.0004	20	0.0031	0.0004	20	0.0033	0.0004	20	0.0031	0.0004	18
Pituitary gl/BrWt												
ratio	0.0079	0.0010	20	0.0077	0.0008	20	0.0080	0.0011	20	0.0079	0.0010	19
Prostate gl												
g	1.811	0.460	20	1.822	0.576	20	1.709	0.280	20	1.721	0.357	19
Prostate gl/BWt												
%	0.3400	0.0830	20	0.3408	0.1108	20	0.3273	0.0569	20	0.3177	0.0700	18
Prostate gl/BrWt												
ratio	0.8428	0.2084	20	0.8500	0.2713	20	0.7822	0.1300	20	0.8083	0.1715	19

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

Table 49-1. Summary of Organ Weight Values – Male (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

	0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Sem. ves. w/ coag. gl g	1.916	0.380	20	2.250[a]	0.397	20	1.844	0.512	20	2.051	0.363	19
Sem. ves. w/ coag. gl/BWt %	0.3626	0.0822	20	0.4215	0.0821	20	0.3521	0.0949	20	0.3877	0.0818	18
Sem. ves. w/ coag. gl/BrWt ratio	0.8947	0.1825	20	1.0510[a]	0.2017	20	0.8453	0.2410	20	0.9625	0.1745	19
Spleen g	0.931	0.151	20	0.876	0.152	20	0.868	0.145	20	0.897	0.154	19
Spleen/BWt %	0.1741	0.0217	20	0.1634	0.0281	20	0.1652	0.0227	20	0.1671	0.0234	18
Spleen/BrWt ratio	0.4335	0.0689	20	0.4084	0.0731	20	0.3974	0.0696	20	0.4204	0.0708	19
Testes g	3.744	0.360	20	3.832	0.256	20	3.817	0.356	20	3.881	0.249	19
Testes/BWt %	0.7054	0.0829	20	0.7179	0.0786	20	0.7293	0.0634	20	0.7253	0.0672	18
Testes/BrWt ratio	1.7462	0.1792	20	1.7870	0.1361	20	1.7466	0.1702	20	1.8214	0.1323	19

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

[a] Significantly different from control; ($p<0.05$)

Table 49-1. Summary of Organ Weight Values – Male (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

	0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Thymus												
g	0.403	0.114	20	0.391	0.110	20	0.351	0.094	20	0.409	0.118	19
Thymus/BWt												
%	0.0753	0.0199	20	0.0729	0.0205	20	0.0667	0.0158	20	0.0742	0.0199	18
Thymus/BrWt												
ratio	0.1870	0.0500	20	0.1834	0.0564	20	0.1609	0.0450	20	0.1919	0.0561	19
Thyroid/parathyroid gl												
g	0.026	0.004	20	0.026	0.003	20	0.026	0.004	20	0.026	0.005	19
Thyroid/parathyroid gl/BWt												
%	0.0049	0.0007	20	0.0048	0.0006	20	0.0050	0.0008	20	0.0049	0.0008	18
Thyroid/parathyroid gl/BrWt												
ratio	0.0121	0.0020	20	0.0121	0.0016	20	0.0120	0.0017	20	0.0123	0.0023	19

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

Table 49-2. Summary of Organ Weight Values – Female
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

	0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Body weight												
g	285	25	20	280	30	20	280	22	20	283	22	20
Brain												
g	1.950	0.081	20	1.961	0.085	20	1.945	0.109	20	2.018	0.101	20
Brain/BWt												
%	0.6878	0.0642	20	0.7076	0.0813	20	0.6982	0.0580	20	0.7179	0.0628	20
Adrenal gl												
g	0.080	0.022	20	0.072	0.016	20	0.071	0.013	20	0.072	0.017	20
Adrenal gl/BWt												
%	0.0280	0.0080	20	0.0260	0.0070	20	0.0253	0.0042	20	0.0256	0.0060	20
Adrenal gl/BrWt												
ratio	0.0408	0.0113	20	0.0367	0.0087	20	0.0366	0.0072	20	0.0358	0.0082	20
Heart												
g	1.059	0.100	20	1.062	0.118	20	0.977	0.095	20	1.068	0.117	20
Heart/BWt												
%	0.3718	0.0313	20	0.3797	0.0287	20	0.3496	0.0270	20	0.3790	0.0442	20
Heart/BrWt												
ratio	0.5440	0.0573	20	0.5427	0.0672	20	0.5032	0.0482	20	0.5306	0.0658	20

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

Table 49-2. Summary of Organ Weight Values – Female (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

	0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Kidneys												
g	2.169	0.309	20	2.060	0.186	20	2.012	0.257	20	2.063	0.196	20
Kidneys/BWt %	0.7656	0.1380	20	0.7382	0.0578	20	0.7194	0.0726	20	0.7302	0.0443	20
Kidneys/BrWt ratio	1.1131	0.1569	20	1.0521	0.1033	20	1.0333	0.0939	20	1.0233[a]	0.0955	20
Liver												
g	8.789	1.038	20	8.484	1.188	20	8.067	0.936	20	8.205	0.795	20
Liver/BWt %	3.0922	0.3955	20	3.0334	0.3369	20	2.8798	0.2169	20	2.9025	0.1482	20
Liver/BrWt ratio	4.5092	0.5185	20	4.3417	0.7002	20	4.1503	0.4457	20	4.0690[a]	0.3770	20
Lung w/ bronchi												
g	1.446	0.301	20	1.399	0.165	20	1.358	0.099	20	1.449	0.184	19
Lung w/ bronchi/BWt %	0.5098	0.1178	20	0.5003	0.0458	20	0.4861	0.0263	20	0.5142	0.0729	19
Lung w/ bronchi/BrWt ratio	0.7431	0.1573	20	0.7148	0.0950	20	0.6999	0.0593	20	0.7175	0.0899	19

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

[a] Significantly different from control; ($p<0.05$)

Table 49-2. Summary of Organ Weight Values – Female (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

	0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Ovaries												
g	0.087	0.019	20	0.072	0.029	20	0.082	0.018	20	0.096	0.031	20
Ovaries/BWt												
%	0.0306	0.0065	20	0.0256	0.0102	20	0.0295	0.0062	20	0.0343	0.0108	20
Ovaries/BrWt												
ratio	0.0448	0.0097	20	0.0364	0.0150	20	0.0422	0.0085	20	0.0479	0.0159	20
Pituitary gl												
g	0.0232	0.0055	20	0.0227	0.0037	20	0.0204	0.0037	20	0.0197[a]	0.0038	20
Pituitary gl/BWt												
%	0.0082	0.0021	20	0.0081	0.0012	20	0.0073	0.0013	20	0.0070[a]	0.0012	20
Pituitary gl/BrWt												
ratio	0.0119	0.0028	20	0.0116	0.0021	20	0.0105	0.0020	20	0.0098[b]	0.0019	20
Spleen												
g	0.546	0.069	20	0.517	0.072	20	0.557	0.084	20	0.524	0.077	20
Spleen/BWt												
%	0.1920	0.0244	20	0.1852	0.0245	20	0.1993	0.0262	20	0.1855	0.0215	20
Spleen/BrWt												
ratio	0.2805	0.0363	20	0.2639	0.0383	20	0.2862	0.0366	20	0.2598	0.0356	20

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

[a] Significantly different from control; ($p<0.05$)
[b] Significantly different from control; ($p<0.01$)

Table 49-2. Summary of Organ Weight Values – Female (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

	0 mg/kg/day			30 mg/kg/day			70 mg/kg/day			140 mg/kg/day		
Endpoint	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Thymus g	0.329	0.080	20	0.292	0.064	20	0.297	0.100	20	0.281	0.084	20
Thymus/BWt %	0.1154	0.0272	20	0.1051	0.0251	20	0.1057	0.0330	20	0.0995	0.0277	20
Thymus/BrWt ratio	0.1692	0.0422	20	0.1492	0.0328	20	0.1531	0.0525	20	0.1394	0.0423	20
Thyroid/parathyroid gl g	0.022	0.004	20	0.020	0.003	20	0.019[a]	0.003	20	0.020	0.002	20
Thyroid/parathyroid gl/BWt %	0.0075	0.0010	20	0.0071	0.0014	20	0.0068	0.0010	20	0.0071	0.0009	20
Thyroid/parathyroid gl/BrWt ratio	0.0111	0.0019	20	0.0101	0.0017	20	0.0097	0.0015	20	0.0099	0.0013	20
Uterus w/ cervix g	0.625	0.132	20	0.700	0.205	20	0.585	0.151	20	0.561	0.162	20
Uterus w/ cervix/BWt %	0.2212	0.0554	20	0.2534	0.0846	20	0.2100	0.0575	20	0.1988	0.0539	20
Uterus w/ cervix/BrWt ratio	0.3225	0.0776	20	0.3578	0.1054	20	0.3027	0.0875	20	0.2779	0.0771	20

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

[a] Significantly different from control; ($p<0.05$)

Table 50-1. Summary of Microscopic Observations – Male
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

		0 mg/kg/day		70 mg/kg/day		140 mg/kg/day	
Tissue Observation	Severity	DOS	SNC	DOS	SNC	DOS	SNC
Number of Animals Examined		0	20	0	2	1	19
adrenal glands		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
aorta		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
bone marrow, femur		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
bone marrow, sternum		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
bone, femur		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
bone, sternum		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
brain		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19

DOD – Died or euthanized on study
SNC – Scheduled necropsy
( ) – Number observed

Table 50-1. Summary of Microscopic Observations – Male (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

		0 mg/kg/day		70 mg/kg/day		140 mg/kg/day	
Tissue Observation	Severity	DOS	SNC	DOS	SNC	DOS	SNC
Number of Animals Examined		0	20	0	2	1	19
coagulating glands		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
epididymides		(0)	(20)	(0)	(0)	(1)	(19)
oligospermia/germ cell debris, unilateral	- severe	0	1	0	0	0	0
within normal limits		0	19	0	0	1	19
esophagus		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
eyes		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
eyes, optic nerves		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
galt		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
harderian glands		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
heart		(0)	(20)	(0)	(0)	(1)	(19)
cardiomyopathy	- minimal	0	8	0	0	0	6

DOD – Died or euthanized on study
SNC – Scheduled necropsy
( ) – Number observed

Table 50-1. Summary of Microscopic Observations – Male (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

		0 mg/kg/day		70 mg/kg/day		140 mg/kg/day	
Tissue Observation	Severity	DOS	SNC	DOS	SNC	DOS	SNC
Number of Animals Examined		0	20	0	2	1	19
heart		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	12	0	0	1	13
joint, tibiofemoral		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
kidneys		(0)	(20)	(0)	(0)	(1)	(19)
cyst	- minimal	0	1	0	0	0	0
nephropathy, chronic progressive	- minimal	0	5	0	0	0	3
within normal limits		0	14	0	0	1	16
lacrimal glands, exorbital		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
large intestine, cecum		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
large intestine, colon		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
large intestine, rectum		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19

DOD – Died or euthanized on study
SNC – Scheduled necropsy
( ) – Number observed

Table 50-1. Summary of Microscopic Observations – Male (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

		0 mg/kg/day		70 mg/kg/day		140 mg/kg/day	
Tissue Observation	Severity	DOS	SNC	DOS	SNC	DOS	SNC
Number of Animals Examined		0	20	0	2	1	19
larynx		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
liver		(0)	(20)	(0)	(0)	(1)	(19)
hyperplasia, bile duct	- minimal	0	1	0	0	0	1
infiltration, mononuclear cell	- minimal	0	20	0	0	1	19
necrosis, focal	- minimal	0	1	0	0	0	0
polyarteritis	- minimal	0	1	0	0	0	0
lung		(0)	(20)	(0)	(0)	(1)	(19)
histiocytosis, alveolar	- minimal	0	0	0	0	0	1
within normal limits		0	20	0	0	1	18
lymph node, mandibular		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
lymph node, mesenteric		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
nerve, sciatic		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
nose		(0)	(20)	(0)	(0)	(1)	(19)
erosion/ulcer	- moderate	0	0	0	0	1	0

DOD – Died or euthanized on study
SNC – Scheduled necropsy
( ) – Number observed

Table 50-1. Summary of Microscopic Observations – Male (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

		0 mg/kg/day		70 mg/kg/day		140 mg/kg/day	
Tissue Observation	Severity	DOS	SNC	DOS	SNC	DOS	SNC
Number of Animals Examined		0	20	0	2	1	19
nose		(0)	(20)	(0)	(0)	(1)	(19)
hemorrhage	- moderate	0	0	0	0	1	0
inflammation, subacute/chronic	- mild	0	0	0	0	1	0
within normal limits		0	20	0	0	0	19
pancreas		(0)	(20)	(0)	(0)	(1)	(19)
atrophy, acinar	- minimal	0	5	0	0	0	4
hemorrhage/pigment/inflammation/fibrosis, islets	- minimal	0	3	0	0	0	3
inflammation, subacute/chronic	- minimal	0	2	0	0	0	1
within normal limits		0	12	0	0	1	14
parathyroid glands		(0)	(18)	(0)	(0)	(0)	(19)
within normal limits		0	18	0	0	0	19
pituitary gland		(0)	(20)	(0)	(0)	(1)	(19)
cyst	- minimal	0	1	0	0	0	1
within normal limits		0	19	0	0	1	18
prostate gland		(0)	(20)	(0)	(0)	(1)	(19)
inflammation, subacute/chronic	- minimal	0	5	0	0	1	6
within normal limits		0	15	0	0	0	13
salivary gland, mandibular		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19

DOD – Died or euthanized on study
SNC – Scheduled necropsy
( ) – Number observed

Table 50-1. Summary of Microscopic Observations – Male (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

Tissue Observation	Severity	0 mg/kg/day DOS	 SNC	70 mg/kg/day DOS	 SNC	140 mg/kg/day DOS	 SNC
Number of Animals Examined		0	20	0	2	1	19
seminal vesicles		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
skeletal muscle, biceps femoris		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
skin		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
small intestine, duodenum		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
small intestine, ileum		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
small intestine, jejunum		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
spinal cord		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
spleen		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19

DOD – Died or euthanized on study
SNC – Scheduled necropsy
( ) – Number observed

Table 50-1. Summary of Microscopic Observations – Male (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

		0 mg/kg/day		70 mg/kg/day		140 mg/kg/day	
Tissue Observation	Severity	DOS	SNC	DOS	SNC	DOS	SNC
Number of Animals Examined		0	20	0	2	1	19
stomach, glandular		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
stomach, nonglandular		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
testes		(0)	(20)	(0)	(0)	(1)	(19)
degeneration/atrophy, seminiferous tubules, unilateral	- severe	0	1	0	0	0	0
dilation, seminiferous tubules, unilateral	- mild	0	1	0	0	0	0
within normal limits		0	19	0	0	1	19
thymus		(0)	(20)	(0)	(2)	(1)	(19)
hemorrhage	- minimal	0	0	0	2	0	0
within normal limits		0	20	0	0	1	19
thyroid gland		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
tongue		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
trachea		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19
urinary bladder		(0)	(20)	(0)	(0)	(1)	(19)
within normal limits		0	20	0	0	1	19

DOD – Died or euthanized on study
SNC – Scheduled necropsy
( ) – Number observed

Table 50-2. Summary of Microscopic Observations – Female
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

Tissue Observation	Severity	0 mg/kg/day DOS	 SNC	70 mg/kg/day DOS	 SNC	140 mg/kg/day DOS	 SNC
Number of Animals Examined		0	20	0	2	0	20
adrenal glands		(0)	(20)	(0)	(0)	(0)	(20)
angiectasis/cystic degeneration, focal cortical	- minimal	0	0	0	0	0	1
hypertrophy, focal cortical		0	1	0	0	0	1
	- minimal	0	0	0	0	0	1
	- mild	0	1	0	0	0	0
within normal limits		0	19	0	0	0	18
aorta		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
bone marrow, femur		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
bone marrow, sternum		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
bone, femur		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
bone, sternum		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20

DOD – Died or euthanized on study
SNC – Scheduled necropsy
( ) – Number observed

Table 50-2. Summary of Microscopic Observations – Female (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

		0 mg/kg/day		70 mg/kg/day		140 mg/kg/day	
Tissue Observation	Severity	DOS	SNC	DOS	SNC	DOS	SNC
Number of Animals Examined		0	20	0	2	0	20
brain		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
esophagus		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
eyes		(0)	(20)	(0)	(1)	(0)	(20)
rupture, iatrogenic globe	- no grade	0	0	0	1	0	0
within normal limits		0	20	0	0	0	20
eyes, optic nerves		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
galt		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
harderian glands		(0)	(20)	(0)	(0)	(0)	(20)
infiltration, lymphocytic	- mild	0	0	0	0	0	1
within normal limits		0	20	0	0	0	19
heart		(0)	(20)	(0)	(0)	(0)	(20)
cardiomyopathy	- minimal	0	3	0	0	0	3
within normal limits		0	17	0	0	0	17

DOD – Died or euthanized on study
SNC – Scheduled necropsy
( ) – Number observed

Table 50-2. Summary of Microscopic Observations – Female (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

Tissue Observation	Severity	0 mg/kg/day DOS	 SNC	70 mg/kg/day DOS	 SNC	140 mg/kg/day DOS	 SNC
Number of Animals Examined		0	20	0	2	0	20
joint, tibiofemoral		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
kidneys		(0)	(20)	(0)	(0)	(0)	(20)
cyst		0	2	0	0	0	0
	- minimal	0	1	0	0	0	0
	- mild	0	1	0	0	0	0
mineralization	- minimal	0	0	0	0	0	2
nephropathy, chronic progressive		0	2	0	0	0	1
	- minimal	0	0	0	0	0	1
	- mild	0	1	0	0	0	0
	- moderate	0	1	0	0	0	0
within normal limits		0	16	0	0	0	17
lacrimal glands, exorbital		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
large intestine, cecum		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
large intestine, colon		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20

DOD – Died or euthanized on study
SNC – Scheduled necropsy
( ) – Number observed

Table 50-2. Summary of Microscopic Observations – Female (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

Tissue Observation	Severity	0 mg/kg/day DOS	 SNC	70 mg/kg/day DOS	 SNC	140 mg/kg/day DOS	 SNC
Number of Animals Examined		0	20	0	2	0	20
large intestine, rectum		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
larynx		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
liver		(0)	(20)	(0)	(0)	(0)	(20)
infiltration, mononuclear cell	- minimal	0	19	0	0	0	20
necrosis, focal	- minimal	0	0	0	0	0	1
within normal limits		0	1	0	0	0	0
lung		(0)	(20)	(0)	(0)	(0)	(20)
histiocytosis, alveolar	- minimal	0	2	0	0	0	0
inflammation, subacute/chronic	- minimal	0	0	0	0	0	1
within normal limits		0	18	0	0	0	19
lymph node, mandibular		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
lymph node, mesenteric		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
mammary gland		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20

DOD – Died or euthanized on study
SNC – Scheduled necropsy
( ) – Number observed

Table 50-2. Summary of Microscopic Observations – Female (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

		0 mg/kg/day		70 mg/kg/day		140 mg/kg/day	
Tissue Observation	Severity	DOS	SNC	DOS	SNC	DOS	SNC
Number of Animals Examined		0	20	0	2	0	20
nerve, sciatic		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
nose		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
ovaries		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
oviducts		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
pancreas		(0)	(20)	(0)	(0)	(0)	(20)
atrophy, acinar	- minimal	0	4	0	0	0	4
inflammation, subacute/chronic	- minimal	0	1	0	0	0	1
within normal limits		0	16	0	0	0	15
parathyroid glands		(0)	(17)	(0)	(0)	(0)	(16)
within normal limits		0	17	0	0	0	16
pituitary gland		(0)	(20)	(0)	(0)	(0)	(20)
cyst	- minimal	0	1	0	0	0	0
within normal limits		0	19	0	0	0	20

DOD – Died or euthanized on study
SNC – Scheduled necropsy
( ) – Number observed

Table 50-2. Summary of Microscopic Observations – Female (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

Tissue Observation	Severity	0 mg/kg/day DOS	 SNC	70 mg/kg/day DOS	 SNC	140 mg/kg/day DOS	 SNC
Number of Animals Examined		0	20	0	2	0	20
salivary gland, mandibular		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
skeletal muscle, biceps femoris		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
skin		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
small intestine, duodenum		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
small intestine, ileum		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
small intestine, jejunum		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
spinal cord		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
spleen		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20

DOD – Died or euthanized on study
SNC – Scheduled necropsy
( ) – Number observed

Table 50-2. Summary of Microscopic Observations – Female (continued)
MPI Research Study No. 1646-029
S2218: A 13 Week Dietary Administration Toxicity Study in Rat

Tissue Observation	Severity	0 mg/kg/day DOS	 SNC	70 mg/kg/day DOS	 SNC	140 mg/kg/day DOS	 SNC
Number of Animals Examined		0	20	0	2	0	20
stomach, glandular		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
stomach, nonglandular		(0)	(20)	(0)	(1)	(0)	(20)
hyperplasia, squamous cell	- mild	0	0	0	1	0	0
inflammation, subacute/chronic	- minimal	0	0	0	1	0	0
within normal limits		0	20	0	0	0	20
thymus		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
thyroid gland		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
tongue		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
trachea		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
urinary bladder		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
uterus with cervix		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20
vagina		(0)	(20)	(0)	(0)	(0)	(20)
within normal limits		0	20	0	0	0	20

DOD – Died or euthanized on study
SNC – Scheduled necropsy
( ) – Number observed

S2218 Sulfate Salt (S8069) Range-Finder Developmental Toxicity Study

Summary of Study Design

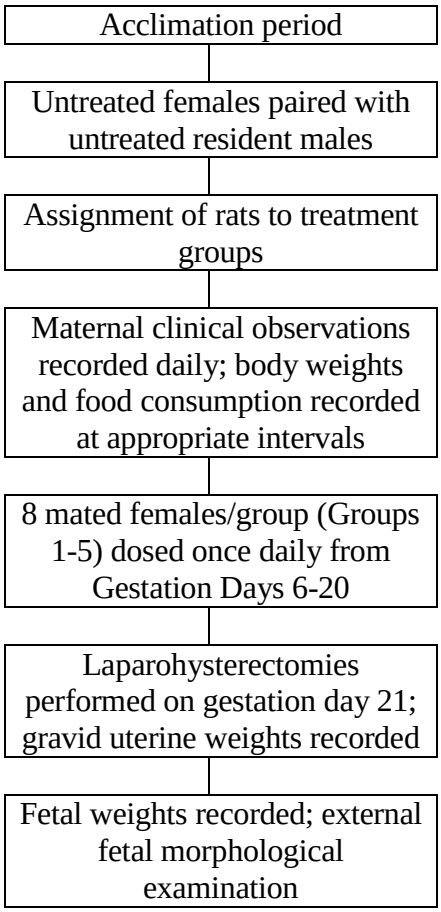


Table 51

Summary of Maternal Survival and Pregnancy Status
An Oral (Gavage) Dose Range-Finding Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884039

DOSE GROUP:	1		2		3		4		5	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
FEMALES ON STUDY	8		8		8		8		8	
FEMALES THAT ABORTED OR DELIVERED	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FEMALES THAT DIED	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FEMALES THAT ABORTED	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
NONGRAVID	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
GRAVID	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FEMALES THAT WERE EUTHANIZED	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
NONGRAVID	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
GRAVID	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
FEMALES EXAMINED AT SCHEDULED NECROPSY	8	100.0	8	100.0	8	100.0	8	100.0	8	100.0
FEMALES THAT ABORTED	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
NONGRAVID	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
GRAVID	8	100.0	8	100.0	8	100.0	8	100.0	8	100.0
WITH RESORPTIONS ONLY	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
WITH VIABLE FETUSES	8	100.0	8	100.0	8	100.0	8	100.0	8	100.0
TOTAL FEMALES GRAVID	8	100.0	8	100.0	8	100.0	8	100.0	8	100.0

1- 0 MG/KG/DAY 2- 125 MG/KG/DAY 3- 250 MG/KG/DAY 4- 500 MG/KG/DAY 5- 1000 MG/KG/DAY

Table 52

Summary of Clinical Findings: Total Occurrence/No. of Animals
An Oral (Gavage) Dose Range-Finding Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884039

GROUP:	1	2	3	4	5
NORMAL					
-NO SIGNIFICANT CLINICAL OBSERVATIONS	174/8	166/8	170/8	158/8	172/8
DISPOSITION					
-SCHEDULED EUTHANASIA; GESTATION DAY 21	8/8	8/8	8/8	8/8	8/8
BODY/INTEGUMENT					
-HAIR LOSS FORELIMB(S)	2/1	8/1	5/1	16/3	4/2
-HAIR LOSS VENTRAL TRUNK	0/0	2/1	0/0	0/0	0/0
-HAIR LOSS HINDLIMB(S)	0/0	1/1	0/0	0/0	0/0
EYES/EARS/NOSE					
-DRIED RED MATERIAL AROUND NOSE	0/0	0/0	1/1	0/0	0/0
BODY/INTEG. II					
-SCABBING DORSAL TRUNK	0/0	0/0	0/0	2/1	0/0
-SCABBING FORELIMB(S)	0/0	0/0	0/0	1/1	0/0

1- 0 MG/KG/DAY 2- 125 MG/KG/DAY 3- 250 MG/KG/DAY 4- 500 MG/KG/DAY 5- 1000 MG/KG/DAY

Table 53

Summary of Post-Dose Findings: Total Occurrence/No. of Animals
An Oral (Gavage) Dose Range-Finding Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884039

GROUP:	1	2	3	4	5
NORMAL					
1 HOUR POST-DOSING					
-NO SIGNIFICANT CLINICAL OBSERVATIONS	120/8	120/8	120/8	120/8	117/8
EYES/EARS/NOSE					
1 HOUR POST-DOSING					
-WET CLEAR MATERIAL AROUND NOSE	0/0	0/0	0/0	0/0	1/1
-WET RED MATERIAL AROUND NOSE	0/0	0/0	0/0	0/0	1/1
EXCRETA					
1 HOUR POST-DOSING					
-RED VAGINAL DISCHARGE	0/0	0/0	0/0	0/0	1/1
ORAL/DENTAL					
1 HOUR POST-DOSING					
-WET CLEAR MATERIAL AROUND MOUTH	0/0	0/0	0/0	0/0	2/2
SPECIAL II					
TIME OF DOSE					
-UNDETERMINED AMOUNT OF DOSE EXPELLED	1/1	0/0	0/0	1/1	3/2

1- 0 MG/KG/DAY 2- 125 MG/KG/DAY 3- 250 MG/KG/DAY 4- 500 MG/KG/DAY 5- 1000 MG/KG/DAY

Table 54

Summary of Maternal Body Weights During Gestation (g)
An Oral (Gavage) Dose Range-Finding Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884039

GROUP:	0 MG/KG/DAY	125 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 0					
MEAN	247.	252.	250.	248.	247.
S.D.	9.9	6.9	8.0	10.8	10.0
N	8	8	8	8	8
DAY 6					
MEAN	278.	282.	281.	278.	278.
S.D.	13.8	13.6	13.5	14.4	12.9
N	8	8	8	8	8
DAY 7					
MEAN	281.	285.	284.	282.	278.
S.D.	14.5	13.8	16.7	13.0	13.9
N	8	8	8	8	8
DAY 8					
MEAN	287.	295.	288.	286.	281.
S.D.	15.0	13.3	15.0	14.4	13.3
N	8	8	8	8	8
DAY 9					
MEAN	292.	295.	294.	289.	282.
S.D.	16.1	16.7	14.1	16.3	6.6
N	8	8	8	8	8
DAY 10					
MEAN	295.	302.	301.	295.	289.
S.D.	16.8	13.7	15.0	16.3	8.8
N	8	8	8	8	8

None significantly different from control group
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

Table 54 (continued)

Summary of Maternal Body Weights During Gestation (g)
An Oral (Gavage) Dose Range-Finding Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884039

GROUP:	0 MG/KG/DAY	125 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 11					
MEAN	303.	308.	309.	304.	298.
S.D.	15.1	15.0	14.7	16.0	8.3
N	8	8	8	8	8
DAY 12					
MEAN	308.	316.	314.	309.	305.
S.D.	15.2	18.0	14.7	15.1	10.2
N	8	8	8	8	8
DAY 13					
MEAN	311.	320.	317.	312.	310.
S.D.	14.3	16.0	16.4	15.8	12.6
N	8	8	8	8	8
DAY 14					
MEAN	315.	324.	320.	316.	315.
S.D.	14.5	17.2	14.8	17.1	13.8
N	8	8	8	8	8
DAY 15					
MEAN	324.	330.	328.	321.	324.
S.D.	18.0	19.9	15.5	14.7	16.5
N	8	8	8	8	8
DAY 16					
MEAN	335.	343.	339.	333.	333.
S.D.	17.6	18.6	15.1	17.1	16.5
N	8	8	8	8	8

None significantly different from control group
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

Table 54 (continued)

Summary of Maternal Body Weights During Gestation (g)
An Oral (Gavage) Dose Range-Finding Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884039

GROUP:	0 MG/KG/DAY	125 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 17					
MEAN	347.	354.	351.	347.	348.
S.D.	18.6	17.4	15.5	15.1	17.3
N	8	8	8	8	8
DAY 18					
MEAN	362.	373.	370.	364.	364.
S.D.	19.1	21.9	18.3	19.6	17.8
N	8	8	8	8	8
DAY 19					
MEAN	379.	391.	387.	382.	382.
S.D.	20.0	20.7	18.3	18.4	20.0
N	8	8	8	8	8
DAY 20					
MEAN	395.	408.	405.	397.	400.
S.D.	20.1	18.7	20.1	23.7	19.5
N	8	8	8	8	8
DAY 21					
MEAN	413.	427.	428.	416.	423.
S.D.	21.2	16.2	21.0	28.7	20.9
N	8	8	8	8	8

None significantly different from control group
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

Table 55

Summary of Gravid Uterine Weights and Net Body Weight Changes (g)
An Oral (Gavage) Dose Range-Finding Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884039

GROUP:	0 MG/KG/DAY	125 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
INITIAL BODY WT.					
MEAN	247.	252.	250.	248.	247.
S.D.	9.9	6.9	8.0	10.8	10.0
N	8	8	8	8	8
TERMINAL BODY WT.					
MEAN	413.	427.	428.	416.	423.
S.D.	21.2	16.2	21.0	28.7	20.9
N	8	8	8	8	8
GRAVID UTERINE WT.					
MEAN	106.9	110.8	105.2	106.6	109.0
S.D.	12.21	6.75	8.69	14.91	8.55
N	8	8	8	8	8
NET BODY WT.					
MEAN	306.2	316.5	322.5	309.1	313.7
S.D.	14.92	12.72	15.01	19.82	15.58
N	8	8	8	8	8
NET BODY WT. CHANGE					
MEAN	59.4	64.7	72.8	61.6	66.7
S.D.	7.74	7.86	8.86	14.12	12.58
N	8	8	8	8	8

None significantly different from control group

Table 56

Summary of Food Consumption During Gestation (g/animal/day)
An Oral (Gavage) Dose Range-Finding Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884039

GROUP:	0 MG/KG/DAY	125 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 0- 6					
MEAN	18.	18.	17.	15.	17.
S.D.	1.6	2.1	2.4	5.9	1.8
N	7	8	7	8	8
DAY 6- 7					
MEAN	19.	19.	18.	19.	17.
S.D.	1.7	3.6	3.2	0.9	3.0
N	8	8	8	8	8
DAY 7- 8					
MEAN	19.	20.	19.	19.	18.
S.D.	2.9	3.0	2.4	2.6	3.8
N	8	8	8	8	8
DAY 8- 9					
MEAN	20.	18.	21.	19.	17.
S.D.	4.2	2.7	2.2	2.6	4.5
N	8	8	8	8	8
DAY 9- 10					
MEAN	19.	19.	21.	19.	18.
S.D.	2.1	2.5	2.1	1.5	4.6
N	8	8	8	8	8
DAY 10- 11					
MEAN	20.	19.	22.	21.	20.
S.D.	2.1	3.9	2.9	3.0	1.2
N	8	8	8	8	8

None significantly different from control group
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

Table 56 (continued)

Summary of Food Consumption During Gestation (g/animal/day)
An Oral (Gavage) Dose Range-Finding Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884039

GROUP:	0 MG/KG/DAY	125 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 11- 12					
MEAN	22.	23.	21.	22.	22.
S.D.	1.8	3.1	2.4	1.8	2.8
N	8	8	8	8	8
DAY 12- 13					
MEAN	22.	22.	23.	22.	22.
S.D.	2.0	2.1	2.9	2.6	3.2
N	8	8	8	8	8
DAY 13- 14					
MEAN	20.	21.	22.	21.	21.
S.D.	1.8	2.1	2.1	2.0	2.6
N	8	8	8	8	8
DAY 14- 15					
MEAN	23.	21.	22.	23.	22.
S.D.	3.0	2.5	1.6	1.8	3.1
N	8	8	8	8	8
DAY 15- 16					
MEAN	24.	24.	24.	23.	22.
S.D.	3.9	3.3	2.3	2.4	3.1
N	8	8	8	8	8
DAY 16- 17					
MEAN	24.	25.	25.	25.	24.
S.D.	1.9	2.7	2.6	2.8	2.5
N	8	8	8	8	8
DAY 17- 18					
MEAN	24.	26.	27.	26.	25.
S.D.	2.7	4.0	2.7	2.8	2.1
N	8	8	8	8	8

None significantly different from control group
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

Table 56 (continued)

Summary of Food Consumption During Gestation (g/animal/day)
An Oral (Gavage) Dose Range-Finding Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884039

GROUP:	0 MG/KG/DAY	125 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 18- 19					
MEAN	25.	26.	26.	26.	26.
S.D.	2.1	1.7	1.8	1.9	2.5
N	8	8	8	7	8
DAY 19- 20					
MEAN	24.	24.	25.	22.	25.
S.D.	2.8	3.1	4.6	5.5	2.3
N	8	8	8	8	8
DAY 20- 21					
MEAN	23.	23.	27.*	23.	24.
S.D.	2.8	2.2	1.7	3.5	3.8
N	8	8	8	8	8
DAY 6- 9					
MEAN	19.	19.	20.	19.	17.
S.D.	2.4	2.0	1.5	1.3	2.3
N	8	8	8	8	8
DAY 9- 12					
MEAN	20.	20.	21.	21.	20.
S.D.	1.2	2.3	1.8	1.6	2.6
N	8	8	8	8	8
DAY 12- 15					
MEAN	22.	21.	22.	22.	22.
S.D.	1.6	1.6	1.6	1.0	2.8
N	8	8	8	8	8
DAY 15- 21					
MEAN	24.	25.	26.	24.	24.
S.D.	1.8	1.2	1.9	1.0	2.0
N	8	8	8	8	8
DAY 6- 21					
MEAN	22.	22.	23.	22.	22.
S.D.	1.2	1.7	1.2	0.9	1.8
N	8	8	8	8	8

* = Significantly different from the control group at 0.05 using Dunnett's test
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

Table 57

Summary of Maternal Macroscopic Findings
An Oral (Gavage) Dose Range-Finding Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884039

GROUP:	1	2	3	4	5
NUMBER EXAMINED	8	8	8	8	8
NO SIGNIFICANT CHANGES OBSERVED	7	6	7	6	8
OVIDUCTS: CYST(S)	0	0	1	0	0
UTERUS: CONTENTS, DARK RED	0	1	0	2	0
LIVER: AREA(S), WHITE	1	0	0	0	0
AMNIOTIC SAC: CONTENTS, BROWN	0	1	0	0	0
UTERUS: DISCOLORATION, DARK RED	0	1	0	0	0
PLACENTAE: ENLARGED	0	1	0	0	0

1- 0 MG/KG/DAY 2- 125 MG/KG/DAY 3- 250 MG/KG/DAY 4- 500 MG/KG/DAY 5- 1000 MG/KG/DAY

Table 58

Summary of Fetal Data at Scheduled Necropsy
An Oral (Gavage) Dose Range-Finding Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884039

GROUP		SEX M	SEX F	VIABLE FETUSES	DEAD FETUSES	RESORPTIONS EARLY	RESORPTIONS LATE	POST IMPLANTATION LOSS	IMPLANTATION SITES	CORPORA LUTEA	PRE IMPLANTATION LOSS	FETAL WEIGHTS IN GRAMS	NO. OF GRAVID FEMALES
1	TOTAL	63	52	115	0	1	0	1	116	123	7	NA	8
	MEAN	7.9	6.5	14.4	0.0	0.1	0.0	0.1	14.5	15.4	0.9	5.6	
	S.D.	2.17	2.27	1.19	0.00	0.35	0.00	0.35	1.20	1.41	1.13	0.35	
	S.E.	0.77	0.80	0.42	0.00	0.13	0.00	0.13	0.42	0.50	0.40	0.12	
2	TOTAL	61	56	117	0	6	1	7	124	129	5	NA	8
	MEAN	7.6	7.0	14.6	0.0	0.8	0.1	0.9	15.5	16.1	0.6	5.7	
	S.D.	2.13	2.62	1.30	0.00	0.89	0.35	0.83	1.20	1.25	0.92	0.22	
	S.E.	0.75	0.93	0.46	0.00	0.31	0.13	0.30	0.42	0.44	0.32	0.08	
3	TOTAL	53	55	108	0	9	0	9	117	126	9	NA	8
	MEAN	6.6	6.9	13.5	0.0	1.1	0.0	1.1	14.6	15.8	1.1	5.9	
	S.D.	2.26	2.03	1.41	0.00	1.13	0.00	1.13	1.60	2.60	1.25	0.21	
	S.E.	0.80	0.72	0.50	0.00	0.40	0.00	0.40	0.56	0.92	0.44	0.07	
4	TOTAL	61	51	112	0	4	0	4	116	121	5	NA	8
	MEAN	7.6	6.4	14.0	0.0	0.5	0.0	0.5	14.5	15.1	0.6	5.6	
	S.D.	2.13	2.00	1.77	0.00	0.76	0.00	0.76	2.14	1.89	1.06	0.32	
	S.E.	0.75	0.71	0.63	0.00	0.27	0.00	0.27	0.76	0.67	0.38	0.11	
5	TOTAL	56	58	114	0	3	0	3	117	120	3	NA	8
	MEAN	7.0	7.3	14.3	0.0	0.4	0.0	0.4	14.6	15.0	0.4	5.8	
	S.D.	1.41	0.89	1.16	0.00	0.74	0.00	0.74	1.19	1.07	0.74	0.27	
	S.E.	0.50	0.31	0.41	0.00	0.26	0.00	0.26	0.42	0.38	0.26	0.10	

None significantly different from control group
NA = NOT APPLICABLE
MEAN NUMBER OF VIABLE FETUSES, MEAN NUMBER OF IMPLANTATION SITES, MEAN NUMBER OF CORPORA LUTEA,
FETAL WEIGHTS COMPARED USING DUNNETT'S TEST

1- 0 MG/KG/DAY2- 125 MG/KG/DAY 3- 250 MG/KG/DAY 4- 500 MG/KG/DAY 5- 1000 MG/KG/DAY

Table 59

Summary of Fetal Data at Scheduled Necropsy (% Per Litter)
An Oral (Gavage) Dose Range-Finding Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884039

GROUP:	0 MG/KG/DAY	125 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
CORPORA LUTEA					
MEAN	15.4	16.1	15.8	15.1	15.0
S.D.	1.41	1.25	2.60	1.89	1.07
N	8	8	8	8	8
IMPLANTATION SITES					
MEAN	14.5	15.5	14.6	14.5	14.6
S.D.	1.20	1.20	1.60	2.14	1.19
N	8	8	8	8	8
VIABLE FETUSES (%)					
MEAN	99.2	94.4	92.6	96.9	97.6
S.D.	2.37	5.14	7.17	4.59	4.90
N	8	8	8	8	8
DEAD FETUSES (%)					
MEAN	0.0	0.0	0.0	0.0	0.0
S.D.	0.00	0.00	0.00	0.00	0.00
N	8	8	8	8	8
EARLY RESORPTIONS (%)					
MEAN	0.8	4.7	7.4	3.1	2.5
S.D.	2.37	5.45	7.19	4.59	4.91
N	8	8	8	8	8
LATE RESORPTIONS (%)					
MEAN	0.0	0.9	0.0	0.0	0.0
S.D.	0.00	2.51	0.00	0.00	0.00
N	8	8	8	8	8

PROPORTIONAL (%) DATA COMPARED USING THE MANN-WHITNEY TEST
CORPORA LUTEA AND IMPLANTATION SITES COMPARED USING DUNNETT'S TEST
None significantly different from control group

Table 59 (continued)

Summary of Fetal Data at Scheduled Necropsy (% Per Litter)
An Oral (Gavage) Dose Range-Finding Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884039

GROUP:	0 MG/KG/DAY	125 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
TOTAL RESORPTIONS (%)					
MEAN	0.8	5.6	7.4	3.1	2.5
S.D.	2.37	5.14	7.19	4.59	4.91
N	8	8	8	8	8
PRE-IMPLANTATION LOSS (%)					
MEAN	5.4	3.7	6.4	4.2	2.5
S.D.	6.68	5.44	6.39	7.47	4.76
N	8	8	8	8	8
POST-IMPLANTATION LOSS (%)					
MEAN	0.8	5.6	7.4	3.1	2.5
S.D.	2.37	5.14	7.19	4.59	4.91
N	8	8	8	8	8
MALES (%)					
MEAN	55.0	52.6	48.9	54.4	48.8
S.D.	15.00	14.70	14.92	12.96	7.49
N	8	8	8	8	8
FEMALES (%)					
MEAN	45.0	47.4	51.1	45.6	51.2
S.D.	15.00	14.70	14.92	12.96	7.49
N	8	8	8	8	8
MALE FETAL WEIGHTS (%)					
MEAN	5.7	5.8	6.0	5.8	6.0
S.D.	0.42	0.27	0.27	0.39	0.29
N	8	8	8	8	8
FEMALE FETAL WEIGHTS (g)					
MEAN	5.4	5.6	5.7	5.6	5.6
S.D.	0.36	0.16	0.25	0.26	0.28
N	8	8	8	8	8
COMBINED FETAL WEIGHTS (g)					
MEAN	5.6	5.7	5.9	5.6	5.8
S.D.	0.35	0.22	0.21	0.32	0.27
N	8	8	8	8	8

PROPORTIONAL (%) DATA COMPARED USING THE MANN-WHITNEY TEST
FETAL WEIGHTS COMPARED USING DUNNETT'S TEST
None significantly different from control group

Table 60

Summary of Fetuses and Litters with Malformations (absolute no.)
An Oral (Gavage) Dose Range-Finding Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884039

DAY 21

	FETUSES					LITTERS				
DOSE GROUP:	1	2	3	4	5	1	2	3	4	5
NUMBER EXAMINED EXTERNALLY	115	117	108	112	114	8	8	8	8	8
NUMBER WITH FINDINGS	0	0	0	0	0	0	0	0	0	0
TOTAL NUMBER WITH MALFORMATIONS EXTERNAL :	0	0	0	0	0	0	0	0	0	0

1- 0 MG/KG/DAY 2- 125 MG/KG/DAY 3- 250 MG/KG/DAY 4- 500 MG/KG/DAY 5- 1000 MG/KG/DAY

Table 61

Summary of Fetuses and Litters with Variations (absolute no.)
An Oral (Gavage) Dose Range-Finding Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884039

DAY 21

	FETUSES					LITTERS				
DOSE GROUP:	1	2	3	4	5	1	2	3	4	5
NUMBER EXAMINED EXTERNALLY	115	117	108	112	114	8	8	8	8	8
NUMBER WITH FINDINGS	0	0	0	0	0	0	0	0	0	0

1- 0 MG/KG/DAY 2- 125 MG/KG/DAY 3- 250 MG/KG/DAY 4- 500 MG/KG/DAY 5- 1000 MG/KG/DAY

Oral (Gavage) Developmental Toxicity Study S2218 Sulfate Salt (S8069) (definitive phase)

Summary of Study Design

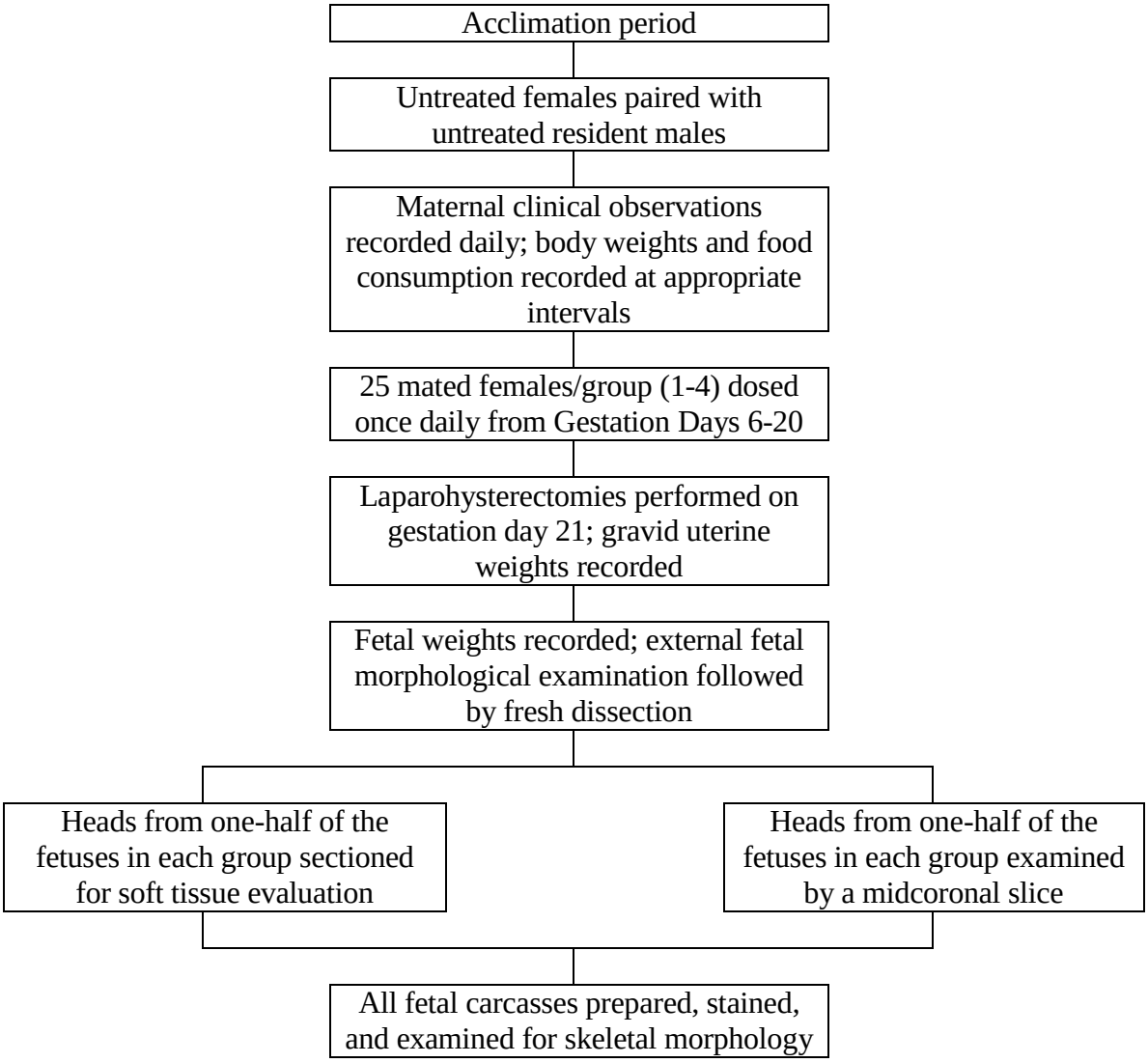


Table 62

Summary of Maternal Survival and Pregnancy Status
Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats (oral gavage)
Project No.: WIL-884040

DOSE GROUP :	1		2		3		4	
	NO.	%	NO.	%	NO.	%	NO.	%
FEMALES ON STUDY	25		25		25		25	
FEMALES THAT ABORTED OR DELIVERED	0	0.0	0	0.0	0	0.0	0	0.0
FEMALES THAT DIED	0	0.0	0	0.0	1	4.0	1	4.0
FEMALES THAT ABORTED	0	0.0	0	0.0	0	0.0	0	0.0
NONGRAVID	0	0.0	0	0.0	0	0.0	0	0.0
GRAVID	0	0.0	0	0.0	0	0.0	1	100.0
FEMALES THAT WERE EUTHANIZED	0	0.0	0	0.0	0	0.0	0	0.0
NONGRAVID	0	0.0	0	0.0	0	0.0	0	0.0
GRAVID	0	0.0	0	0.0	1	100.0	0	0.0
FEMALES EXAMINED AT SCHEDULED NECROPSY	25	100.0	25	100.0	24	96.0	24	96.0
FEMALES THAT ABORTED	0	0.0	0	0.0	0	0.0	0	0.0
NONGRAVID	0	0.0	1	4.0	1	4.2	1	4.2
GRAVID	25	100.0	24	96.0	23	95.8	23	95.8
WITH RESORPTIONS ONLY	0	0.0	0	0.0	0	0.0	0	0.0
WITH VIABLE FETUSES	25	100.0	24	100.0	23	100.0	23	100.0
TOTAL FEMALES GRAVID	25	100.0	24	96.0	24	96.0	24	96.0

1- 0 MG/KG/DAY 2- 250 MG/KG/DAY 3- 500 MG/KG/DAY 4- 1000 MG/KG/DAY

Table 63

Summary of Clinical Findings: Total Occurrence/No. of Animals
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

DOSE GROUP :	1	2	3	4
NORMAL				
-NO SIGNIFICANT CLINICAL OBSERVATIONS	508/25	536/25	476/25	528/25
DISPOSITION				
-SENT TO NECROPSY IN EXTREMIS	0/ 0	0/ 0	1/ 1	0/ 0
-FOUND DEAD	0/ 0	0/ 0	0/ 0	1/ 1
-SENT TO NECROPSY; DELIVERED	0/ 0	0/ 0	1/ 1	0/ 0
-SCHEDULED EUTHANASIA; GESTATION DAY 21	25/25	25/25	23/23	24/24
BODY/INTEGUMENT				
-HAIR LOSS FORELIMB(S)	37/ 6	14/ 3	45/ 4	15/ 4
-HAIR LOSS HINDLIMB(S)	1/ 1	0/ 0	2/ 1	0/ 0
-THIN	0/ 0	0/ 0	3/ 1	0/ 0
-DERMAL ATONIA	0/ 0	0/ 0	1/ 1	0/ 0
-UNKEMPT APPEARANCE	0/ 0	0/ 0	1/ 1	0/ 0
-HAIR LOSS VENTRAL TRUNK	0/ 0	0/ 0	1/ 1	0/ 0
CARDIO-PULMONARY				
-RALES	0/ 0	0/ 0	1/ 1	1/ 1
EYES/EARS/NOSE				
-DRIED RED MATERIAL AROUND NOSE	2/ 2	0/ 0	1/ 1	1/ 1
EXCRETA				
-DECREASED DEFECATION	0/ 0	0/ 0	2/ 1	0/ 0
BODY/INTEG. II				
-SCABBING FORELIMB(S)	0/ 0	0/ 0	1/ 1	0/ 0
-SCABBING DORSAL TRUNK	3/ 1	0/ 0	0/ 0	0/ 0
-WET YELLOW MATERIAL UROGENITAL AREA	0/ 0	0/ 0	1/ 1	1/ 1
-SCABBING FACIAL AREA	0/ 0	0/ 0	1/ 1	0/ 0
-WET CLEAR MATERIAL UROGENITAL AREA	0/ 0	0/ 0	1/ 1	0/ 0
ORAL/DENTAL				
-DRIED RED MATERIAL AROUND MOUTH	0/ 0	0/ 0	0/ 0	1/ 1
SPECIAL II				
-TAIL BROKEN	0/ 0	0/ 0	17/ 1	0/ 0

1- 0 MG/KG/DAY 2- 250 MG/KG/DAY 3- 500 MG/KG/DAY 4- 1000 MG/KG/DAY

Table 64

Summary of Post-Dose Findings: Total Occurrence/No. of Animals
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

DOSE GROUP	1	2	3	4
NORMAL				
1 HOUR POST-DOSING				
-NO SIGNIFICANT CLINICAL OBSERVATIONS	374/25	373/25	370/25	361/25
UNSCHED OBS (>75 MINS)				
-NO SIGNIFICANT CLINICAL OBSERVATIONS	1/1	1/1	0/0	0/0
CARDIO-PULMONARY				
TIME OF DOSE				
-RALES	0/0	0/0	0/0	1/1
1 HOUR POST-DOSING				
-RALES	0/0	0/0	0/0	7/6
EYES/EARS/NOSE				
1 HOUR POST-DOSING				
-DRIED RED MATERIAL AROUND NOSE	0/0	0/0	0/0	1/1
ORAL/DENTAL				
TIME OF DOSE				
-SALIVATION	0/0	0/0	0/0	4/4
1 HOUR POST-DOSING				
-WET CLEAR MATERIAL AROUND MOUTH	0/0	1/1	1/1	3/3
SPECIAL II				
TIME OF DOSE				
-UNDETERMINED AMOUNT OF DOSE EXPELLED	4/3	6/6	6/6	4/4
-ANIMAL DIFFICULT TO DOSE (MORE THAN 2 ATTEMPTS)	1/1	1/1	2/2	1/1

1- 0 MG/KG/DAY 2- 250 MG/KG/DAY 3- 500 MG/KG/DAY 4- 1000 MG/KG/DAY

Table 65

Summary of Maternal Body Weights During Gestation (g)
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

GROUP	0 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 0				
MEAN	253.	255.	254.	252.
S.D.	11.4	11.0	12.6	11.7
N	25	24	24	24
DAY 6				
MEAN	286.	287.	285.	283.
S.D.	12.7	11.2	14.8	13.5
N	25	24	24	24
DAY 7				
MEAN	289.	289.	285.	285.
S.D.	14.1	11.6	16.3	13.8
N	25	24	24	24
DAY 8				
MEAN	293.	290.	287.	288.
S.D.	14.2	12.7	16.4	13.2
N	25	24	24	24
DAY 9				
MEAN	298.	295.	291.	287.
S.D.	15.6	11.7	18.0	18.6
N	25	24	24	24
DAY 10				
MEAN	303.	299.	296.	292.
S.D.	14.5	11.5	18.3	16.1
N	25	24	24	24

None significantly different from control group
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

Table 65 (continued)

Summary of Maternal Body Weights During Gestation (g)
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

GROUP	0 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 11				
MEAN	308.	306.	302.	298.
S.D.	15.8	12.4	19.0	17.5
N	25	24	24	24
DAY 12				
MEAN	314.	310.	304.	303.
S.D.	17.1	12.6	22.2	17.0
N	25	24	24	24
DAY 13				
MEAN	319.	315.	311.	309.
S.D.	18.1	12.7	25.0	18.1
N	25	24	24	24
DAY 14				
MEAN	325.	320.	314.	315.
S.D.	17.4	13.5	26.7	18.2
N	25	24	24	24
DAY 15				
MEAN	334.	327.	322.	321.
S.D.	17.5	13.2	26.7	17.1
N	25	24	24	24
DAY 16				
MEAN	342.	337.	332.	333.
S.D.	18.3	13.9	30.3	19.1
N	25	24	24	24

None significantly different from control group
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

Table 65 (continued)

Summary of Maternal Body Weights During Gestation (g)
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

GROUP	0 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 17				
MEAN	354.	351.	350.	346.
S.D.	18.4	13.1	23.4	20.9
N	25	24	23	24
DAY 18				
MEAN	372.	365.	365.	360.
S.D.	20.1	17.4	24.5	24.1
N	25	24	23	23
DAY 19				
MEAN	387.	381.	381.	376.
S.D.	20.3	16.3	26.3	27.6
N	25	24	23	23
DAY 20				
MEAN	405.	399.	398.	393.
S.D.	22.3	18.1	27.1	28.8
N	25	24	23	23
DAY 21				
MEAN	424.	417.	418.	411.
S.D.	22.9	20.6	28.6	30.5
N	25	24	22	23

None significantly different from control group
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

Table 66

Summary of Gravid Uterine Weights and Net Body Weight Changes (g)
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

GROUP:	0 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
INITIAL BODY WT.				
MEAN	253.	255.	254.	251.
S.D.	11.4	11.0	12.7	11.8
N	25	24	22	23
TERMINAL BODY WT.				
MEAN	424.	417.	418.	411.
S.D.	22.9	20.6	28.6	30.5
N	25	24	22	23
GRAVID UTERINE WT.				
MEAN	110.7	107.1	109.8	106.6
S.D.	15.14	15.42	15.19	17.00
N	25	24	22	23
NET BODY WT.				
MEAN	313.5	310.2	308.4	304.3
S.D.	20.48	13.12	20.25	20.86
N	25	24	22	23
NET BODY WT. CHANGE				
MEAN	60.1	55.7	54.3	53.2
S.D.	12.07	10.89	12.33	16.76
N	25	24	22	23

None significantly different from control group

Table 67

Summary of Food Consumption During Gestation (g/animal/day)
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

GROUP:	0 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 0- 6				
MEAN	20.	20.	19.	19.
S.D.	1.6	2.1	1.9	1.8
N	25	24	24	24
DAY 6- 7				
MEAN	21.	22.	21.	21.
S.D.	3.5	3.7	5.7	6.1
N	25	24	24	24
DAY 7- 8				
MEAN	21.	22.	21.	23.
S.D.	2.5	3.3	4.2	5.0
N	25	24	24	24
DAY 8- 9				
MEAN	23.	22.	22.	20.
S.D.	3.7	2.6	6.3	7.7
N	25	24	24	24
DAY 9- 10				
MEAN	21.	22.	21.	21.
S.D.	3.3	2.4	5.9	4.7
N	25	24	24	24
DAY 10- 11				
MEAN	21.	23.	22.	20.
S.D.	4.5	2.7	3.5	3.9
N	25	24	24	24

None significantly different from control group
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

Table 67 (continued)

Summary of Food Consumption During Gestation (g/animal/day)
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

GROUP:	0 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 11- 12				
MEAN	23.	23.	23.	23.
S.D.	4.5	3.6	6.5	5.4
N	25	24	24	24
DAY 12- 13				
MEAN	23.	24.	23.	24.
S.D.	3.6	3.4	7.0	4.3
N	25	24	23	23
DAY 13- 14				
MEAN	22.	22.	22.	24.
S.D.	3.1	3.1	7.5	7.4
N	25	24	23	24
DAY 14- 15				
MEAN	24.	24.	23.	23.
S.D.	2.6	5.0	6.5	5.4
N	25	24	23	24
DAY 15- 16				
MEAN	25.	24.	24.	24.
S.D.	3.4	3.4	5.7	4.3
N	24	24	24	24
DAY 16- 17				
MEAN	25.	26.	25.	24.
S.D.	3.5	2.5	4.1	4.6
N	25	24	23	24
DAY 17- 18				
MEAN	27.	25.	26.	24.
S.D.	5.4	5.7	4.0	5.2
N	25	24	23	23

None significantly different from control group
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

Table 67 (continued)

Summary of Food Consumption During Gestation (g/animal/day)
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

GROUP:	0 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
DAY 18- 19				
MEAN	27.	27.	25.	24.
S.D.	4.4	4.6	4.1	6.0
N	25	24	23	23
DAY 19- 20				
MEAN	26.	25.	24.	26.
S.D.	4.3	3.6	4.1	5.1
N	24	24	23	23
DAY 20- 21				
MEAN	24.	24.	24.	23.
S.D.	3.7	3.7	3.3	7.7
N	23	23	22	23
DAY 6- 9				
MEAN	22.	22.	21.	21.
S.D.	2.3	2.4	4.2	4.0
N	25	24	24	24
DAY 9- 12				
MEAN	22.	23.	22.	21.
S.D.	2.4	2.3	4.0	3.7
N	25	24	24	24
DAY 12- 15				
MEAN	23.	23.	23.	24.
S.D.	2.0	2.1	5.4	3.5
N	25	24	24	24
DAY 15- 21				
MEAN	26.	25.	25.	24.
S.D.	2.2	2.4	2.6	4.2
N	25	24	23	23
DAY 6- 21				
MEAN	24.	24.	23.	23.
S.D.	1.9	1.9	2.5	3.0
N	25	24	23	23

None significantly different from control group
NONGRAVID WEIGHT(S) NOT INCLUDED IN CALCULATION OF MEAN

Table 68

Summary of Maternal Macroscopic Findings
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

GROUP:	1	2	3	4
NUMBER EXAMINED	25	25	25	25
NO SIGNIFICANT CHANGES OBSERVED	23	23	20	22
NONGRAVID -- AMMONIUM SULFIDE NEGATIVE	0	1	1	1
LUNGS: ADHESIONS	0	0	1	0
HEART: MASS	0	0	1	0
ESOPHAGUS: PERFORATION	0	0	1	0
REASON FOR EUTH: INTUBATION ERROR	0	0	1	0
EUTHANIZED IN EXTREMIS	0	0	1	0
FOUND DEAD	0	0	0	1
KIDNEYS: CYST(S)	1	1	0	0
LIVER: ROUGH SURFACE	0	1	0	0
UTERUS: CONTENTS, DARK RED	1	0	1	1
DELIVERED	0	0	1	0
UTERUS: CONTENTS, CLEAR FLUID	0	1	0	0
PLACENTAE: FUSED	0	0	1	0

1- 0 MG/KG/DAY 2- 250 MG/KG/DAY 3- 500 MG/KG/DAY 4- 1000 MG/KG/DAY

Table 69

Summary of Fetal Data at Scheduled Necropsy
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

GROUP		SEX M	SEX F	VIABLE FETUSES	DEAD FETUSES	RESORPTIONS EARLY	RESORPTIONS LATE	POST IMPLANTATION LOSS	IMPLANTATION SITES	CORPORA LUTEA	PRE IMPLANTATION LOSS	FETAL WEIGHTS IN GRAMS	NO. OF GRAVID FEMALES
1	TOTAL	178	177	355	0	21	0	21	376	403	27	NA	25
	MEAN	7.1	7.1	14.2	0.0	0.8	0.0	0.8	15.0	16.1	1.1	5.8	
	S.D.	2.28	2.02	2.08	0.00	1.31	0.00	1.31	2.37	2.37	1.91	0.36	
	S.E.	0.46	0.40	0.42	0.00	0.26	0.00	0.26	0.47	0.47	0.38	0.07	
2	TOTAL	158	173	331	0	23	0	23	354	363	9	NA	24
	MEAN	6.6	7.2	13.8	0.0	1.0	0.0	1.0	14.8	15.1	0.4	5.9	
	S.D.	1.44	1.41	1.96	0.00	1.08	0.00	1.08	1.54	1.51	0.58	0.31	
	S.E.	0.29	0.29	0.40	0.00	0.22	0.00	0.22	0.31	0.31	0.12	0.06	
3	TOTAL	151	188	339	0	16	0	16	355	370	15	NA	23
	MEAN	6.6	8.2	14.7	0.0	0.7	0.0	0.7	15.4	16.1	0.7	5.6	
	S.D.	2.11	1.77	2.30	0.00	0.82	0.00	0.82	2.04	1.90	0.93	0.39	
	S.E.	0.44	0.37	0.48	0.00	0.17	0.00	0.17	0.43	0.40	0.19	0.08	
4	TOTAL	168	160	328	0	7	0	7	335	348	13	NA	23
	MEAN	7.3	7.0	14.3	0.0	0.3	0.0	0.3	14.6	15.1	0.6	5.6	
	S.D.	2.57	2.34	2.34	0.00	0.63	0.00	0.63	2.09	2.42	1.16	0.37	
	S.E.	0.54	0.49	0.49	0.00	0.13	0.00	0.13	0.43	0.50	0.24	0.08	

None significantly different from control group
NA = NOT APPLICABLE
MEAN NUMBER OF VIABLE FETUSES, MEAN NUMBER OF IMPLANTATION SITES, MEAN NUMBER OF CORPORA LUTEA,
FETAL WEIGHTS COMPARED USING DUNNETT'S TEST

1- 0 MG/KG/DAY 2- 250 MG/KG/DAY 3- 500 MG/KG/DAY 4- 1000 MG/KG/DAY

Table 70

Summary of Fetal Data at Scheduled Necropsy (% Per Litter)
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

Group:	0 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
CORPORA LUTEA				
MEAN	16.1	15.1	16.1	15.1
S.D.	2.37	1.51	1.90	2.42
N	25	24	23	23
IMPLANTATION SITES				
MEAN	15.0	14.8	15.4	14.6
S.D.	2.37	1.54	2.04	2.09
N	25	24	23	23
VIABLE FETUSES (%)				
MEAN	94.9	93.4	95.3	97.7
S.D.	7.57	7.69	5.64	5.05
N	25	24	23	23
DEAD FETUSES (%)				
MEAN	0.0	0.0	0.0	0.0
S.D.	0.00	0.00	0.00	0.00
N	25	24	23	23
EARLY RESORPTIONS (%)				
MEAN	5.1	6.6	4.7	2.3
S.D.	7.57	7.69	5.64	5.05
N	25	24	23	23
LATE RESORPTIONS (%)				
MEAN	0.0	0.0	0.0	0.0
S.D.	0.00	0.00	0.00	0.00
N	25	24	23	23
TOTAL RESORPTIONS (%)				
MEAN	5.1	6.6	4.7	2.3
S.D.	7.57	7.69	5.64	5.05
N	25	24	23	23

PROPORTIONAL (%) DATA COMPARED USING THE MANN-WHITNEY TEST
CORPORA LUTEA AND IMPLANTATION SITES COMPARED USING DUNNETT'S TEST
None significantly different from control group

Table 70 (Continued)

Summary of Fetal Data at Scheduled Necropsy (% Per Litter)
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

Group:	0 MG/KG/DAY	250 MG/KG/DAY	500 MG/KG/DAY	1000 MG/KG/DAY
PRE-IMPLANTATION LOSS (%)				
MEAN	6.3	2.5	4.1	3.3
S.D.	11.11	3.64	5.80	6.29
N	25	24	23	23
POST-IMPLANTATION LOSS (%)				
MEAN	5.1	6.6	4.7	2.3
S.D.	7.57	7.69	5.64	5.05
N	25	24	23	23
MALES (%)				
MEAN	49.8	47.6	44.1	51.0
S.D.	12.97	7.83	10.42	15.55
N	25	24	23	23
FEMALES (%)				
MEAN	50.2	52.4	55.9	49.0
S.D.	12.97	7.83	10.42	55.15
N	25	24	23	23
MALE FETAL WEIGHTS (g)				
MEAN	6.0	6.0	5.8	5.8
S.D.	0.36	0.34	0.41	0.40
N	25	24	23	23
FEMALE FETAL WEIGHTS (g)				
MEAN	5.7	5.7	5.5	5.5
S.D.	0.36	0.32	0.40	0.36
N	25	24	23	23
COMBINED FETAL WEIGHTS (g)				
MEAN	5.8	5.9	5.6	5.6
S.D.	0.36	0.31	0.39	0.37
N	25	24	23	23

PROPORTIONAL (%) DATA COMPARED USING THE MANN-WHITNEY TEST
FETAL WEIGHTS COMPARED USING DUNNETT'S TEST
None significantly different from control group

Table 71

Summary of Fetuses and Litters with Malformations (Absolute No.)
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

DAY 21

	FETUSES				LITTERS			
DOSE GROUP:	1	2	3	4	1	2	3	4
NUMBER EXAMINED EXTERNALLY	355	331	339	328	25	24	23	23
OMPHALOCELE	1	0	0	0	1	0	0	0
MICROPHTHALMIA AND/OR ANOPHTHALMIA	1	0	0	0	1	0	0	0
NUMBER EXAMINED VISCERALLY	355	331	339	328	25	24	23	23
RETROESOPHAGEAL AORTIC ARCH	0	1	1	0	0	1	1	0
INTERVENTRICULAR SEPTAL DEFECT	0	2	1	1	0	1	1	1
KIDNEY AND URETER ABSENT	0	0	1	0	0	0	1	0
UTERUS- PORTION ABSENT	0	0	1	0	0	0	1	0
NUMBER EXAMINED SKELETALLY	355	331	339	328	25	24	23	23
STERNOSCHISIS	1	0	0	0	1	0	0	0
STERNEBRAE FUSED	0	0	1	0	0	0	1	0
STERNEBRA(E) MALALIGNED (SEVERE)	0	0	1	0	0	0	1	0
VERTEBRAL ANOMALY WITH OR WITHOUT ASSOCIATED RIB ANOMALY	0	0	1	0	0	0	1	0
TOTAL NUMBER WITH MALFORMATIONS								
EXTERNAL :	2	0	0	0	2	0	0	0
SOFT TISSUE :	0	3	3	1	0	2	3	1
SKELETAL :	1	0	3	0	1	0	3	0
COMBINED :	3	3	4	1	3	2	4	1

1- 0 MG/KG/DAY 2- 250 MG/KG/DAY 3- 500 MG/KG/DAY 4- 1000 MG/KG/DAY

Table 72

Summary of Litter Proportions of Malformations (% Per Litter)
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

DAY 21

DOSE GROUP:		1	2	3	4
NUMBER OF LITTERS EXAMINED EXTERNALLY		25	24	23	23
OMPHALOCELE	MEAN	0.3	0.0	0.0	0.0
	S.D.	1.33	0.00	0.00	0.00
MICROPHTHALMIA AND/OR ANOPHTHALMIA	MEAN	0.3	0.0	0.0	0.0
	S.D.	1.33	0.00	0.00	0.00
NUMBER OF LITTERS EXAMINED VISCERALLY		25	24	23	23
RETROESOPHAGEAL AORTIC ARCH	MEAN	0.0	0.3	0.3	0.0
	S.D.	0.00	1.57	1.30	0.00
INTERVENTRICULAR SEPTAL DEFECT	MEAN	0.0	0.6	0.2	0.3
	S.D.	0.00	2.72	1.16	1.49
KIDNEY AND URETER ABSENT	MEAN	0.0	0.0	0.3	0.0
	S.D.	0.00	0.00	1.39	0.00
UTERUS- PORTION ABSENT	MEAN	0.0	0.0	0.3	0.0
	S.D.	0.00	0.00	1.39	0.00
NUMBER OF LITTERS EXAMINED SKELETALLY		25	24	23	23
STERNOSCISIS	MEAN	0.2	0.0	0.0	0.0
	S.D.	1.18	0.00	0.00	0.00
STERNEBRAE FUSED	MEAN	0.0	0.0	0.3	0.0
	S.D.	0.00	0.00	1.30	0.00
STERNEBRAE(E)MALALIGNED (SEVERE)	MEAN	0.0	0.0	0.4	0.0
	S.D.	0.00	0.00	1.74	0.00
VERTEBRAL ANOMALY WITH OR WITHOUT ASSOCIATED RIB ANOMALY	MEAN	0.0	0.0	0.3	0.0
	S.D.	0.00	0.00	1.39	0.00

1- 0 MG/KG/DAY 2- 250 MG/KG/DAY 3- 500 MG/KG/DAY 4- 1000 MG/KG/DAY
None significantly different from control group

Table 72 (Continued)

Summary of Litter Proportions of Malformations (% Per Litter)
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

DAY 21

DOSE GROUP:		1	2	3	4
NUMBER OF LITTERS EXAMINED		25	24	23	23
TOTAL MALFORMATIONS					
PERCENT PER LITTER WITH EXTERNAL MALFORMATIONS	MEAN	0.5	0.0	0.0	0.0
	S.D.	1.85	0.00	0.00	0.00
PERCENT PER LITTER WITH SOFT TISSUE MALFORMATIONS	MEAN	0.0	0.9	0.8	0.3
	S.D.	0.00	3.08	2.13	1.49
PERCENT PER LITTER WITH SKELETAL MALFORMATIONS	MEAN	0.2	0.0	0.9	0.0
	S.D.	1.18	0.00	2.46	0.00
TOTAL PERCENT PER LITTER WITH MALFORMATIONS	MEAN	0.8	0.9	1.2	0.3
	S.D.	2.13	3.08	2.63	1.49

1- 0 MG/KG/DAY 2- 250 MG/KG/DAY 3- 500 MG/KG/DAY 4- 1000 MG/KG/DAY
None significantly different from control group

Table 73

Summary of Fetuses and Litters with Variations (Absolute No.)
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

	FETUSES				LITTERS			
DOSE GROUP:	1	2	3	4	1	2	3	4
NUMBER EXAMINED EXTERNALLY	355	331	339	328	25	24	23	23
NUMBER WITH FINDINGS	0	0	0	0	0	0	0	0
NUMBER EXAMINED VISCERALLY	355	331	339	328	25	24	23	23
RENAL PAPILLA(E) NOT DEVELOPED AND/OR DISTENDED URETER(S)	14	9	5	4	8	7	4	4
LIVER- ACCESSORY LOBULE(S)	0	1	4	0	0	1	2	0
MAJOR BLOOD VESSEL VARIATION	0	1	0	0	0	1	0	0
NUMBER EXAMINED SKELETALLY	355	331	339	328	25	24	23	23
14TH RUDIMMENTARY RIB(S)	26	29	35	28	13	11	15	13
VERTEBRAL CENTRA NOT FULLY OSSIFIED	0	0	1	0	0	0	1	0
27 PRESACRAL VERTIBRAE	2	0	0	0	2	0	0	0
REDUCED OSSIFACATION OF THE 13TH RIB	1	0	1	1	1	0	1	1
7TH CERVICAL RIB(S)	0	3	3	2	0	3	3	2
STERNEBRA(E) MALALIGNED(SLIGHT OR MODERATE)	2	1	7	8	2	1	5	6
STERNEBRA(E) #5 AND/OR #6 UNOSSIFIED	1	0	1	1	1	0	1	1
ACCESSORY SKULL BONE(S)	0	1	0	0	0	1	0	0
7TH STERNEBRA	2	0	0	1	1	0	0	1
HYOID UNOSSIFIED	1	0	1	0	1	0	1	0
EXTRA SITE OF OSSIFICATION VENTRAL TO CERVICAL CENTRUM #2	1	0	0	0	1	0	0	0
14TH FULL RIB(S)	2	0	0	0	2	0	0	0
VERTEBRAL CENTRA UNOSSIFIED	0	0	0	2	0	0	0	1
BENT RIB(S)	1	0	0	0	1	0	0	0
STERNEBRA(E) #1,#2,#3 AND/OR #4 UNOSSIFIED	0	0	1	0	0	0	1	0

1- 0 MG/KG/DAY 2- 250 MG/KG/DAY 3- 500 MG/KG/DAY 4- 1000 MG/KG/DAY

Table 74

Summary of Litter Proportions of Variations (% Per Litter)
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

DAY 21

DOSE GROUP:		1	2	3	4
NUMBER OF LITTERS EXAMINED EXTERNALLY		25	24	23	23
NUMBER OF LITTERS WITH FINDINGS		0	0	0	0
NUMBER OF LITTERS EXAMINED VISCERALLY		25	24	23	23
RENAL PAPILLA(E) NOT DEVELOPED AND/OR DISTENDED URETER(S)	MEAN	3.9	2.8	1.4	1.2
	S.D.	6.66	5.39	3.29	2.63
LIVER- ACCESSORY LOBULE(S)	MEAN	0.0	0.3	1.0	0.0
	S.D.	0.00	1.36	3.63	0.00
MAJOR BLOOD VESSEL VARIATION	MEAN	0.0	0.4	0.0	0.0
	S.D.	0.00	1.86	0.00	0.00
NUMBER OF LITTERS EXAMINED SKETETALLY		25	24	23	23
14TH RUDIMENTARY RIB(S)	MEAN	7.9	8.7	10.4	9.1
	S.D.	16.64	11.82	12.64	11.67
VERTEBRAL CENTRA NOT FULLY OSSIFIED	MEAN	0.0	0.0	0.3	0.0
	S.D.	0.00	0.00	1.30	0.00
27 PRESACRAL VERTEBRAE	MEAN	0.5	0.0	0.0	0.0
	S.D.	1.81	0.00	0.00	0.00
REDUCED OSSIFICATION OF THE 13TH RIB(S)	MEAN	0.3	0.0	0.4	0.3
	S.D.	1.43	0.00	1.74	1.23
7TH CERVICAL RIB(S)	MEAN	0.0	1.0	0.9	0.7
	S.D.	0.00	2.77	2.37	2.21
STERNEBRA(E) MALALIGNED(SLIGHT OR MODERATE)	MEAN	0.6	0.3	2.0	2.4
	S.D.	1.99	1.46	4.46	5.07
STERNEBRA(E) #5 AND/OR #6 UNOSSIFIED	MEAN	0.2	0.0	0.2	0.4
	S.D.	1.18	0.00	1.16	1.90
ACCESSORY SKULL BONE(S)	MEAN	0.0	0.4	0.0	0.0
	S.D.	0.00	2.04	0.00	0.00
7TH STERNEBRA	MEAN	0.4	0.0	0.0	0.3
	S.D.	2.22	0.00	0.00	1.23
HYOID UNOSSIFIED	MEAN	0.3	0.0	0.2	0.0
	S.D.	1.33	0.00	1.16	0.00

1- 0 MG/KG/DAY 2- 250 MG/KG/DAY 3- 500 MG/KG/DAY 4- 1000 MG/KG/DAY
None significantly different from control group

Table 74 (continued)

Summary of Litter Proportions of Variations (% Per Litter)
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

DAY 21

DOSE GROUP:		1	2	3	4
NUMBER OF LITTERS EXAMINED SKETETALLY		25	24	23	23
EXTRA SITE OF OSSIFICATION VENTRAL TO CERVICAL CENTRUM #2	MEAN	0.2	0.0	0.0	0.0
	S.D.	1.18	0.00	0.00	0.00
14TH FULL RIB(S)	MEAN	0.6	0.0	0.0	0.0
	S.D.	2.00	0.00	0.00	0.00
VERTEBRAL CENTRA UNOSSIFIED	MEAN	0.0	0.0	0.0	0.5
	S.D.	0.00	0.00	0.00	2.61
BENT RIB(S)	MEAN	0.5	0.0	0.0	0.0
	S.D.	2.50	0.00	0.00	0.00
STERNEBRA(E) #1,#2,#3 AND/OR #4 UNOSSIFIED	MEAN	0.0	0.0	0.3	0.0
	S.D.	0.00	0.00	1.39	0.00

1- 0 MG/KG/DAY 2- 250 MG/KG/DAY 3- 500 MG/KG/DAY 4- 1000 MG/KG/DAY
None significantly different from control group

Table 74 (Continued)

Summary of Litter Proportions of Variations (% Per Litter)
An Oral (Gavage) Developmental Toxicity Study of S2218 Sulfate Salt (S8069) in Rats
Project No.: WIL-884040

DAY 21

DOSE GROUP:		1	2	3	4
NUMBER OF LITTERS EXAMINED		25	24	23	23
TOTAL VARIATIONS					
PERCENT PER LITTER WITH EXTERNAL VARIATIONS	MEAN	0.0	0.0	0.0	0.0
	S.D.	0.00	0.00	0.00	0.00
PERCENT PER LITTER WITH SOFT TISSUE VARIATIONS	MEAN	3.9	3.4	2.4	1.2
	S.D.	6.66	6.43	5.43	2.63
PERCENT PER LITTER WITH SKELETAL VARIATIONS	MEAN	10.5	10.4	13.6	13.3
	S.D.	17.76	11.96	12.72	12.65
TOTAL PERCENT PER LITTER WITH VARIATIONS	MEAN	13.5	12.9	16.0	14.2
	S.D.	18.00	14.64	12.21	12.45

1- 0 MG/KG/DAY 2- 250 MG/KG/DAY 3- 500 MG/KG/DAY 4- 1000 MG/KG/DAY
None significantly different from control group