

**APPENDIX E: DETAILED CLINICAL OBSERVATIONS ASSESSMENT METHODS
SCORING KEY**

PRODUCT IDENTIFICATION

Silk Fibroin

Removal from Cage/Hand-held Observations	
<u>Ease of Removal/Handling</u>	0. Slight/moderate resistance – animal is easy to handle, may squirm or vocalize occasionally 1. No resistance – animal is flaccid when being handled 2. High resistance – animal is difficult to handle, and/or squirms continuously 3. Aggressive – biting or lunging behavior specifically directed at handler
<u>Emaciation</u>	0. Absent 1. Present (confirmed using body weights)
<u>Eyes</u>	0. Normal 1. Exophthalmos – abnormal protrusion of eyeball present 2. Enophthalmus – posterior displacement of the eye (sunken eyeball) 3. Eye lesion – mechanical damage or other (e.g., orbital bleeding)
<u>Fur/Skin Appearance</u>	0. Normal 1. Unkempt – coat rough or ungroomed, may be slightly stained 2. Stained/wetness (e.g., ano-genital staining) 3. Hair loss 4. Other – includes but is not limited; eschar, wound, laceration or other skin lesions
<u>Lacrimation</u>	0. Absent 1. Present – lacrimation noticeable 2. Excessive – animal has excessive amount of tearing
<u>Mucous Membranes (color)</u>	0. Normal 1. Blanch to pink tone 2. Dusky rose to deep flush 3. Cyanosis (blue) 4. Excessive or abnormal secretion
<u>Muscle Tone</u>	0. Normal – muscles are resilient and firm and the hind legs go through their full range of motion 1. Increased – muscles are rigid; hind limbs will not go through their full range of motion 2. Decreased – muscles are flaccid; hind limbs have little or no resistance to movement
<u>Palpebral Closure</u>	0. Eyes wide open 1. Eyes halfway shut 2. Eyes completely shut
<u>Piloerection</u>	0. Absent 1. Present
<u>Pupillary reflex</u>	0. Normal 1. Slow or absent- pupil reaction is slow or absent.
<u>Respiratory Pattern</u>	0. Normal 1. Slow 2. Rapid 3. Rales (Moist or Dry) 4. Gasping 5. Labored - Dyspnea
<u>Salivation</u>	0. None 1. Present - salivation is noticeable around the edge of the mouth 2. Excessive - salivation extends to the fur around the jaw
<u>Vocalization</u>	0. Absent 1. Present - animal vocalizes unprovoked or continuously vocalizes when being handled.

Open Field Observations	
<u>Activity/Arousal</u>	<p>0. Alternating behaviors – animal goes through normal repertoire of behaviors during observation period; these consist of exploring, sniffing, grooming, rearing, etc.</p> <p>1. Inactive/Alert – animal sits in one place during the observation period but appears to be aware of its surroundings. It may go through its normal repertoire of activities but the majority of the observation period is spent not moving.</p> <p>2. Hypoactive/Not alert – animal sits in one place during the observation period; animal appears to be unaware of its surroundings or in a stupor.</p> <p>3. Hyperactive/Hyperalert – animal appears excited; animal may dart and freeze during the observation period or animal may sit in one place and jump at any sound or movement.</p>
<u>Convulsions</u>	<p>0. None</p> <p>1. Clonic – alternating periods of contraction and relaxation of muscles</p> <p>2. Tonic – prolonged period of muscle contractions</p>
<u>Defecation</u>	<p>0. None/Normal</p> <p>1. Soft (partially formed)</p> <p>2. Diarrhea (watery feces usually of increased volume)</p>
<u>Gait</u>	<p>0. Normal</p> <p>1. Ataxic Gait – inability of truncal, pelvic and limb muscles to move in unison so animal is not able to move in straight line (lurch).</p> <p>2. Hypotonic gait – impaired gait (limp) due to limb weakness or paralysis in which the animal is unable to support its weight but can move forward in a straight line without lurching.</p> <p>3. Impaired Gait – includes steppage (due to dorsiflexion of foot or toe the animal drags its forelimbs, walks on its knuckles or lifts its forelimbs unusually high to avoid dragging its toes over the ground); spastic (shuffling gait with legs rigidly extended and not lifted during movement; waddling (lateral wobbling of the pelvis); dysmetric (incoordinating movement with a coarse tremor due to overshooting goal).</p> <p>4. Total gait incapacity – applies when these are severe gait abnormalities or combinations of gait abnormality.</p>
<u>Locomotion (speed and vigor of movement)</u>	<p>0. Normal</p> <p>1. Somewhat impaired</p> <p>2. Totally impaired</p>
<u>Other</u>	<p>0. Absent</p> <p>1. Present</p> <p>NOTE: When present, a comment will identify finding</p>
<u>Posture</u>	<p>0. Normal (awake) – e.g., alert, sitting, standing, or rearing or Normal (sleeping) – e.g. curled up, usually with head down</p> <p>1. Hunched – e.g., abnormal posture</p> <p>2. Flattened (prone) –e.g., limbs spread out lying flat or on one side</p>
<u>Tremors</u>	<p>0. None</p> <p>1. Slight – e.g., localized involuntary oscillatory movement</p> <p>2. Severe – e.g., more to more than one area or involving whole body</p>
<u>Twitches</u>	<p>0. None</p> <p>1. Slight – brief coarse involuntary muscle contraction</p> <p>2. Moderate – increased frequency and severity</p> <p>3. Fasciculation – wave-like ripples of a muscle or group of muscles</p>
<u>Unusual Behaviors</u>	<p>0. Absent</p> <p>1. Present – Stereotypies/Bizarre behavior/Aggression be specific in describing all unusual behaviors on data sheet</p>
<u>Urination</u>	<p>0. None/Normal</p> <p>1. Excessive</p>
<u>Vocalizations</u>	<p>0. Absent</p> <p>1. Present</p>

APPENDIX F: INDIVIDUAL ANIMAL DETAILED CLINICAL OBSERVATIONS

PRODUCT IDENTIFICATION

Silk Fibroin

APPENDIX G: INDIVIDUAL ANIMAL WEEKLY BODY WEIGHTS

PRODUCT IDENTIFICATION

Silk Fibroin

Individual Animal Body Weights
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Male Bodyweight (g)

0 mg/kg/day Group 1	Day(s) Relative to Start Date					
	1	8	15	22	29	30
7001	240	282	330	382	428	399
7002	222	271	326	371	410	380
7003	226	266	314	344	407	360
7004	226	273	322	342	389	355
7005	245	275	365	423	481	444
7006	220	245	320	374	441	389
7007	235	283	326	391	436	402
7008	212	266	316	365	406	379
7009	250	304	350	401	434	404
7010	243	301	352	409	454	432
Mean	231.9	276.6	332.1	380.2	428.6	394.4
SD	12.5	17.3	17.4	26.5	26.9	28.4
N	10	10	10	10	10	10

Individual Animal Body Weights
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Male Bodyweight (g)

125 mg/kg/day Group 2	Day(s) Relative to Start Date					
	1	8	15	22	29	30
7021	247	289	333	364	397	371
7022	223	291	339	393	431	412
7023	226	283	327	378	413	379
7024	212	257	295	338	374	336
7025	225	270	311	364	395	372
7026	241	296	340	380	413	391
7027	221	276	326	389	440	420
7028	239	287	336	368	408	383
7029	248	288	331	380	420	389
7030	240	285	337	374	410	384
Mean	232.2	282.2	327.5	372.8	410.1	383.7
SD	12.3	11.6	14.2	15.6	18.7	23.1
N	10	10	10	10	10	10

Individual Animal Body Weights
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Male Bodyweight (g)

250 mg/kg/day Group 3	Day(s) Relative to Start Date					
	1	8	15	22	29	30
7041	240	295	340	391	430	406
7042	239	293	346	399	430	408
7043	224	285	344	390	420	407
7044	211	260	324	369	407	383
7045	226	265	315	344	393	352
7046	247	300	346	391	436	395
7047	230	282	325	365	395	373
7048	253	308	357	401	440	409
7049	243	290	340	382	423	400
7050	217	267	315	359	392	364
Mean	233.0	284.5	335.2	379.1	416.6	389.7
SD	13.6	16.0	14.4	18.9	18.4	20.6
N	10	10	10	10	10	10

Individual Animal Body Weights
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Male Bodyweight (g)

500 mg/kg/day Group 4	Day(s) Relative to Start Date					
	1	8	15	22	29	30
7061	211	269	327	376	419	385
7062	244	312	359	413	447	415
7063	250	306	358	400	435	409
7064	232	303	367	420	466	419
7065	233	292	334	386	425	402
7066	225	279	329	375	425	388
7067	240	290	340	395	447	413
7068	223	285	330	391	459	406
7069	217	260	303	355	396	370
7070	242	303	361	415	463	427
Mean	231.7	289.9	340.8	392.6	438.2	403.4
SD	12.6	16.9	20.1	20.5	22.3	17.5
N	10	10	10	10	10	10

Individual Animal Body Weights
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Bodyweight (g)

0 mg/kg/day Group 1	Day(s) Relative to Start Date					
	1	8	15	22	29	31
7011	181	208	220	236	245	233
7012	208	220	242	270	282	261
7013	200	211	221	235	245	228
7014	215	240	270	280	295	274
7015	222	240	255	271	282	266
7016	225	248	247	275	279	275
7017	197	221	247	254	253	246
7018	190	207	228	238	250	232
7019	206	224	255	259	275	253
7020	198	224	247	245	280	247
Mean	204.2	224.3	243.2	256.3	268.6	251.5
SD	13.9	14.2	16.0	17.2	18.4	17.3
N	10	10	10	10	10	10

Individual Animal Body Weights
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Bodyweight (g)

125 mg/kg/day Group 2	Day(s) Relative to Start Date					
	1	8	15	22	29	31
7031	188	201	213	224	238	201
7032	209	231	267	273	305	284
7033	203	212	232	246	256	244
7034	226	240	260	266	284	262
7035	205	232	250	257	269	250
7036	195	208	220	215	230	220
7037	197	207	223	241	250	238
7038	212	234	243	270	280	262
7039	223	250	283	301	320	291
7040	191	211	218	231	238	225
Mean	204.9	222.6	240.9	252.4	267.0	247.7
SD	12.8	16.7	23.7	26.1	30.1	28.2
N	10	10	10	10	10	10

Individual Animal Body Weights
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Bodyweight (g)

250 mg/kg/day Group 3	Day(s) Relative to Start Date					
	1	8	15	22	29	31
7051	210	234	248	253	282	259
7052	217	243	271	291	306	289
7053	234	258	268	287	301	280
7054	199	222	247	265	283	270
7055	194	217	237	255	262	250
7056	187	200	212	228	235	218
7057	208	223	233	253	271	251
7058	202	217	237	240	249	239
7059	206	231	237	258	262	252
7060	196	219	225	240	242	230
Mean	205.3	226.4	241.5	257.0	269.3	253.8
SD	13.3	16.0	18.0	19.9	23.9	21.9
N	10	10	10	10	10	10

Individual Animal Body Weights
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Bodyweight (g)

500 mg/kg/day Group 4	Day(s) Relative to Start Date					
	1	8	15	22	29	31
7071	207	217	246	268	304	267
7072	218	230	261	280	311	276
7073	189	200	218	240	248	229
7074	195	212	222	235	242	232
7075	213	237	250	258	264	260
7076	206	235	242	265	277	256
7077	197	214	232	239	271	244
7078	200	216	234	237	257	242
7079	229	246	266	297	305	287
7080	205	207	226	238	253	240
Mean	205.9	221.4	239.7	255.7	273.2	253.3
SD	11.8	14.8	16.2	21.5	25.3	19.2
N	10	10	10	10	10	10

APPENDIX H: INDIVIDUAL ANIMAL MEAN DAILY BODY WEIGHT GAIN

PRODUCT IDENTIFICATION

Silk Fibroin

Individual Animal Mean Daily Body Weight Gain
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Male Mean Daily Body Weight Gain (g/day)

0 mg/kg/day Group 1	Day(s) Relative to Start Date			
	1 → 8	8 → 15	15 → 22	22 → 29
7001	6.0	6.9	7.4	6.6
7002	7.0	7.9	6.4	5.6
7003	5.7	6.9	4.3	9.0
7004	6.7	7.0	2.9	6.7
7005	4.3	12.9	8.3	8.3
7006	3.6	10.7	7.7	9.6
7007	6.9	6.1	9.3	6.4
7008	7.7	7.1	7.0	5.9
7009	7.7	6.6	7.3	4.7
7010	8.3	7.3	8.1	6.4
Mean	6.39	7.93	6.87	6.91
SD	1.52	2.14	1.93	1.55
N	10	10	10	10

Individual Animal Mean Daily Body Weight Gain
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Male Mean Daily Body Weight Gain (g/day)

125 mg/kg/day Group 2	Day(s) Relative to Start Date			
	1 → 8	8 → 15	15 → 22	22 → 29
7021	6.0	6.3	4.4	4.7
7022	9.7	6.9	7.7	5.4
7023	8.1	6.3	7.3	5.0
7024	6.4	5.4	6.1	5.1
7025	6.4	5.9	7.6	4.4
7026	7.9	6.3	5.7	4.7
7027	7.9	7.1	9.0	7.3
7028	6.9	7.0	4.6	5.7
7029	5.7	6.1	7.0	5.7
7030	6.4	7.4	5.3	5.1
Mean	7.14	6.47	6.47	5.33
SD	1.23	0.62	1.49	0.81
N	10	10	10	10

Individual Animal Mean Daily Body Weight Gain
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Male Mean Daily Body Weight Gain (g/day)

250 mg/kg/day Group 3	Day(s) Relative to Start Date			
	1 → 8	8 → 15	15 → 22	22 → 29
7041	7.9	6.4	7.3	5.6
7042	7.7	7.6	7.6	4.4
7043	8.7	8.4	6.6	4.3
7044	7.0	9.1	6.4	5.4
7045	5.6	7.1	4.1	7.0
7046	7.6	6.6	6.4	6.4
7047	7.4	6.1	5.7	4.3
7048	7.9	7.0	6.3	5.6
7049	6.7	7.1	6.0	5.9
7050	7.1	6.9	6.3	4.7
Mean	7.36	7.24	6.27	5.36
SD	0.84	0.92	0.93	0.93
N	10	10	10	10

Individual Animal Mean Daily Body Weight Gain
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Male Mean Daily Body Weight Gain (g/day)

500 mg/kg/day Group 4	Day(s) Relative to Start Date			
	1 → 8	8 → 15	15 → 22	22 → 29
7061	8.3	8.3	7.0	6.1
7062	9.7	6.7	7.7	4.9
7063	8.0	7.4	6.0	5.0
7064	10.1	9.1	7.6	6.6
7065	8.4	6.0	7.4	5.6
7066	7.7	7.1	6.6	7.1
7067	7.1	7.1	7.9	7.4
7068	8.9	6.4	8.7	9.7
7069	6.1	6.1	7.4	5.9
7070	8.7	8.3	7.7	6.9
Mean	8.31	7.27	7.40	6.51
SD	1.17	1.03	0.74	1.42
N	10	10	10	10

Individual Animal Mean Daily Body Weight Gain
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Mean Daily Body Weight Gain (g/day)

0 mg/kg/day Group 1	Day(s) Relative to Start Date			
	1 → 8	8 → 15	15 → 22	22 → 29
7011	3.9	1.7	2.3	1.3
7012	1.7	3.1	4.0	1.7
7013	1.6	1.4	2.0	1.4
7014	3.6	4.3	1.4	2.1
7015	2.6	2.1	2.3	1.6
7016	3.3	-0.1	4.0	0.6
7017	3.4	3.7	1.0	-0.1
7018	2.4	3.0	1.4	1.7
7019	2.6	4.4	0.6	2.3
7020	3.7	3.3	-0.3	5.0
Mean	2.87	2.70	1.87	1.76
SD	0.82	1.42	1.37	1.35
N	10	10	10	10

Individual Animal Mean Daily Body Weight Gain
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Mean Daily Body Weight Gain (g/day)

125 mg/kg/day Group 2	Day(s) Relative to Start Date			
	1 → 8	8 → 15	15 → 22	22 → 29
7031	1.9	1.7	1.6	2.0
7032	3.1	5.1	0.9	4.6
7033	1.3	2.9	2.0	1.4
7034	2.0	2.9	0.9	2.6
7035	3.9	2.6	1.0	1.7
7036	1.9	1.7	-0.7	2.1
7037	1.4	2.3	2.6	1.3
7038	3.1	1.3	3.9	1.4
7039	3.9	4.7	2.6	2.7
7040	2.9	1.0	1.9	1.0
Mean	2.53	2.61	1.64	2.09
SD	0.96	1.38	1.25	1.03
N	10	10	10	10

Individual Animal Mean Daily Body Weight Gain
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Mean Daily Body Weight Gain (g/day)

250 mg/kg/day Group 3	Day(s) Relative to Start Date			
	1 → 8	8 → 15	15 → 22	22 → 29
7051	3.4	2.0	0.7	4.1
7052	3.7	4.0	2.9	2.1
7053	3.4	1.4	2.7	2.0
7054	3.3	3.6	2.6	2.6
7055	3.3	2.9	2.6	1.0
7056	1.9	1.7	2.3	1.0
7057	2.1	1.4	2.9	2.6
7058	2.1	2.9	0.4	1.3
7059	3.6	0.9	3.0	0.6
7060	3.3	0.9	2.1	0.3
Mean	3.01	2.16	2.21	1.76
SD	0.68	1.11	0.91	1.16
N	10	10	10	10

Individual Animal Mean Daily Body Weight Gain
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Mean Daily Body Weight Gain (g/day)

500 mg/kg/day Group 4	Day(s) Relative to Start Date			
	1 → 8	8 → 15	15 → 22	22 → 29
7071	1.4	4.1	3.1	5.1
7072	1.7	4.4	2.7	4.4
7073	1.6	2.6	3.1	1.1
7074	2.4	1.4	1.9	1.0
7075	3.4	1.9	1.1	0.9
7076	4.1	1.0	3.3	1.7
7077	2.4	2.6	1.0	4.6
7078	2.3	2.6	0.4	2.9
7079	2.4	2.9	4.4	1.1
7080	0.3	2.7	1.7	2.1
Mean	2.21	2.61	2.29	2.50
SD	1.07	1.07	1.25	1.65
N	10	10	10	10

APPENDIX I: FOOD CONSUMPTION BY CAGE

PRODUCT IDENTIFICATION

Silk Fibroin

Food Consumption by Cage
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

		Day numbers relative to Start Date										
Group	Sex	Cage	No In Cage	From:	1	6	8	13	15	20	22	27
				To:	6	8	13	15	20	22	27	29
1	m	1	2		23.9	24.5	27.3	27.8	29.9	26.8	29.3	27.8
		2	2		24.2	22.3	25.6	28.3	25.6	24.8	26.3	24.8
		3	2		26.3	18.0	29.3	33.3	31.9	28.3	33.3	31.8
		4	2		23.8	24.8	25.4	28.5	28.2	29.3	30.5	27.3
		5	2		27.4	28.5	29.4	30.8	28.8	28.5	29.6	29.5
				Mean	25.12	23.60	27.40	29.70	28.88	27.50	29.80	28.20
				S.D.	1.63	3.85	1.93	2.29	2.31	1.79	2.51	2.61
				N	5	5	5	5	5	5	5	5

* = Result to left has an associated comment or marker
Food consumption units are g/animal/day

Group 1 - 0 mg/kg/day Group 1 Group 2 - 125 mg/kg/day Group 2
Group 3 - 250 mg/kg/day Group 3 Group 4 - 500 mg/kg/day Group 4

Food Consumption by Cage
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

		Day numbers relative to Start Date										
Group	Sex	Cage	No In Cage	From:	1	6	8	13	15	20	22	27
				To:	6	8	13	15	20	22	27	29
2	m	11	2		25.3	25.8	27.6	29.0	28.0	23.5	27.9	23.5
		12	2		25.0	26.3	26.4	28.3	27.9	28.3	28.5	27.5
		13	2		26.1	27.5	27.0	30.0	32.3	28.5	29.8	27.0
		14	2		23.2	24.5	25.6	27.8	26.1	23.8	26.4	26.0
		15	2		24.4	23.5	26.9	29.8	27.0	26.0	27.1	25.0
				Mean	24.80	25.50	26.70	28.95	28.26	26.00	27.94	25.80
				S.D.	1.08	1.55	0.75	0.96	2.39	2.38	1.31	1.60
				N	5	5	5	5	5	5	5	5

* = Result to left has an associated comment or marker
Food consumption units are g/animal/day

Group 1 - 0 mg/kg/day Group 1 Group 2 - 125 mg/kg/day Group 2
Group 3 - 250 mg/kg/day Group 3 Group 4 - 500 mg/kg/day Group 4

Food Consumption by Cage
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

		Day numbers relative to Start Date										
Group	Sex	Cage	No In Cage	From:	1	6	8	13	15	20	22	27
				To:	6	8	13	15	20	22	27	29
3	m	21	2		24.4	28.5	27.7	29.5	27.1	27.8	28.4	25.0
		22	2		27.7	27.0	29.1	33.5	30.7	28.3	30.3	29.0
		23	2		24.2	25.0	27.4	28.0	27.3	27.3	27.1	28.3
		24	2		27.9	28.3	30.6	30.5	29.6	27.5	28.6	27.8
		25	2		24.4	22.8	27.0	30.3	28.0	27.5	29.9	27.8
				Mean	25.72	26.30	28.36	30.35	28.54	27.65	28.86	27.55
				S.D.	1.90	2.42	1.48	2.01	1.56	0.38	1.28	1.51
				N	5	5	5	5	5	5	5	5

* = Result to left has an associated comment or marker
Food consumption units are g/animal/day

Group 1 - 0 mg/kg/day Group 1 Group 2 - 125 mg/kg/day Group 2
Group 3 - 250 mg/kg/day Group 3 Group 4 - 500 mg/kg/day Group 4

Food Consumption by Cage
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

		Day numbers relative to Start Date										
Group	Sex	Cage	No In Cage	From:	1	6	8	13	15	20	22	27
				To:	6	8	13	15	20	22	27	29
4	m	31	2		26.6	30.0	29.2	29.0	28.9	30.3	30.5	27.5
		32	2		28.4	29.0	30.5	33.0	29.6	30.5	32.3	28.3
		33	2		25.9	26.8	27.7	28.5	28.8	26.0	29.0	27.5
		34	2		25.0	26.8	27.3	26.8	30.6	31.3	31.8	32.8
		35	2		24.9	27.3	28.1	29.3	29.7	30.0	30.9	30.8
				Mean	26.16	27.95	28.56	29.30	29.52	29.60	30.90	29.35
				S.D.	1.43	1.47	1.30	2.29	0.73	2.07	1.28	2.32
				N	5	5	5	5	5	5	5	5

* = Result to left has an associated comment or marker
Food consumption units are g/animal/day

Group 1 - 0 mg/kg/day Group 1 Group 2 - 125 mg/kg/day Group 2
Group 3 - 250 mg/kg/day Group 3 Group 4 - 500 mg/kg/day Group 4

Food Consumption by Cage
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

		Day numbers relative to Start Date										
Group	Sex	Cage	No In Cage	From:	1	6	8	13	15	20	22	27
				To:	6	8	13	15	20	22	27	29
1	f	6	2		20.3	20.5	20.7	22.8	20.8	20.5	22.0	19.3
		7	2		19.8	19.5	20.1	22.8	20.9	19.8	20.4	20.0
		8	2		22.0	19.3	22.9	21.3	21.6	19.3	22.1	18.8
		9	2		18.6	17.5	18.6	20.0	17.8	17.5	17.9	15.3
		10	2		21.4	22.0	22.1	24.3	20.3	17.3	20.6	20.0
				Mean	20.42	19.75	20.88	22.20	20.28	18.85	20.60	18.65
				S.D.	1.34	1.66	1.69	1.62	1.46	1.42	1.70	1.97
				N	5	5	5	5	5	5	5	5

* = Result to left has an associated comment or marker
Food consumption units are g/animal/day

Group 1 - 0 mg/kg/day Group 1 Group 2 - 125 mg/kg/day Group 2
Group 3 - 250 mg/kg/day Group 3 Group 4 - 500 mg/kg/day Group 4

Food Consumption by Cage
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

		Day numbers relative to Start Date										
Group	Sex	Cage	No In Cage	From:	1	6	8	13	15	20	22	27
				To:	6	8	13	15	20	22	27	29
2	f	16	2		18.6	18.8	19.8	22.0	19.5	17.0	19.8	20.3
		17	2		20.8	20.5	21.2	24.8	21.2	19.8	21.0	18.8
		18	2		18.6	18.0	19.1	22.8	18.1	13.3	17.0	18.5
		19	2		20.1	18.5	20.9	22.5	21.4	20.0	22.6	18.5
		20	2		20.0	18.8	20.2	22.8	20.5	18.5	21.0	18.5
				Mean	19.62	18.90	20.24	22.95	20.14	17.70	20.28	18.90
				S.D.	0.98	0.95	0.84	1.05	1.36	2.76	2.09	0.76
				N	5	5	5	5	5	5	5	5

* = Result to left has an associated comment or marker
Food consumption units are g/animal/day

Group 1 - 0 mg/kg/day Group 1 Group 2 - 125 mg/kg/day Group 2
Group 3 - 250 mg/kg/day Group 3 Group 4 - 500 mg/kg/day Group 4

Food Consumption by Cage
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

		Day numbers relative to Start Date										
Group	Sex	Cage	No In Cage	From:	1	6	8	13	15	20	22	27
				To:	6	8	13	15	20	22	27	29
3	f	26	2		22.2	21.5	22.6	23.5	22.3	20.8	22.7	21.3
		27	2		20.3	21.3	20.9	21.5	20.3	18.8	20.9	20.0
		28	2		18.4	18.3	18.9	22.0	19.6	20.0	20.6	18.5
		29	2		19.8	19.0	19.7	20.3	19.3	18.0	20.5	16.8
		30	2		18.7	17.5	18.0	20.0	18.3	18.0	18.3	17.0
				Mean	19.88	19.50	20.02	21.45	19.96	19.10	20.60	18.70
				S.D.	1.51	1.79	1.79	1.42	1.49	1.23	1.57	1.93
				N	5	5	5	5	5	5	5	5

* = Result to left has an associated comment or marker
Food consumption units are g/animal/day

Group 1 - 0 mg/kg/day Group 1 Group 2 - 125 mg/kg/day Group 2
Group 3 - 250 mg/kg/day Group 3 Group 4 - 500 mg/kg/day Group 4

Food Consumption by Cage
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Group	Sex	Cage	No In Cage	Day numbers relative to Start Date								
				From: To:	1 6	6 8	8 13	13 15	15 20	20 22	22 27	27 29
4	f	36	2	23.7	21.8	21.5	25.0	23.8	25.0	24.8	23.8	
		37	2	18.7	18.5	20.1	24.3	21.0	19.3	20.9	19.5	
		38	2	21.6	22.5	20.9	24.0	21.6	19.0	22.5	21.3	
		39	2	20.3	21.5	19.7	24.5	20.6	17.5	21.5	23.3	
		40	2	20.1	20.5	20.4	20.8	19.9	18.8	20.6	20.5	
				Mean	20.88	20.95	20.52	23.70	21.38	19.90	22.06	21.65
				S.D.	1.88	1.55	0.70	1.69	1.49	2.93	1.69	1.81
				N	5	5	5	5	5	5	5	5

* = Result to left has an associated comment or marker
Food consumption units are g/animal/day

Group 1 - 0 mg/kg/day Group 1 Group 2 - 125 mg/kg/day Group 2
Group 3 - 250 mg/kg/day Group 3 Group 4 - 500 mg/kg/day Group 4

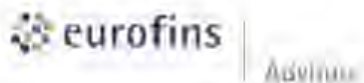
APPENDIX J: CLINICAL PATHOLOGY

PRODUCT IDENTIFICATION

Silk Fibroin

Submitted by:

Eurofins Advinus
21 & 22 Phase II, Peenya Industrial Area
Bengaluru, 560 058, India



CLINICAL PATHOLOGY PHASE REPORT

STUDY TITLE

SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS

PSL STUDY NUMBER: 51651

EUROFINS ADVINUS STUDY PHASE NUMBER: G18871

PRINCIPAL INVESTIGATOR: [REDACTED]

**PATHOLOGY PHASE REPORT COMPLETED ON
01 APRIL 2020**

SPONSOR

**CAMBRIDGE CROPS, INC
444 SOMERVILLE AVE,
SOMERVILLE, MA 02143**

TEST FACILITY

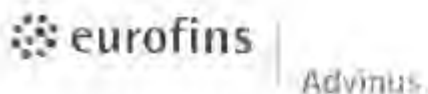
**PRODUCT SAFETY LABS
2394 US HIGHWAY 130
DAYTON, NEW JERSEY 08810**

TEST SITE

**EUROFINS ADVINUS LIMITED
#21 & 22, PEENYA INDUSTRIAL AREA - PHASE II
BENGALURU - 560 058, INDIA**

**PSL Study No.: 51651
Eurofins Advinus Study Phase No.: G18871_PATH/Clinical Pathology Phase Report
Copy No. 1/1**

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**GLP COMPLIANCE STATEMENT AND DECLARATION**

PSL Study No. : 51651
Eurofins Advinus Study Phase No. : G18871
Eurofins Advinus Study Phase Code : PATH
Principal Investigator : ██████████
Location : Department of Safety Assessment, Pathology section, Eurofins Advinus Limited, Bengaluru, India

I hereby confirm that the Phase of Clinical Pathology data interpretation of the above mentioned study was performed and documented in compliance with U.S. FDA GLP: 21 CFR Part 58, 1987 which is compatible with OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM (98)17, OECD, Paris, 1998. A copy of audited clinical pathology data generated at the PSL was provided for the preparation of clinical pathology data interpretation phase report.

It is assured that the reported results faithfully represent the raw data generated at PSL during the experimental work. No circumstances have been left unreported which may have affected the quality or integrity of the data or which might have a potential bearing on the validity and reproducibility of this study phase.

██████████
K. C. Jayachandra, M.V.Sc., DABT
Principal Investigator, Pathology Section,
Dept. of Safety Assessment
Eurofins Advinus Limited, Bengaluru

P. J. Jayachandra
Date



QUALITY ASSURANCE STATEMENT

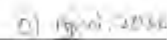
The clinical pathology data interpretation phase (Eurofins Advinus Study phase No. G18871) of PSL Study No. 51651 entitled "Silk Fibroin: A 28-Day Oral Gavage Toxicity Study in Rats" was inspected in accordance with U.S. FDA GLP: 21 CFR Part 58, 1987 which is compatible with OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM (98)7, OECD, Paris, 1998.

The clinical pathology data interpretation phase report was reviewed and findings reported to Principal Investigator, Study Director, Lead QAU, Test Site Management and Test Facility Management on the dates shown below:

Inspection / Audit		Reporting to Principal Investigator and Test Site Management	Reporting to Study Director, Lead QAU and Test Facility Management
Date	Phase	Date	Date
14 November 2019	Initiation Phase Study plan review	14 November 2019	15 November 2019
20 February 2020	Reporting Phase Draft clinical pathology phase report review	20 February 2020	20 February 2020
01 April 2020	Final clinical pathology phase report review	01 April 2020	01 April 2020

Report review was performed according to the Standard Operating Procedures of the test site's Quality Assurance Unit. The report of the clinical pathology data interpretation phase of the study was inspected against the approved study plan and pertinent raw data provided by the study director, and it accurately reflects the data.

Head, QAU-GLP
Eurofins Advinus Limited,
Bengaluru


Date



LIST OF ABBREVIATIONS AND SYMBOLS

General

or -	-	no data
Hemol...	-	hemolyzed
INS.../INS-I	-	insufficient sample
N	-	number of values used in calculation
NCOAG.../NO CO	=	not coagulated
SDevs	-	standard deviation
Sligh...	=	slightly cloudy
Trace...	-	trace intact
TI	-	trace intact
TH	-	trace hemolyzed
Moderat		Moderate

Hematology

ABAS	-	absolute basophil
AEOS	-	absolute eosinophil
ALUC	-	absolute large unstained cell
ALYM	-	absolute lymphocyte
AMON	-	absolute monocyte
ANEU	-	absolute neutrophil (all forms)
ARET	-	absolute reticulocyte
HCT	=	hematocrit
HGB	-	Hemoglobin
LUC	=	Large unstained cells
MCH	-	mean corpuscular (cell) hemoglobin
MCHC	-	mean corpuscular (cell) hemoglobin concentration
MCV	-	mean corpuscular (cell) volume
PLT	-	platelet count
RBC	-	red blood cell count
RDW	-	red cell distribution width
WBC	-	white blood cell count

Coagulation

APTT	-	activated partial thromboplastin time
PT	-	prothrombin time
COAG	=	No Coagulation



LIST OF ABBREVIATIONS AND SYMBOLS contd.

Clinical Chemistry

ALB	-	albumin
ALKP	-	alkaline phosphatase
ALT	-	alanine aminotransferase
AST	-	aspartate aminotransferase
BUN	-	urea nitrogen
CA	-	calcium
CHOL	-	cholesterol
CL	-	chloride
CREAT	-	creatinine
GLOB	-	globulin
GLU	-	glucose
K	-	potassium
NA	-	sodium
PHOS	-	inorganic phosphorus
SDH	-	sorbitol dehydrogenase
TBIL	-	total bilirubin
TP	-	total protein
TRIG	-	tri glycerides

Urinalysis

BACT	-	Bacteria
D	-	Dark
L	-	Light
QUAL	-	quality
SG	-	specific gravity
TL	-	Trace Low
UBIL	-	urine bilirubin
UBLO	-	urine blood
UCLA	-	clarity
UCOL	-	color
UGLU	-	urine glucose
ULEU	-	urine leukocyte
UKET	-	urine ketone
UPRO	-	urine total protein
URO	-	urobilinogen
UVOL	-	Volume
YEL	-	Yellow
WNL	-	Within Normal Limits



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**TEST SITE STUDY PERSONNEL**

TEST SITE:	Eurofins Advinus Limited # 21 & 22, Peenya Industrial Area - Phase II, Bengaluru 560058 India
Principal Investigator:	[REDACTED]
Report Review:	
Test site management:	
Test site QA:	
Report compilation:	[REDACTED]



1. STUDY PHASE DETAILS

Study Title : Silk Fibroin: A 28-Day Oral Gavage Toxicity Study in Rats

Study Phase : Pathology

Test Facility Study Number : 51651

Test Site Study Phase No. : G18871

Test Facility : Product Safety Labs, LLC (PSL)
2394 US Highway 130
Dayton, New Jersey 08810

Test Site : Eurofins Advinus Limited
21 & 22,
Peenya Industrial Area – Phase II
Bengaluru 560058
India

Sponsor : Cambridge Crops, Inc
444 Somerville Ave,
Somerville, MA 02143

Sponsor Representative : [REDACTED]
Cambridge Crops, Inc
444 Somerville Ave,
Somerville, MA 02143
Tel: 301-580-3965
[REDACTED]

Study Director : [REDACTED]
Study Director
Tel: 732-438-5100 x1542
Email: [REDACTED]

Lead QAU : [REDACTED]
Director, Quality Assurance
Product Safety Labs
[REDACTED]



Study Phase Schedule

Study Phase Initiation Date : 12 November 2019
Final pathology Phase Report : 01 April 2020
(Study Phase Completion Date)



2. OBJECTIVE

The objective of this study was to evaluate the potential sub-chronic toxicity of Silk Fibroin in male and female rats likely to arise from repeated exposure, via oral gavage, over a test period of at least 28 days. A no-observed-adverse-effect-level (NOAEL) was determined. This clinical pathology phase report includes interpretation of hematology, coagulation, clinical chemistry and urinalysis data and the conclusions drawn from respective data.

3. STUDY DESIGN

Experimental procedures applicable to clinical pathology are summarized in the tables below. More details can be found in the final study report.

The selected male and female rats were assigned to control and various treated groups as shown below:

Group	Number of Rats Males/Females	Oral Gavage Dose of Test Substance (mg/kg/day)	Dose Volume (mL/kg)	Concentration (mg/mL) ^b
1	10/10	0 (Vehicle control) ^a	10	0
2	10/10	125		12.5
3	10/10	250		25
4	10/10	500		50

a: Distilled water

b: Appropriate concentration of the test substance as received in vehicle to achieve the target dose level

4. METHODS

4.1. Clinical Pathology Investigations

4.1.1 Sample Collection

Clinical pathology analyses were conducted on samples collected on Days 30 (males) and 31 (females) for hematology, coagulation, clinical chemistry, and urinalysis. The samples were analyzed at PSL (Test facility) and the electronic copies of the results were shared with Eurofins Advinus (Test site) for interpretation of the data.

4.1.2 Hematology and Coagulation

Complete blood counts, including reticulocytes, were determined on an ADVIA 120 Hematology System. Coagulation times were determined on a Siemens Sysmex CA620 automated coagulation system.



The following hematological and coagulation parameters were determined by PSL and the electronic copies of results were shared with test site for inclusion in the clinical pathology phase report:

erythrocyte count (RBC)	hemoglobin concentration (HGB)
hematocrit (HCT)	mean corpuscular volume (MCV)
mean corpuscular hemoglobin (MCH)	red cell distribution width (RDW)
absolute reticulocyte count (ARET)	platelet count (PLT)
total white blood cell (WBC) and differential leukocyte count	
mean corpuscular hemoglobin concentration (MCHC) was calculated	

prothrombin time (PT)
activated partial thromboplastin time (APTT)

4.1.3 Clinical Chemistry

The following parameters were determined on a COBAS C311 automated clinical chemistry analyzer at PSL and the electronic copies of results were shared with test site for inclusion in the pathology phase report:

serum aspartate aminotransferase (AST)	serum alanine aminotransferase (ALT)
sorbitol dehydrogenase (SDH)	alkaline phosphatase (ALKP)
total bilirubin (BILL)	urine nitrogen (BUN)
blood creatinine (CREAT)	total cholesterol (CHOL)
triglycerides (TRIG)	fasting glucose (GLUC)
total serum protein (TP)	albumin (ALB)
globulin (GLOB)	calcium (CALC)
inorganic phosphorus (IPHS)	sodium (NA)
potassium (K)	chloride (CL)

4.1.4 Urinalysis

The following parameters were determined at PSL and the electronic copies of results were shared with test site for inclusion in the pathology phase report:

quality (QUAL)	pH	ketone (KET)
color (COL)	glucose (UGLC)	bilirubin (UBIL)
clarity (CLAR)	specific gravity (SG)	blood (BLD)
volume (UVOL)	protein (UMTP)	urobilinogen (URO)
microscopic urine sediment examination		



5. RESULTS AND DISCUSSION

5.1. CLINICAL PATHOLOGY

5.1.1 HEMATOLOGY

Refer Tables [1](#) and [2](#), Appendix [1](#)

There were no test substance-related changes in hematology parameters.

All the changes in hematology were considered unrelated to test substance, because they occurred sporadically, were considered due to biological variance among rats as magnitude of variation was minimal.

5.1.2 COAGULATION

Refer Tables [3](#) and [4](#), Appendix [2](#)

There were no test substance-related changes in coagulation parameters.

5.1.3 CLINICAL CHEMISTRY

Refer Tables [5](#) and [6](#), Appendix [3](#)

There were no test substance-related changes in clinical chemistry parameters.

All the changes in clinical chemistry were considered unrelated to test substance, because they occurred sporadically, were considered due to biological variance among rats as magnitude of variation was minimal.

5.1.4 URINALYSIS

Refer Tables [7](#) and [8](#), Appendix [4](#)

There were no test substance-related changes in urinalysis parameters.



6. SUMMARY

Administration of test substance Silk Fibroin by oral gavage route in Sprague Dawley rats for at least 28 consecutive days at dose levels of 0, 125, 250 and 500 mg/kg/day did not induce any test substance-related changes in hematology, coagulation, clinical chemistry and urinalysis parameters.



7. ARCHIVES

Eurofins Advinus has archived the following documents of the study such as copy of the study plan, study plan amendments, draft clinical pathology phase report, the original signed pathology phase report (copy 1/1) and correspondence generated at Eurofins Advinus for the clinical pathology phase for at least 9 years following the completion of the study phase. Archiving beyond 9 years will be decided after consulting the Sponsor.

8. REPORT DISTRIBUTION

An electronic PDF copy (1/1) of pathology phase report generated at the Test Site was sent to the study director/Test Facility (PSL). The original signed final pathology phase report (1/1) was archived at the Test site (Eurofins Advinus).



9. TABLES

TABLE L Summary of Haematology Parameters – Males

Refer Appendix L

Group n	RBC (x10 ⁶ /µL)	WBC (x10 ³ /µL)	Hgb (g/dL)	Haematology						
				HCT (%)	MCV (fL)	MCH (pg)	RDW (%)	PLT (x10 ³ /µL)	XNEU (x10 ³ /µL)	
Control	10	10	10	10	10	10	10	10	10	10
	Mean	8.387	9.836	15.73	52.35	63.39	19.00	12.31	1102.1	1.260
	Sdev	0.3027	3.2190	0.403	1.859	3.197	0.680	0.496	114.77	0.3196
2	10	10	10	10	10	10	10	10	10	10
	Mean	8.341	9.670	15.67	52.21	62.61	18.83	12.00	1192.6	1.243
	Sdev	0.6971	3.9527	0.998	4.273	1.149	0.680	0.356	90.03	0.3799
3	10	10	10	10	10	10	10	10	10	10
	Mean	8.245	8.643	15.93	53.72	64.22	19.55	11.90	984.3	1.026
	Sdev	0.5894	1.6761	0.641	2.391	1.825	0.747	0.532	325.89	0.3512
4	10	10	10	10	10	10	10	10	10	10
	Mean	7.909	8.078	15.38	51.02	64.30	19.25	12.38	1142.8	1.054
	Sdev	0.4059	1.9373	0.553	2.825	1.366	0.570	0.567	110.00	1.0884

TABLE 1 contd. Summary of Haematology Parameters – Males

Refer Appendix 1

Group #		ALYM (x10 ⁹ /µL)	AMON (x10 ⁹ /µL)	AEOS (x10 ⁹ /µL)	Hematology			MC1C (g/dL)
					ABAS (x10 ⁹ /µL)	ALUC (x10 ⁹ /µL)	ARET (x10 ⁹ /µL)	
Control	(n)	10	10	10	10	10	10	10
	Means	7.945	0.39	0.056	0.029	0.154	226.6	30.01
	Sddevs	1.9854	0.204	0.0360	0.0218	0.0560	56.52	0.540
2	(n)	10	10	10	10	10	10	10
	Means	7.848	0.29	0.072	0.025	0.140	206.4	30.00
	Sddevs	2.5629	0.115	0.0353	0.0108	0.0577	29.50	0.751
3	(n)	10	10	10	10	10	10	10
	Means	7.166	0.23	0.066	0.025	0.129	224.4	30.18
	Sddevs	1.4543	0.088	0.0400	0.0118	0.0482	28.11	0.437
4	(n)	10	10	10	10	10	10	10
	Means	7.446	0.29	0.056	0.021	0.116	243.2	27.42
	Sddevs	1.5176	0.060	0.0303	0.0099	0.0575	52.97	8.459

TABLE 2. Summary of Haematology Parameters – Females

Refer Appendix 1

Lincop n	RBC (x10 ⁶ /µL)	WBC (x10 ⁹ /µL)	HGB (g/dL)	Haematology						
				HCT (%)	MCV (fL)	MCH (pg)	RDW (%)	PLT (x10 ⁹ /µL)	ANCU (x10 ⁹ /µL)	
Control	(n)	10	10	10	10	10	10	10	10	10
	Mean	4.240	7.684	13.46	30.81	90.86	18.51	11.20	1092.7	0.885
	Stdev	0.4709	2.3791	0.7889	2.824	0.947	0.328	0.422	133.06	0.2851
2	(n)	10	10	10	10	10	10	10	10	10
	Mean	4.343	7.789	13.33	30.19	90.08	18.33	11.01	1084.3	0.871
	Stdev	0.6043	1.6943	0.902	3.273	1.483	0.370	0.351	82.26	0.2674
7	(n)	10	10	10	10	10	10	10	10	10
	Mean	4.216	6.465	13.23	49.67	90.44	18.53	11.25	1015.4	0.809
	Stdev	0.6070	0.9602	1.215	4.283	1.208	0.442	0.430	160.48	0.3144
4	(n)	10	10	10	10	10	10	10	10	10
	Mean	4.265	7.404	13.32	30.82	91.65	18.55	11.20	975.7	0.983
	Stdev	0.3794	1.553	0.646	1.712	2.022	0.395	0.467	107.09	0.5375

TABLE 2 contd. Summary of Haematology Parameters – Females

Refer Appendix 1

Group #		Haematology						
		ALYM (x10 ⁹ /µL)	AMJN (x10 ⁹ /µL)	AEOS (x10 ⁹ /µL)	ABAS (x10 ⁹ /µL)	ALUC (x10 ⁹ /µL)	ARET (x10 ⁹ /µL)	MCHC (g/dL)
Control	(n)	10	10	10	10	10	10	10
	Means	6.298	0.26	0.660	0.027	0.151	180.7	30.14
	Stdevs	2.0486	0.103	0.0133	0.0134	0.0671	44.86	0.583
2	(n)	10	10	9	10	10	10	10
	Means	5.409	0.23	0.057	0.025	0.153	167.9	30.52
	Stdevs	1.6946	0.069	0.0216	0.0097	0.0372	25.32	0.569
3	(n)	10	10	10	10	10	10	10
	Means	5.199	0.22	0.075	0.023	0.134	178.4	30.61
	Stdevs	0.9558	0.076	0.0701	0.0142	0.0490	38.27	0.507
4	(n)	10	10	10	10	10	10	10
	Means	5.900	0.26	0.074	0.029	0.150	176.2	30.09
	Stdevs	1.6475	0.157	0.0222	0.0166	0.0701	36.59	0.458

TABLE 3. Summary of Coagulation Parameters – Males

Table Appendix 5

Group #		Coagulation	
		APTT (sec)	PT (sec)
Control	(n)	10	10
	Means	16.3	9.6
	Sdevs	1.24	0.28
2	(n)	10	10
	Means	16.8	9.5
	Sdevs	3.09	0.23
3	(n)	9	9
	Means	18.7	9.4
	Sdevs	7.03	0.60
4	(n)	10	10
	Means	18.5	9.6
	Sdevs	3.77	0.25

TABLE 4. Summary of Coagulation Parameters – Females

Refer Appendix 5

Group #	Coagulation	
	APTT (sec)	PT (sec)
Control	(n)	10
	Means	16.1
	Stdevs	1.27
1	(n)	10
	Means	16.2
	Stdevs	1.12
3	(n)	10
	Means	15.9
	Stdevs	1.19
4	(n)	10
	Means	16.4
	Stdevs	1.40

TABLE 5. Summary of Clinical Chemistry Parameters – Males

Refer Appendix 3

Group #		N	Serum Chemistry								
			Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	AST (U/L)	ALT (U/L)	ALP (U/L)	BUN (mg/dL)	CA (mg/dL)	CHOL (mg/dL)
Control	(n)	10	10	10	10	10	10	10	10	10	10
	Means	140.4	6.997	98.67	80.0	27.100	132.3	12.8	10.54	56.9	
	Sdevs	3.81	1.0184	2.320	14.89	6.2790	27.24	3.48	0.820	14.69	
2	(n)	10	10	10	10	10	10	10	10	10	
	Means	140.9	7.426	99.18	75.2	28.500	151.1	13.3	10.40	60.9	
	Sdevs	3.00	1.6202	2.523	14.95	6.0964	23.82	3.34	0.640	10.23	
3	(n)	10	10	10	10	10	10	10	10	10	
	Means	139.7	7.499	98.57	65.7	34.000	133.3	12.6	10.22	63.1	
	Sdevs	2.75	0.8967	1.754	11.17	5.2493	25.71	3.90	0.877	10.65	
4	(n)	10	10	10	10	10	10	10	10	10	
	Means	140.0	7.076	95.60	66.1	34.900	132.7	12.8	10.16	56.0	
	Sdevs	7.88	0.9773	2.720	9.40	4.2282	34.14	0.02	0.783	14.35	

TABLE 5 contd. Summary of Clinical Chemistry Parameters – Males

Refer Appendix 3

Lipop #		C-REACT (mg/dL)	GLU (mg/dL)	PHOS (mg/dL)	Serum Chemistry					
					TBL (mg/dL)	TRIG (mg/dL)	SDH (U/L)	TP (g/dL)	ALB (g/dL)	GLDH (g/dL)
Control	Unit	10	10	10	10	10	10	10	10	10
	Means	0.163	105.2	9.47	0.066	45.5	9.28	5.71	3.64	2.09
	Sdevs	0.0331	36.30	0.733	0.0097	9.99	2.033	0.405	0.317	0.215
2	Unit	10	10	10	10	10	10	10	10	10
	Means	0.170	113.4	9.61	0.062	40.8	7.85	5.83	3.76	2.03
	Sdevs	0.0052	25.50	1.119	0.0155	9.75	2.614	0.327	0.237	0.125
3	Unit	10	10	10	10	10	10	10	10	10
	Means	0.174	119.3	9.30	0.064	42.0	8.83	5.88	3.79	2.10
	Sdevs	0.0043	31.11	0.947	0.0126	12.02	2.503	0.261	0.322	0.082
4	Unit	10	10	10	10	10	10	10	10	10
	Means	0.170	125.4	9.46	0.070	52.4	9.96	5.77	3.76	2.01
	Sdevs	0.0546	22.19	0.758	0.0226	19.07	3.302	0.564	0.344	0.251

TABLE 6. Summary of Clinical Chemistry Parameters – Females

Refer Appendix J

Group n	No	G (mmol/L)	U (mmol/L)	Serum Chemistry						
				AST (U/L)	ALT (U/L)	ALP (U/L)	BUN (mg/dL)	CA (mg/dL)	Cr (mg/dL)	
Control	(n)	10	10	10	10	10	10	10	10	10
	Means	133.5	8.432	94.73	32.0	27.700	62.6	13.9	10.46	78.2
	Stdevs	6.00	0.6382	4.513	29.00	7.1969	20.72	2.02	1.256	15.82
2	(n)	10	10	10	10	10	10	10	10	10
	Means	134.4	7.150	95.67	30.7	25.200	64.3	15.1	10.39	75.1
	Stdevs	6.00	1.0689	5.285	22.62	4.2111	16.59	2.08	0.872	19.81
3	(n)	10	10	10	10	10	10	10	10	10
	Means	136.4	7.561	97.98	32.2	37.300	65.1	14.0	10.07	72.3
	Stdevs	6.32	2.4808	3.721	67.16	28.4412	16.91	2.11	0.615	12.23
4	(n)	10	10	10	10	10	10	10	10	10
	Means	136.1	7.022	96.78	33.9	48.100	70.8	14.2	10.51	75.0
	Stdevs	5.26	1.1857	3.192	28.86	39.1619	26.66	1.24	1.068	10.76

TABLE 6 contd. Summary of Clinical Chemistry Parameters – Females

Refer Appendix 1

Group	n	CREAT (mg/dL)	GLU (mg/dL)	PHOS (mg/dL)	Serum Chemistry					
					TBL (mg/dL)	TBLG (mg/dL)	SGOT (U/L)	TP (g/dL)	ALB (g/dL)	GLOB (g/dL)
Control	(n)	10	10	10	10	10	10	10	10	10
	Means	0.201	140.6	7.88	0.077	45.4	7.36	6.91	4.86	2.07
	Stdevs	0.0357	36.79	0.666	0.0186	16.61	0.878	0.491	0.548	0.135
2	(n)	10	10	10	10	10	10	10	10	10
	Means	0.230	121.8	8.25	0.085	37.9	5.65	6.74	4.68	2.06
	Stdevs	0.0488	41.74	1.033	0.0190	12.99	2.170	0.595	0.527	0.237
3	(n)	10	10	10	10	10	10	10	10	10
	Means	0.199	111.6	7.88	0.082	42.2	18.16	8.49	4.50	1.99
	Stdevs	0.0287	31.39	1.214	0.0175	9.82	30.935	0.821	0.655	0.360
4	(n)	10	10	10	10	10	10	10	10	10
	Means	0.225	121.8	8.37	0.090	41.3	11.69	8.84	4.69	2.15
	Stdevs	0.0433	35.91	1.024	0.0110	17.70	12.405	0.585	0.398	0.278

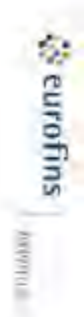
TABLE 7. Summary of Clinical Analysis of Urine – Males

Refer Appendix 3

Group #		URIC (EU/dL)	pH	SG	Urinalysis	
					(VOL (ml.))	UPRO (mg/dL)
Control	(n)	10	10	10	10	10
	Means	0.20	6.70	1.0245	8.76	32.5
	Sddev	0.000	0.350	0.00641	11.148	25.74
2	(n)	10	10	10	10	10
	Means	0.20	6.65	1.0240	9.16	32.0
	Sddev	0.000	0.474	0.00658	5.734	17.87
3	(n)	10	10	10	10	10
	Means	0.20	6.75	1.0240	10.03	19.5
	Sddev	0.000	0.354	0.00568	6.790	10.12
4	(n)	10	10	10	10	10
	Means	0.20	6.65	1.0235	10.18	19.3
	Sddev	0.000	0.340	0.00784	5.115	13.35

TABLE 8. Summary of Clinical Analysis of Urine – FemalesRef: [Appendix A](#)

Group #		URO (EU/ML)	pH	SG	Urimalysis	
					UVOL (ml.)	UPRO (mg/dL)
Control	(n)	9	9	9	9	9
	Means	0.20	6.44	1.0178	10.12	1.7
	Stdevs	0.000	0.300	0.00667	6.654	5.00
2	(n)	8	8	8	8	8
	Means	0.20	6.94	1.0213	6.70	23.8
	Stdevs	0.000	0.563	0.00835	5.409	33.23
3	(n)	10	10	10	10	10
	Means	0.20	6.55	1.0215	8.39	10.5
	Stdevs	0.000	0.438	0.00626	7.279	14.23
4	(n)	9	9	9	9	9
	Means	0.20	6.39	1.0256	7.44	15.0
	Stdevs	0.000	0.220	0.00682	6.146	12.99



10. APPENDICES

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APPENDIX 1. Individual Animal Haematology Parameters

Animal #	Sex	Day / Group / Week / n of Phase	Scent-Sent-Scan Name	RBC (x10 ¹² /µL)	WBC (x10 ⁹ /µL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)
7001	D M	Ctrl 30/5	S 1-1	8.44	9.27	13.7	51.7	61.3	18.6
7002	D M	Ctrl 30/5	S 1-1	8.32	8.42	13.4	51.6	63.6	19.0
7003	D M	Ctrl 30/5	S 1-1	8.04	8.26	13.2	49.8	62.0	18.8
7004	D M	Ctrl 30/5	S 1-1	8.84	6.22	15.6	53.3	60.3	17.6
7005	D M	Ctrl 30/5	S 1-1	8.31	11.23	16.0	53.2	66.0	19.2
7006	D M	Ctrl 30/5	S 1-1	8.62	12.80	16.7	56.6	63.6	19.8
7007	D M	Ctrl 30/5	S 1-1	8.11	10.89	15.6	50.8	62.6	19.2
7008	D M	Ctrl 30/5	S 1-1	7.98	12.74	13.8	52.3	67.1	20.3
7009	D M	Ctrl 30/5	S 1-1	8.36	7.41	15.7	52.9	63.2	18.8
7010	D M	Ctrl 30/5	S 1-1	8.25	10.82	15.6	51.3	62.2	18.9
7021	D M	2 30/5	S 1-1	8.51	6.18	16.7	54.8	64.9	19.6
7022	D M	2 30/5	S 1-1	8.03	10.15	15.8	51.3	63.9	19.2
7023	D M	2 30/5	S 1-1	8.14	14.49	15.5	50.7	62.2	19.0
7024	D M	2 30/5	S 1-1	7.65	8.84	14.9	48.1	62.9	19.5
7025	D M	2 30/5	S 1-1	9.15	5.83	16.3	56.2	61.4	17.8
7026	D M	2 30/5	S 1-1	9.00	13.51	17.0	57.2	63.8	18.9
7027	D M	2 30/5	S 1-1	7.93	10.92	13.2	50.1	63.2	19.1
7028	D M	2 30/5	S 1-1	8.54	9.90	16.6	58.3	61.1	17.5
7029	D M	2 30/5	S 1-1	7.35	6.44	13.7	45.0	61.3	18.7
7030	D M	2 30/5	S 1-1	8.71	10.44	13.4	50.4	62.2	19.0
7041	D M	3 30/5	S 1-1	7.68	7.31	13.8	50.8	66.2	20.1
7042	D M	3 30/5	S 1-1	8.23	7.84	13.2	53.2	64.6	18.9
7043	D M	3 30/5	S 1-1	8.52	9.83	16.4	55.1	64.7	19.2
7044	D M	3 30/5	S 1-1	7.96	10.18	15.4	51.1	64.2	19.2

U – Dosing Phase

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, n = UnScheduled Necropsy

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APPENDIX 1 contd. Individual Animal Haematology Parameters

Animal #	Sex	Day of Eusap Week	of Phase	Semi- Scan Name	RBC (x10 ⁶ /µL)	WBC (x10 ³ /µL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)
7045	D M	3	30/5	S 1-1	7.82	8.33	15.4	50.7	64.9	19.7
7046	D M	3	30/5	S 1-1	7.23	8.18	15.1	48.6	67.2	21.0
7047	D M	3	30/5	S 1-1	8.75	6.60	16.5	51.4	62.3	18.8
7048	D M	3	30/5	S 1-1	8.43	10.54	16.1	54.1	64.2	19.1
7049	D M	3	30/5	S 1-1	8.56	11.15	16.3	53.6	62.7	19.0
7050	D M	3	30/5	S 1-1	9.27	6.47	17.1	56.6	61.1	18.4
7061	D M	4	30/5	S 1-1	7.89	7.56	16.0	52.4	66.1	20.2
7062	D M	4	30/5	S 1-1	7.55	12.91	15.1	48.3	64.0	20.0
7063	D M	4	30/5	S 1-1	7.40	10.23	14.6	47.2	63.0	19.5
7064	D M	4	30/5	S 1-1	8.45	9.05	16.2	55.5	65.6	19.1
7065	D M	4	30/5	S 1-1	7.88	10.44	15.2	49.3	62.6	19.2
7066	D M	4	30/5	S 1-1	7.37	9.13	14.7	47.8	64.9	19.9
7067	D M	4	30/5	S 1-1	8.07	9.07	15.7	53.0	65.6	19.5
7068	D M	4	30/5	S 1-1	7.88	7.00	15.0	50.6	64.2	19.0
7069	D M	4	30/5	S 1-1	7.83	8.09	15.8	52.0	66.2	19.6
7070	D M	4	30/5	S 1-1	8.66	6.30	15.9	54.1	63.1	18.2
7011	D F	Cul	31/5	S 1-1	8.98	6.17	16.5	54.2	60.4	18.4
7012	D F	Cul	31/5	S 1-1	8.67	11.34	15.5	51.7	60.1	18.1
7013	D F	Cul	31/5	S 1-1	8.47	6.91	16.0	52.0	61.5	18.9
7014	D F	Cul	31/5	S 1-1	7.68	8.20	14.5	47.3	61.6	18.8
7015	D F	Cul	31/5	S 1-1	7.58	8.23	16.1	45.5	60.0	18.5
7016	D F	Cul	31/5	S 1-1	8.35	6.72	15.9	53.0	61.9	18.6
7017	D F	Cul	31/5	S 1-1	8.64	7.16	16.2	53.5	61.9	18.9
7018	D F	Cul	31/5	S 1-1	8.21	4.39	15.1	49.9	60.7	18.4

D = Dosing Phase

S = Scheduled Animal Room; U = UnScheduled Animal Room; N = Scheduled Necropsy; n = UnScheduled Necropsy

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APPENDIX 1 contd. Individual Animal Haematology Parameters

Animal #	Sex	Group	Day / Week # of Phase	Semi- Sess Name	RBC (x10 ⁶ /µL)	WBC (x10 ³ /µL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)
7019	D F	Ctrl	31/5	S 1-1	7.99	5.71	14.9	49.0	61.3	18.6
7020	D F	Ctrl	31/5	S 1-1	8.82	11.94	15.8	52.0	59.0	17.9
7031	D F	2	31/5	S 1-1	7.39	7.21	13.7	44.8	60.6	18.5
7012	D F	2	31/5	S 1-1	7.98	11.41	14.6	48.1	60.3	18.3
7033	D F	2	31/5	S 1-1	8.47	5.00	16.2	51.3	60.6	19.1
7034	D F	2	31/5	S 1-1	7.97	7.05	14.7	48.0	60.3	18.4
7035	D F	2	31/5	S 1-1	8.51	7.13	15.5	50.5	59.4	18.2
7036	D F	2	31/5	S 1-1	8.78	7.44	16.1	52.4	59.6	18.3
7037	D F	2	31/5	S 1-1	7.81	9.34	14.5	46.1	59.1	18.5
7038	D F	2	31/5	S 1-1	8.60	8.57	16.1	53.2	61.9	18.7
7039	D F	2	31/5	S 1-1	8.56	7.12	15.9	53.1	62.1	18.6
7040	D F	2	31/5	S 1-1	9.56	7.64	16.2	54.4	56.9	16.9
7051	D F	3	31/5	S 1-1	7.45	6.79	13.7	43.8	58.8	18.4
7052	D F	3	31/5	S 1-1	7.82	5.63	14.8	47.1	60.3	18.9
7053	D F	3	31/5	S 1-1	8.16	7.25	14.5	48.3	59.3	17.8
7054	D F	3	31/5	S 1-1	8.09	6.95	15.6	51.0	61.0	19.3
7055	D F	3	31/5	S 1-1	7.62	5.74	14.1	45.5	59.7	18.4
7056	D F	3	31/5	S 1-1	8.81	6.25	16.1	53.3	60.5	18.5
7057	D F	3	31/5	S 1-1	7.56	6.61	13.7	44.8	59.3	18.1
7058	D F	3	31/5	S 1-1	8.04	5.15	16.6	54.4	60.2	18.4
7059	D F	3	31/5	S 1-1	8.66	5.86	16.1	53.3	61.6	18.9
7060	D F	3	31/5	S 1-1	8.95	8.46	16.8	55.2	61.7	18.8
7071	D F	4	31/5	S 1-1	7.94	3.98	15.1	50.9	64.1	19.2
7072	D F	4	31/5	S 1-1	7.75	7.04	15.1	50.0	64.6	19.5

D= Dosing Phase

S= Scheduled Animal Room, U= UnScheduled Animal Room, N= Scheduled Neurology, n= UnScheduled Neurology

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APPENDIX 1 contd. Individual Animal Haematology Parameters

Animal #	Sex	Day of Group Week	Study Week	Study Name	RBC ($\times 10^6/\mu\text{L}$)	WBC ($\times 10^3/\mu\text{L}$)	HGB ($\mu\text{g/dL}$)	HCT (%)	MCV (fL)	MCH (pg)
7073	D F	4	31/5	S 1-1	8.25	4.91	15.5	51.2	62.0	18.8
7074	D F	4	31/5	S 1-1	7.76	7.57	14.2	47.9	61.6	18.3
7075	D F	4	31/5	S 1-1	8.11	9.90	15.1	50.4	62.2	18.7
7076	D F	4	31/5	S 1-1	8.27	12.05	19.2	52.0	62.8	18.4
7077	D F	4	31/5	S 1-1	8.66	7.82	16.2	52.9	61.0	18.7
7078	D F	4	31/5	S 1-1	8.85	5.84	16.5	53.7	60.7	18.6
7079	D F	4	31/5	S 1-1	8.51	3.69	15.2	51.0	59.8	17.8
7080	D F	4	31/5	S 1-1	8.55	7.24	11.9	49.3	57.7	17.5

D = Dosing Phase

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, n = UnScheduled Necropsy

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APPENDIX 1 contd. Individual Animal Haematology Parameters

Animal #	Sex	Group	Day / Week of Phase	Study Site Name	RDW (%)	PLT (x10 ⁹ /L)	ANEU (x10 ⁹ /L)	ALYM (x10 ⁹ /L)	AMON (x10 ⁹ /L)	AEOS (x10 ⁹ /L)	ABAS (x10 ⁹ /L)	ALUC (x10 ⁹ /L)
7001	D M	Ctrl	30:5	S 1-1	12.1	1126	1.31	7.29	0.3	0.10	0.02	0.16
7002	D M	Ctrl	30:5	S 1-1	12.0	1093	1.50	6.30	0.2	0.04	0.02	0.13
7003	D M	Ctrl	30:5	S 1-1	12.3	1051	1.66	6.49	0.2	0.11	0.01	0.06
7004	D M	Ctrl	30:5	S 1-1	12.1	1004	0.97	4.93	0.2	0.01	0.02	0.07
7005	D M	Ctrl	30:5	S 1-1	12.4	1251	1.38	9.19	0.6	0.05	0.03	0.21
7006	D M	Ctrl	30:5	S 1-1	11.7	1170	1.00	11.07	0.6	0.04	0.09	0.23
7007	D M	Ctrl	30:5	S 1-1	12.4	1342	1.34	8.45	0.9	0.02	0.02	0.16
7008	D M	Ctrl	30:5	S 1-1	12.6	1189	1.44	10.57	0.5	0.01	0.02	0.19
7009	D M	Ctrl	30:5	S 1-1	12.9	1308	0.60	6.23	0.4	0.02	0.02	0.14
7010	D M	Ctrl	30:5	S 1-1	11.6	1073	1.44	8.63	0.8	0.11	0.02	0.19
7021	D M	2	30:5	S 1-1	11.6	1082	1.30	4.56	0.2	0.04	0.05	0.07
7022	D M	2	30:5	S 1-1	11.9	1317	1.12	8.10	0.3	0.00	0.02	0.12
7023	D M	2	30:5	S 1-1	12.2	1166	0.76	11.78	0.5	0.15	0.04	0.22
7024	D M	2	30:5	S 1-1	12.3	1130	1.61	6.29	0.2	0.09	0.01	0.09
7025	D M	2	30:5	S 1-1	12.5	1290	0.65	4.85	0.1	0.04	0.02	0.06
7026	D M	2	30:5	S 1-1	11.4	1053	1.75	11.16	0.4	0.06	0.04	0.13
7027	D M	2	30:5	S 1-1	12.3	1147	1.17	9.16	0.3	0.05	0.01	0.22
7028	D M	2	30:5	S 1-1	12.4	1284	0.96	8.37	0.3	0.07	0.02	0.16
7029	D M	2	30:5	S 1-1	12.2	1242	0.94	5.05	0.3	0.05	0.01	0.14
7030	D M	2	30:5	S 1-1	12.2	1214	0.97	8.86	0.3	0.09	0.02	0.19
7041	D M	3	30:5	S 1-1	11.6	1266	0.67	6.28	0.2	0.06	0.02	0.10
7042	D M	3	30:5	S 1-1	12.1	1173	0.79	6.70	0.2	0.07	0.02	0.11
7043	D M	3	30:5	S 1-1	11.3	1101	1.22	8.07	0.3	0.06	0.02	0.13
7044	D M	3	30:5	S 1-1	11.8	1047	0.97	8.74	0.3	0.03	0.02	0.10

U = Dosing Phase

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, n = UnScheduled Necropsy

APPENDIX 1 contd. Individual Animal Haematology Parameters

Animal #	Sex	Day / Group / Week / of Phase	Scat- Spec- Name	RDW (%)	PCT (x10 ⁹ /µL)	ANBL (x10 ⁹ /µL)	ALYM (x10 ⁹ /µL)	AMON (x10 ⁹ /µL)	AFOS (x10 ⁹ /µL)	ABAS (x10 ⁹ /µL)	ALTC (x10 ⁹ /µL)
7045	D M	3 30/5	S 1-1	13.0	798	1.84	6.06	0.2	0.20	0.01	0.06
7046	D M	3 30/5	S 1-1	12.8	103	1.01	6.81	0.2	0.01	0.01	0.13
7047	D M	3 30/5	S 1-1	11.8	1423	0.22	5.48	0.2	0.00	0.02	0.21
7048	D M	3 30/5	S 1-1	11.8	1162	1.01	8.94	0.3	0.05	0.05	0.16
7049	D M	3 30/5	S 1-1	12.0	1116	1.27	9.21	0.4	0.05	0.05	0.19
7050	D M	3 30/5	S 1-1	11.9	954	0.76	8.44	0.1	0.04	0.04	0.08
7061	D M	4 30/5	S 1-1	11.7	1157	1.00	6.14	0.2	0.04	0.05	0.10
7062	D M	4 30/5	S 1-1	12.5	1097	1.92	10.41	0.4	0.05	0.04	0.12
7063	D M	4 30/5	S 1-1	12.4	1134	1.18	8.61	0.2	0.09	0.02	0.09
7064	D M	4 30/5	S 1-1	12.5	1173	0.73	7.87	0.3	0.05	0.05	0.10
7065	D M	4 30/5	S 1-1	12.0	1130	1.36	8.52	0.7	0.17	0.01	0.10
7066	D M	4 30/5	S 1-1	11.9	976	1.19	7.37	0.4	0.06	0.01	0.12
7067	D M	4 30/5	S 1-1	13.9	1157	0.70	7.89	0.3	0.04	0.03	0.19
7068	D M	4 30/5	S 1-1	13.6	1258	0.89	5.66	0.2	0.08	0.01	0.14
7069	D M	4 30/5	S 1-1	12.6	1067	1.12	6.41	0.1	0.04	0.02	0.14
7070	D M	4 30/5	S 1-1	12.2	1083	4.39	5.67	0.2	0.02	0.02	0.05
7011	D F	Ctrl 31/5	S 1-1	10.8	989	0.82	4.89	0.2	0.06	0.02	0.13
7012	D F	Ctrl 31/5	S 1-1	11.7	1323	1.06	9.51	0.4	0.07	0.05	0.30
7013	D F	Ctrl 31/5	S 1-1	11.8	1348	1.09	5.29	0.2	0.06	0.04	0.12
7014	D F	Ctrl 31/5	S 1-1	11.3	970	0.85	6.92	0.3	0.06	0.02	0.12
7015	D F	Ctrl 31/5	S 1-1	11.3	1000	0.99	6.91	0.2	0.05	0.01	0.08
7016	D F	Ctrl 31/5	S 1-1	11.1	1137	0.85	5.41	0.1	0.06	0.03	0.11
7017	D F	Ctrl 31/5	S 1-1	10.7	1136	0.65	5.97	0.3	0.06	0.04	0.17
7018	D F	Ctrl 31/5	S 1-1	11.0	1062	0.23	7.89	0.1	0.04	0.02	0.10

U = Dosing Phase

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, n = UnScheduled Necropsy

APPENDIX I contd. Individual Animal Haematology Parameters

Animal #	Sex	Day / Group Week of Phase	Scout- Sens Name	RDW (%)	PLT (x10 ⁹ /uL)	ANEU (x10 ⁹ /uL)	ALYM (x10 ⁹ /uL)	AMON (x10 ⁹ /uL)	AEOS (x10 ⁹ /uL)	ABAS (x10 ⁹ /uL)	ALTC (x10 ⁹ /uL)
7019	D F	C00	S1-5 S1-1	11.8	867	1.08	4.21	0.2	0.06	0.01	0.13
7020	D F	C00	S1-5 S1-1	11.1	1237	1.23	9.88	0.5	0.09	0.03	0.23
7031	D F	2	S1-5 S1-1	11.8	1149	0.83	5.63	0.2	0.08	0.02	0.09
7052	D F	2	S1-5 S1-1	11.0	1347	0.62	10.18	0.3	0.09	0.03	0.23
7003	D F	2	S1-5 S1-1	11.3	1050	0.78	4.01	0.1	0.05	0.02	0.07
7024	D F	2	S1-5 S1-1	11.0	1136	0.77	3.70	0.1	0.05	0.02	0.23
7035	D F	2	S1-5 S1-1	10.4	1015	1.08	5.60	0.2	0.03	0.03	0.16
7036	D F	2	S1-5 S1-1	11.0	1220	1.46	5.62	0.2	0.05	0.01	0.10
7037	D F	2	S1-5 S1-1	11.0	1071	0.72	7.89	0.3	0.07	0.03	0.20
7038	D F	2	S1-5 S1-1	10.8	1047	0.80	7.26	0.2	0.08	0.03	0.13
7039	D F	2	S1-5 S1-1	11.3	929	0.57	6.04	0.3	0.04	0.04	0.13
7040	D F	2	S1-5 S1-1	10.3	1079	0.60	6.02	0.3	0.03	0.04	0.23
7051	D F	3	S1-5 S1-1	11.7	987	0.83	5.57	0.2	0.05	0.01	0.07
7052	D F	3	S1-5 S1-1	11.9	969	0.69	4.33	0.3	0.07	0.02	0.23
7053	D F	3	S1-5 S1-1	11.3	1063	1.51	3.09	0.4	0.08	0.03	0.20
7054	D F	3	S1-5 S1-1	11.8	926	1.03	5.22	0.2	0.27	0.05	0.15
7055	D F	3	S1-5 S1-1	11.7	1128	0.90	4.38	0.3	0.06	0.01	0.12
7056	D F	3	S1-5 S1-1	11.2	1107	0.43	5.30	0.1	0.04	0.02	0.14
7057	D F	3	S1-5 S1-1	11.4	908	0.39	5.70	0.2	0.05	0.01	0.12
7058	D F	3	S1-5 S1-1	10.6	1137	0.83	3.83	0.3	0.06	0.04	0.12
7059	D F	3	S1-5 S1-1	10.9	1130	0.43	5.07	0.2	0.04	0.02	0.09
7060	D F	3	S1-5 S1-1	11.0	1057	0.84	7.30	0.2	0.03	0.01	0.10
7071	D F	4	S1-5 S1-1	11.5	677	1.06	4.51	0.2	0.09	0.02	0.12
7072	D F	4	S1-5 S1-1	11.4	978	1.84	4.56	0.3	0.06	0.03	0.21

D = Dosing Phase

S = Scheduled Animal Room, U = UnScheduled Animal Room, S = Scheduled Necropsy, u = UnScheduled Necropsy

APPENDIX I contd. Individual Animal Haematology Parameters

Animal #	Sex	Day Group Week	Day of Phase	Study Site Name	RDW (%)	PLT (x10 ⁹ /dL)	ANEU (x10 ⁹ /dL)	ALYM (x10 ⁹ /dL)	AMON (x10 ⁹ /dL)	AEOS (x10 ⁹ /dL)	ABAS (x10 ⁹ /dL)	ALUC (x10 ⁹ /dL)
7071	D F	-4	315	S I-1	11.0	971	0.62	4.02	0.1	0.06	0.01	0.06
7074	D F	-4	315	S I-1	11.8	877	0.87	6.25	0.3	0.04	0.02	0.14
7074	D F	-4	315	S I-1	11.3	1064	1.30	8.12	0.4	0.07	0.03	0.23
7076	D F	-4	315	S I-1	11.7	643	1.94	9.00	0.7	0.07	0.04	0.27
7077	D F	-4	315	S I-1	11.7	1029	0.65	6.59	0.3	0.09	0.05	0.18
7078	D F	-4	315	S I-1	11.1	1243	0.67	4.29	0.2	0.12	0.02	0.07
7079	D F	-4	315	S I-1	10.8	1379	0.32	4.98	0.2	0.06	0.04	0.10
7080	D F	-4	315	S I-1	10.2	1009	0.65	6.15	0.2	0.08	0.01	0.12

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S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, u = UnScheduled Necropsy

APPENDIX 1 contd. Individual Animal Haematology Parameters

Animal #	Sex	Group	Day / Week # of Phase	Semi- Sect. Name	ARET (x10 ⁹ /µL)	MCHC (g/dL)
7001	D/M	Ctrl	30/3	S 1-1	225	30.4
7002	D/M	Ctrl	30/3	S 1-1	206	29.8
7003	D/M	Ctrl	30/3	S 1-1	217	30.6
7004	D/M	Ctrl	30/3	S 1-1	189	29.2
7005	D/M	Ctrl	30/3	S 1-1	262	29.7
7006	D/M	Ctrl	30/3	S 1-1	205	29.6
7007	D/M	Ctrl	30/3	S 1-1	235	30.7
7008	D/M	Ctrl	30/3	S 1-1	311	30.2
7009	D/M	Ctrl	30/3	S 1-1	221	30.1
7010	D/M	Ctrl	30/3	S 1-1	194	30.3
7021	D/M	2	30/3	S 1-1	180	29.9
7022	D/M	2	30/3	S 1-1	165	30.0
7023	D/M	2	30/3	S 1-1	224	30.6
7024	D/M	2	30/3	S 1-1	196	31.1
7025	D/M	2	30/3	S 1-1	223	29.0
7026	D/M	2	30/3	S 1-1	159	29.7
7027	D/M	2	30/3	S 1-1	238	30.2
7028	D/M	2	30/3	S 1-1	228	28.6
7029	D/M	2	30/3	S 1-1	212	30.4
7030	D/M	2	30/3	S 1-1	230	30.3
7041	D/M	3	30/3	S 1-1	230	30.8
7042	D/M	3	30/3	S 1-1	217	29.8
7043	D/M	3	30/3	S 1-1	190	29.7
7044	D/M	3	30/3	S 1-1	203	30.2

D - Dosing Phase

S - Scheduled Animal Room, U - UnScheduled Animal Room, N - Scheduled Necropsy, u - UnScheduled Necropsy

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APPENDIX 1 contd. Individual Animal Haematology Parameters

Animal #	Sex	Day of Phase	Group Week	Semi-Sem Name	ARET (x10 ⁹ /µL)	MCHE (g/dL)
7044	D M	3	30/5	S 1-1	200	30.3
7046	D M	3	30/5	S 1-1	210	31.0
7047	D M	3	30/5	S 1-1	225	30.2
7048	D M	3	30/5	S 1-1	227	29.8
7049	D M	3	30/5	S 1-1	245	30.3
7050	D M	3	30/5	S 1-1	202	30.2
7061	D M	4	30/5	S 1-1	171	30.6
7062	D M	4	30/5	S 1-1	230	3.4
7063	D M	4	30/5	S 1-1	224	29.8
7064	D M	4	30/5	S 1-1	189	29.7
7065	D M	4	30/5	S 1-1	221	30.8
7066	D M	4	30/5	S 1-1	230	30.6
7067	D M	4	30/5	S 1-1	314	30.5
7068	D M	4	30/5	S 1-1	312	29.6
7069	D M	4	30/5	S 1-1	317	30.3
7070	D M	4	30/5	S 1-1	214	29.0
7071	D F	Ctrl	31/5	S 1-1	134	30.8
7072	D F	Ctrl	31/5	S 1-1	179	29.7
7073	D F	Ctrl	31/5	S 1-1	241	30.1
7074	D F	Ctrl	31/5	S 1-1	166	29.5
7075	D F	Ctrl	31/5	S 1-1	252	30.4
7076	D F	Ctrl	31/5	S 1-1	164	29.3
7077	D F	Ctrl	31/5	S 1-1	139	29.6
7078	D F	Ctrl	31/5	S 1-1	164	30.6

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APPENDIX 1 cont'd. Individual Animal Haematology Parameters

Animal #	Sex	Day (Group Week # of Phase)	Scout- Score Nurse	ARET (x10 ⁹ /µL)	MCHC (g/dL)	
7019	D F	Ctrl	31/5	S 1-1	232	30.9
7020	D F	Ctrl	31/5	S 1-1	135	30.3
7031	D F	2	31/5	S 1-1	156	30.3
7032	D F	2	31/5	S 1-1	197	30.3
7033	D F	2	31/5	S 1-1	187	31.2
7034	D F	2	31/5	S 1-1	129	30.6
7035	D F	2	31/5	S 1-1	168	30.7
7036	D F	2	31/5	S 1-1	179	30.3
7037	D F	2	31/5	S 1-1	160	31.4
7038	D F	2	31/5	S 1-1	181	30.2
7039	D F	2	31/5	S 1-1	198	30.9
7040	D F	2	31/5	S 1-1	127	29.7
7051	D F	3	31/5	S 1-1	126	31.2
7052	D F	3	31/5	S 1-1	225	31.0
7053	D F	3	31/5	S 1-1	209	30.1
7054	D F	3	31/5	S 1-1	228	30.3
7055	D F	3	31/5	S 1-1	174	31.3
7056	D F	3	31/5	S 1-1	198	29.7
7057	D F	3	31/5	S 1-1	186	30.6
7058	D F	3	31/5	S 1-1	117	30.6
7059	D F	3	31/5	S 1-1	168	30.7
7060	D F	3	31/5	S 1-1	154	30.5
7071	D F	4	31/5	S 1-1	179	30.9
7072	D F	4	31/5	S 1-1	224	30.2

D = Dosing Phase

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, u = UnScheduled Necropsy

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APPENDIX 1 contd. Individual Animal Haematology Parameters

Animal #	Sex	Day / Group Week # of Phase	Semi- Semi- Name	WBC ($\times 10^9/\mu\text{L}$)	MCPC (g/dL)
7073	D F	4 31/5	S 1-1	179	30.3
7074	D F	4 31/5	S 1-1	213	29.7
7075	D F	4 31/5	S 1-1	141	30.0
7076	D F	4 31/5	S 1-1	196	29.2
7077	D F	4 31/5	S 1-1	201	30.7
7078	D F	4 31/5	S 1-1	155	30.7
7079	D F	4 31/5	S 1-1	175	29.9
7080	D F	4 31/5	S 1-1	160	30.3

D – Dosing Phase

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APPENDIX 2. Individual Animal Coagulation Parameters

Animal #	Sex	Day / Group / Week / # of Phase	Scout- Sesn Name	APTT (sec)	PT (sec)
7001	D-M	Ctrl 30.5	S 1-1	15	9
7002	D-M	Ctrl 30.5	S 1-1	17	10
7003	D-M	Ctrl 30.5	S 1-1	16	10
7004	D-M	Ctrl 30.5	S 1-1	18	10
7005	D-M	Ctrl 30.5	S 1-1	17	9
7006	D-M	Ctrl 30.5	S 1-1	17	10
7007	D-M	Ctrl 30.5	S 1-1	17	9
7008	D-M	Ctrl 30.5	S 1-1	15	9
7009	D-M	Ctrl 30.5	S 1-1	19	9
7010	D-M	Ctrl 30.5	S 1-1	16	10
7021	D-M	2 30.5	S 1-1	25	10
7022	D-M	2 30.5	S 1-1	16	10
7023	D-M	2 30.5	S 1-1	16	9
7024	D-M	2 30.5	S 1-1	16	10
7025	D-M	2 30.5	S 1-1	17	10
7026	D-M	2 30.5	S 1-1	17	10
7027	D-M	2 30.5	S 1-1	14	9
7028	D-M	2 30.5	S 1-1	15	10
7029	D-M	2 30.5	S 1-1	16	10
7030	D-M	2 30.5	S 1-1	16	9
7041	D-M	3 30.5	S 1-1	19	10
7042	D-M	3 30.5	S 1-1	15	8
7043	D-M	3 30.5	S 1-1	22	10
7044	D-M	3 30.5	S 1-1	17	9

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APPENDIX 2 contd: Individual Animal Coagulation Parameters

Animal #	Sex	Day (Group Week # of Phase)	Serum Spec Name	APTT (sec)	PT (sec)
7045	D M	3 30/5	S 1-1	NO CO...	NO CO...
7046	D M	3 30/5	S 1-1	23	10
7047	D M	3 30/5	S 1-1	22	10
7048	D M	3 30/5	S 1-1	15	9
7049	D M	3 30/5	S 1-1	18	9
7050	D M	3 30/5	S 1-1	18	10
7061	D M	4 30/5	S 1-1	22	10
7062	D M	4 30/5	S 1-1	18	9
7063	D M	4 30/5	S 1-1	27	10
7064	D M	4 30/5	S 1-1	18	10
7065	D M	4 30/5	S 1-1	18	10
7066	D M	4 30/5	S 1-1	15	10
7067	D M	4 30/5	S 1-1	18	9
7068	D M	4 30/5	S 1-1	20	10
7069	D M	4 30/5	S 1-1	17	9
7070	D M	4 30/5	S 1-1	16	10
7011	D F	Ctrl 31/5	S 1-1	16	9
7012	D F	Ctrl 31/5	S 1-1	17	9
7013	D F	Ctrl 31/5	S 1-1	16	9
7014	D F	Ctrl 31/5	S 1-1	17	9
7015	D F	Ctrl 31/5	S 1-1	16	9
7016	D F	Ctrl 31/5	S 1-1	18	9
7017	D F	Ctrl 31/5	S 1-1	18	9
7018	D F	Ctrl 31/5	S 1-1	17	9

D = Dosing Phase

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, n = UnScheduled Necropsy

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APPENDIX 2 contd. Individual Animal Coagulation Parameters

Animal #	Sex	Group	Day / Week of Phase	Semi- Semi Name	APTT (sec)	PT (sec)
7019	D F	Ctl	31/5	S 1-1	15	9
7020	D F	Ctl	31/5	S 1-1	16	9
7001	D F	2	31/5	S 1-1	17	9
7002	D F	2	31/5	S 1-1	17	9
7003	D F	2	31/5	S 1-1	15	9
7004	D F	2	31/5	S 1-1	17	9
7005	D F	2	31/5	S 1-1	15	9
7006	D F	2	31/5	S 1-1	15	9
7007	D F	2	31/5	S 1-1	16	9
7008	D F	2	31/5	S 1-1	19	9
7009	D F	2	31/5	S 1-1	16	9
7040	D F	2	31/5	S 1-1	15	9
7051	D F	3	31/5	S 1-1	16	9
7052	D F	3	31/5	S 1-1	17	9
7053	D F	3	31/5	S 1-1	16	9
7054	D F	3	31/5	S 1-1	15	9
7055	D F	3	31/5	S 1-1	15	9
7056	D F	3	31/5	S 1-1	17	9
7057	D F	3	31/5	S 1-1	16	9
7058	D F	3	31/5	S 1-1	15	9
7059	D F	3	31/5	S 1-1	13	9
7060	D F	3	31/5	S 1-1	17	9
7071	D F	4	31/5	S 1-1	17	9
7072	D F	4	31/5	S 1-1	18	9

D = Dosing Phase

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, n = UnScheduled Necropsy

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APPENDIX 2 contd. Individual Animal Coagulation Parameters

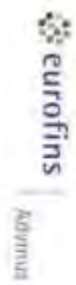
Animal #	Sex	Day / Group / Week	Day / Week of Phase	Semi- Syst. Name	APTT (sec)	PT (sec)
7073	D F	4	31/5	S 1-1	16	9
7074	D F	4	31/5	S 1-1	15	9
7075	D F	4	31/5	S 1-1	15	9
7076	D F	4	31/5	S 1-1	17	9
7077	D F	4	31/5	S 1-1	15	9
7078	D F	4	31/5	S 1-1	19	9
7079	D F	4	31/5	S 1-1	15	9
7080	D F	4	31/5	S 1-1	18	9

 D = Dosing Phase

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, n = UnScheduled Necropsy

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APPENDIX 3. Individual Animal Clinical Chemistry Parameters

Animal #	Sex	Day / Group / Week / # of Phase	Sched- Sex Notes	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	AST (U/L)	ALT (U/L)	ALP (U/L)	BUN (mg/dL)	CA (mg/dL)
7001	D M	Ctrl 30:5	S 1-1	139	8.86	96.4	114	29.00	88	15	10.8
7002	D M	Ctrl 30:5	S 1-1	143	7.10	100.7	88	41.00	156	13	10.6
7003	D M	Ctrl 30:5	S 1-1	142	6.29	101.3	77	31.00	132	14	10.3
7004	D M	Ctrl 30:5	S 1-1	180	6.28	98.7	84	27.00	131	12	10.3
7005	D M	Ctrl 30:5	S 1-1	134	8.79	95.2	71	19.00	81	11	9.8
7006	D M	Ctrl 30:5	S 1-1	145	6.82	100.5	72	26.00	135	13	11.7
7007	D M	Ctrl 30:5	S 1-1	137	6.37	95.1	65	24.00	147	10	10.9
7008	D M	Ctrl 30:5	S 1-1	141	6.47	100.0	75	28.00	173	13	9.8
7009	D M	Ctrl 30:5	S 1-1	147	6.61	100.2	64	19.00	132	14	12.1
7010	D M	Ctrl 30:5	S 1-1	138	5.98	99.6	90	27.00	115	13	9.3
7021	D M	2 30:5	S 1-1	144	7.84	100.6	107	40.00	147	14	10.7
7022	D M	2 30:5	S 1-1	140	4.92	99.7	75	31.00	192	15	10.8
7023	D M	2 30:5	S 1-1	139	6.22	96.8	61	33.00	142	13	10.1
7024	D M	2 30:5	S 1-1	144	5.39	101.3	75	25.00	147	12	10.7
7025	D M	2 30:5	S 1-1	142	5.39	99.8	78	36.00	184	15	11.1
7026	D M	2 30:5	S 1-1	145	7.61	100.2	95	33.00	152	14	10.8
7027	D M	2 30:5	S 1-1	135	6.27	93.6	78	25.00	150	11	9.1
7028	D M	2 30:5	S 1-1	139	10.04	98.5	69	22.00	133	12	10.8
7029	D M	2 30:5	S 1-1	141	5.59	102.7	57	24.00	129	13	9.8
7030	D M	2 30:5	S 1-1	140	6.99	98.4	65	24.00	134	14	10.9
7041	D M	3 30:5	S 1-1	142	7.68	100.9	85	36.00	167	12	10.6
7042	D M	3 30:5	S 1-1	142	8.45	101.0	69	25.00	151	14	11.0
7043	D M	3 30:5	S 1-1	142	8.84	100.0	85	30.00	180	10	9.9
7044	D M	3 30:5	S 1-1	139	7.85	99.2	51	39.00	189	11	9.2

U = Dosing Phase

S = Scheduled Animal Room, U = Unscheduled Animal Room, N = Scheduled Necropsy, u = Unscheduled Necropsy

APPENDIX 3 contd. Individual Animal Clinical Chemistry Parameters

Animal #	Sex	Group	Day / Week of Phase	Scout- Scout Name	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	AST (U/L)	ALT (U/L)	ALP (U/L)	BUN (mg/dL)	Ca (mg/dL)
7045	D M	3	30:5	S 1-1	136	7.14	98.3	51	20.00	112	12	9.8
7046	D M	3	30:5	S 1-1	134	5.63	95.4	51	22.00	114	17	9.4
7047	D M	3	30:5	S 1-1	141	7.58	98.0	59	20.00	113	13	10.9
7048	D M	3	30:5	S 1-1	140	7.08	97.0	58	22.00	147	13	11.1
7049	D M	3	30:5	S 1-1	141	8.05	98.3	74	35.00	122	12	11.3
7050	D M	3	30:5	S 1-1	139	6.89	97.6	72	23.00	120	12	10.9
7061	D M	4	30:5	S 1-1	141	6.27	97.8	79	32.00	126	12	10.2
7062	D M	4	30:5	S 1-1	140	6.01	97.4	80	26.00	80	12	10.9
7063	D M	4	30:5	S 1-1	132	6.38	93.0	53	19.00	93	11	9.2
7064	D M	4	30:5	S 1-1	142	8.88	102.8	63	19.00	114	13	9.6
7065	D M	4	30:5	S 1-1	142	5.44	102.1	74	30.00	112	14	10.0
7066	D M	4	30:5	S 1-1	136	7.01	98.3	55	25.00	82	13	9.9
7067	D M	4	30:5	S 1-1	140	7.70	97.7	71	26.00	141	13	11.0
7068	D M	4	30:5	S 1-1	142	6.78	100.1	59	27.00	144	13	11.3
7069	D M	4	30:5	S 1-1	143	7.78	98.3	72	24.00	138	14	10.0
7070	D M	4	30:5	S 1-1	140	7.99	98.5	71	23.00	97	13	10.8
7011	D F	Ctrl	31:5	S 1-1	136	6.00	94.8	73	24.00	61	16	10.2
7012	D F	Ctrl	31:5	S 1-1	129	7.15	89.8	52	24.00	52	18	10.6
7013	D F	Ctrl	31:5	S 1-1	133	7.25	96.0	66	30.00	72	12	11.3
7014	D F	Ctrl	31:5	S 1-1	124	6.48	104.3	84	27.00	51	12	10.0
7015	D F	Ctrl	31:5	S 1-1	125	5.56	89.7	116	21.00	90	15	9.5
7016	D F	Ctrl	31:5	S 1-1	138	5.98	93.3	84	33.00	64	10	10.4
7017	D F	Ctrl	31:5	S 1-1	134	6.89	93.7	68	28.00	54	14	9.6
7018	D F	Ctrl	31:5	S 1-1	133	6.38	92.0	57	18.00	80	14	9.4

D = Dosing Phase

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, u = UnScheduled Necropsy

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APPENDIX 3 contd. Individual Animal Clinical Chemistry Parameters

Animal #	Sex	Day / Group Week	Session of Phase	Session Name	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	AST (U/L)	ALT (U/L)	ALKP (U/L)	BUN (mg/dL)	CA (mg/dL)
7019	D F	Ctrl	3/5	S 1-1	140	6.62	94.5	81	28.00	39	16	11.7
7020	D F	Ctrl	3/5	S 1-1	141	5.48	99.4	148	44.00	102	16	12.9
7031	D F	2	3/5	S 1-1	141	5.35	98.8	81	26.00	62	19	10.9
7032	D F	2	3/5	S 1-1	140	6.60	97.4	50	19.00	63	15	11.0
7033	D F	2	3/5	S 1-1	139	7.32	98.0	128	28.00	60	17	10.1
7034	D F	2	3/5	S 1-1	133	5.87	90.3	95	29.00	45	17	10.8
7035	D F	2	3/5	S 1-1	123	7.43	105.8	63	15.00	37	13	9.1
7036	D F	2	3/5	S 1-1	128	6.29	90.5	70	25.00	73	18	9.1
7037	D F	2	3/5	S 1-1	132	6.02	89.0	88	21.00	67	12	9.6
7038	D F	2	3/5	S 1-1	132	12.10	94.5	67	21.00	98	15	9.8
7039	D F	2	3/5	S 1-1	135	6.29	92.7	60	22.00	63	14	10.8
7040	D F	2	3/5	S 1-1	141	8.34	99.9	99	24.00	75	14	11.7
7051	D F	3	3/5	S 1-1	134	5.91	96.2	39	29.00	61	14	10.1
7052	D F	3	3/5	S 1-1	138	5.55	97.4	88	27.00	81	13	11.1
7053	D F	3	3/5	S 1-1	129	6.46	94.1	69	18.00	44	18	9.0
7054	D F	3	3/5	S 1-1	136	7.29	93.0	62	26.00	40	16	8.3
7055	D F	3	3/5	S 1-1	139	6.45	97.2	106	25.00	73	14	10.7
7056	D F	3	3/5	S 1-1	133	13.68	96.4	267	103.00	73	15	10.3
7057	D F	3	3/5	S 1-1	150	5.41	108.7	68	20.00	44	10	8.7
7058	D F	3	3/5	S 1-1	128	7.10	101.3	46	27.00	69	13	9.8
7059	D F	3	3/5	S 1-1	118	9.29	97.5	113	22.00	82	13	10.3
7060	D F	3	3/5	S 1-1	139	6.47	98.8	101	38.00	84	14	10.6
7071	D F	4	3/5	S 1-1	134	6.18	92.3	87	58.00	60	18	11.1
7072	D F	4	3/5	S 1-1	128	4.97	98.4	116	58.00	75	16	10.2

D = Dosing Phase

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, n = UnScheduled Necropsy

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APPENDIX 3 contd. Individual Animal Clinical Chemistry Parameters

Animal #	Sex	Group	Day / Week # of Phase	Scout- Sens Name	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	AST (U/L)	ALT (U/L)	ALP (U/L)	BUN (mg/dL)	CA (mg/dL)
7073	D F	4	31/5	S 1-L	122	7.39	93.1	69	25.00	65	18	9.2
7074	D F	4	31/5	S 1-L	130	6.29	91.9	80	22.00	69	16	9.7
7075	D F	4	31/5	S 1-L	140	6.68	93.9	89	27.00	93	14	10.5
7076	D F	4	31/5	S 1-L	126	7.85	100.8	157	149.00	53	13	8.8
7077	D F	4	31/5	S 1-L	141	8.21	97.2	64	24.00	88	12	12.2
7078	D F	4	31/5	S 1-L	140	8.87	92.8	72	26.00	72	14	11.4
7079	D F	4	31/5	S 1-L	140	8.67	96.8	123	26.00	117	14	11.4
7080	D F	4	31/5	S 1-L	140	8.15	92.7	86	28.00	89	16	10.6

D = Dosing Phase

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, n = UnScheduled Necropsy

APPENDIX 3 contd. Individual Animal Clinical Chemistry Parameters

Animal #	Sex	Day / (Group Week # of Phase	Seem- Sens Status	CPRO (mg/dL)	CREAT (mg/dL)	GLU (mg/dL)	PHOS (mg/dL)	TRE (mg/dL)	TRIG (mg/dL)	BUN (U/L)	TP (g/dL)
7001	D M	Ctrl 30S	S 1-1	46	0.18	126	10.6	0.07	53	8.8	5.5
7002	D M	Ctrl 30S	S 1-1	38	0.16	141	9.7	0.05	47	10.6	5.4
7003	D M	Ctrl 30S	S 1-1	40	0.14	119	9.0	0.08	29	8.4	5.5
7004	D M	Ctrl 30S	S 1-1	91	0.15	99	9.3	0.06	37	10.0	5.8
7005	D M	Ctrl 30S	S 1-1	85	0.15	171	8.8	0.07	50	8.6	5.8
7006	D M	Ctrl 30S	S 1-1	71	0.21	219	10.2	0.06	80	11.8	5.6
7007	D M	Ctrl 30S	S 1-1	50	0.14	135	9.5	0.07	48	10.2	5.5
7008	D M	Ctrl 30S	S 1-1	85	0.16	116	9.2	0.05	52	12.0	5.5
7009	D M	Ctrl 30S	S 1-1	67	0.19	129	9.6	0.05	49	8.8	6.3
7010	D M	Ctrl 30S	S 1-1	81	0.15	97	7.9	0.08	31	8.6	5.6
7021	D M	2 30S	S 1-1	32	0.26	72	9.8	0.03	37	4.1	5.6
7022	D M	2 30S	S 1-1	65	0.17	152	11.0	0.08	33	6.3	6.2
7023	D M	2 30S	S 1-1	56	0.15	130	9.3	0.06	39	12.4	5.9
7024	D M	2 30S	S 1-1	66	0.11	113	8.9	0.06	44	8.0	5.7
7025	D M	2 30S	S 1-1	39	0.20	111	11.0	0.06	52	8.1	6.2
7026	D M	2 30S	S 1-1	73	0.20	91	10.5	0.05	37	10.5	5.9
7027	D M	2 30S	S 1-1	51	0.11	113	8.8	0.08	62	10.2	6.0
7028	D M	2 30S	S 1-1	61	0.19	108	10.4	0.08	40	5.3	6.1
7029	D M	2 30S	S 1-1	47	0.16	94	7.6	0.06	31	8.8	5.2
7030	D M	2 30S	S 1-1	81	0.15	151	8.8	0.08	52	8.8	5.8
7041	D M	3 30S	S 1-1	67	0.18	85	9.7	0.08	49	12.0	6.2
7042	D M	3 30S	S 1-1	77	0.26	88	10.3	0.07	35	7.1	6.0
7043	D M	3 30S	S 1-1	72	0.17	84	9.9	0.04	67	12.1	5.7
7044	D M	3 30S	S 1-1	55	0.12	159	8.9	0.06	40	8.7	6.0

D = Dosing Phase

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, u = UnScheduled Necropsy

APPENDIX 3 contd. Individual Animal Clinical Chemistry Parameters

Animal #	Sex	Group	Day / Week	Seam- Scan Name	CHOL (mg/dL)	CREAT (mg/dL)	GLU (mg/dL)	BUN (mg/dL)	BIL (mg/dL)	TBLG (mg/dL)	SDP (U/L)	TP (g/dL)
7045	D M	J	20/5	S J-L	62	0.12	163	8.1	0.06	38	5.9	5.2
7046	D M	J	30/5	S J-L	40	0.21	115	7.9	0.06	25	10.8	5.9
7047	D M	J	30/5	S J-L	69	0.16	150	10.1	0.05	42	7.7	5.8
7048	D M	J	30/5	S J-L	62	0.20	114	8.8	0.06	39	11.6	5.8
7049	D M	J	30/5	S J-L	70	0.19	140	9.5	0.07	56	6.1	5.9
7050	D M	J	30/5	S J-L	56	0.17	95	9.8	0.07	38	6.4	6.3
7061	D M	4	30/5	S J-L	41	0.18	127	9.8	0.05	47	10.5	5.7
7062	D M	4	30/5	S J-L	48	0.16	139	9.8	0.07	47	15.0	6.0
7063	D M	4	30/5	S J-L	45	0.16	139	8.7	0.06	36	6.7	6.4
7064	D M	4	30/5	S J-L	37	0.21	134	10.8	0.06	60	7.3	6.1
7065	D M	4	30/5	S J-L	54	0.23	86	8.7	0.05	43	6.6	5.8
7066	D M	4	30/5	S J-L	43	0.11	129	8.7	0.07	34	9.6	4.4
7067	D M	4	30/5	S J-L	85	0.17	118	10.1	0.11	44	8.2	6.2
7068	D M	4	30/5	S J-L	69	0.15	160	9.5	0.09	95	12.1	5.9
7069	D M	4	30/5	S J-L	70	0.19	104	9.5	0.11	62	15.6	6.0
7070	D M	4	30/5	S J-L	48	0.14	96	10.7	0.05	37	8.0	5.6
7091	D F	Ctrl	31/5	S J-L	52	0.22	144	7.5	0.08	58	5.3	6.2
7012	D F	Ctrl	31/5	S J-L	69	0.19	183	7.9	0.08	71	8.3	6.4
7013	D F	Ctrl	31/5	S J-L	100	0.18	123	9.1	0.07	37	11.8	6.9
7014	D F	Ctrl	31/5	S J-L	73	0.16	183	7.8	0.07	43	8.0	7.7
7015	D F	Ctrl	31/5	S J-L	66	0.19	120	7.6	0.06	26	3.2	6.0
7016	D F	Ctrl	31/5	S J-L	96	0.16	113	7.4	0.08	65	5.3	6.0
7017	D F	Ctrl	31/5	S J-L	62	0.20	104	7.8	0.07	36	5.8	6.8
7018	D F	Ctrl	31/5	S J-L	83	0.20	186	7.8	0.08	30	9.1	7.3

D = Dosing Phase

S = Scheduled Animal Room, J = Unscheduled Animal Room, N = Scheduled Necropsy, U = Unscheduled Necropsy

APPENDIX 3 contd. Individual Animal Clinical Chemistry Parameters

Animal #	Sex	Day 1 Group	Week	Study Site	Site Name	CHOL (mg/dL)	CREAT (mg/dL)	GLU (mg/dL)	BUN (mg/dL)	BIL (mg/dL)	BUN (mg/dL)	ALT (U/L)	TP (g/dL)
7019	D F	C21	11/3	S 1-1		90	0.23	116	6.4	0.10	59	10.4	3.1
7020	D F	C21	11/3	S 1-1		90	0.28	100	8.8	0.08	39	9.9	6.7
7031	D F	2	11/3	S 1-1		100	0.25	160	7.8	0.09	34	6.2	6.8
7032	D F	2	11/3	S 1-1		89	0.23	192	7.0	0.09	43	6.3	7.5
7033	D F	2	11/3	S 1-1		71	0.30	97	8.0	0.07	29	2.7	6.2
7034	D F	2	11/3	S 1-1		92	0.20	139	8.0	0.08	37	4.1	7.5
7035	D F	2	11/3	S 1-1		45	0.15	81	8.6	0.09	33	3.0	6.6
7036	D F	2	11/3	S 1-1		56	0.28	70	7.6	0.08	29	0.7	6.1
7037	D F	2	11/3	S 1-1		64	0.17	135	7.5	0.12	35	2.5	5.9
7038	D F	2	11/3	S 1-1		40	0.22	99	9.4	0.09	40	3.2	7.5
7039	D F	2	11/3	S 1-1		103	0.22	162	7.4	0.07	72	6.2	6.7
7040	D F	2	11/3	S 1-1		71	0.28	82	10.3	0.10	27	2.6	6.6
7051	D F	3	11/3	S 1-1		83	0.24	174	7.0	0.07	61	7.5	6.4
7052	D F	3	11/3	S 1-1		93	0.20	182	7.5	0.10	45	7.6	6.3
7053	D F	3	11/3	S 1-1		73	0.17	130	6.6	0.06	36	9.3	6.0
7054	D F	3	11/3	S 1-1		92	0.16	122	8.2	0.07	54	9.1	7.8
7055	D F	3	11/3	S 1-1		75	0.18	136	8.1	0.09	42	5.6	6.2
7056	D F	3	11/3	S 1-1		74	0.26	102	10.1	0.11	44	102.6	6.4
7057	D F	3	11/3	S 1-1		64	0.15	148	5.8	0.06	33	3.9	5.1
7058	D F	3	11/3	S 1-1		55	0.18	119	8.4	0.08	43	11.1	7.9
7059	D F	3	11/3	S 1-1		69	0.25	92	8.2	0.10	36	7.8	6.4
7060	D F	3	11/3	S 1-1		67	0.20	95	8.8	0.08	28	16.7	6.2
7071	D F	4	11/3	S 1-1		84	0.16	134	8.2	0.08	68	19.7	6.7
7072	D F	4	11/3	S 1-1		71	0.24	123	6.6	0.09	59	16.8	6.7

D = Dosing Phase

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, u = UnScheduled Necropsy

APPENDIX 3 contd. Individual Animal Clinical Chemistry Parameters

Animal #	Sex	Day / Group Week / # of Phas	Semi- Semi- Name	CHOL (mg/dL)	CREAT (mg/dL)	GLU (mg/dL)	PHOS (mg/dL)	BUN (mg/dL)	TRIG (mg/dL)	SDH (U/L)	TP (g/dL)
7073	D F	4 11/5	S 1-1	60	0.17	99	7.2	0.69	16	7.6	7.1
7074	D F	4 11/5	S 1-1	71	0.25	87	8.8	0.66	27	4.7	7.1
7075	D F	4 11/5	S 1-1	56	0.26	83	8.0	0.69	49	7.1	6.4
7076	D F	4 11/5	S 1-1	60	0.20	182	7.8	0.68	23	46.0	8.0
7077	D F	4 11/5	S 1-1	79	0.18	166	10.0	0.12	33	13.1	6.8
7078	D F	4 11/5	S 1-1	91	0.25	71	9.2	0.11	29	8.1	6.7
7079	D F	4 11/5	S 1-1	114	0.28	147	9.2	0.69	66	3.0	6.8
7080	D F	4 11/5	S 1-1	52	0.26	116	8.6	0.16	23	7.0	6.0

D = Dosing Phase

S = Scheduled Animal Room; U = Unscheduled Animal Room; N = Scheduled Necropsy; # = Unscheduled Necropsy

APPENDIX 3 contd.: Individual Animal Clinical Chemistry Parameters

Animal #	Sex	Day / Group Week # of Phase	Semi- Seen Name	ALB (µg/dL)	GLOB (µg/dL)
7001	D M	Ctrl 30/5	S 1-1	3.5	2.0
7002	D M	Ctrl 30/5	S 1-1	3.6	1.8
7003	D M	Ctrl 30/5	S 1-1	3.7	1.8
7004	D M	Ctrl 30/5	S 1-1	3.6	1.9
7005	D M	Ctrl 30/5	S 1-1	3.3	2.5
7006	D M	Ctrl 30/5	S 1-1	4.2	3.4
7007	D M	Ctrl 30/5	S 1-1	3.3	2.2
7008	D M	Ctrl 30/5	S 1-1	3.4	2.1
7009	D M	Ctrl 30/5	S 1-1	4.3	2.0
7010	D M	Ctrl 30/5	S 1-1	3.5	2.1
7021	D M	2 30/5	S 1-1	3.5	2.1
7022	D M	2 30/5	S 1-1	4.0	2.2
7023	D M	2 30/5	S 1-1	3.5	2.0
7024	D M	2 30/5	S 1-1	3.7	2.0
7025	D M	2 30/5	S 1-1	4.0	2.2
7026	D M	2 30/5	S 1-1	3.8	2.1
7027	D M	2 30/5	S 1-1	4.0	2.0
7028	D M	2 30/5	S 1-1	3.9	2.2
7029	D M	2 30/5	S 1-1	3.4	1.8
7030	D M	2 30/5	S 1-1	3.8	2.1
7041	D M	3 30/5	S 1-1	4.1	2.1
7042	D M	3 30/5	S 1-1	3.8	2.2
7043	D M	3 30/5	S 1-1	3.6	2.1
7044	D M	3 30/5	S 1-1	3.8	2.2

D - Dosing Phase

S - Scheduled Animal Room, U - Unscheduled Animal Room, N - Scheduled Necropsy, n - Unscheduled Necropsy

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APPENDIX 3 contd. Individual Animal Clinical Chemistry Parameters

Animal #	Sex	Day / Litter Week # of Phase	Scam- Scan Name	ALB (g/dL)	GLOB (g/dL)
7045	D M	3 30/5	S 1-1	3.0	2.2
7046	D M	3 30/5	S 1-1	3.0	2.0
7047	D M	3 30/5	S 1-1	3.3	2.0
7048	D M	3 30/5	S 1-1	3.3	2.0
7049	D M	3 30/5	S 1-1	3.3	2.1
7050	D M	3 30/5	S 1-1	4.2	2.1
7061	D M	4 30/5	S 1-1	3.7	2.0
7062	D M	4 30/5	S 1-1	4.0	2.0
7063	D M	4 30/5	S 1-1	4.0	2.4
7064	D M	4 30/5	S 1-1	4.1	2.0
7065	D M	4 30/5	S 1-1	3.4	2.0
7066	D M	4 30/5	S 1-1	3.0	1.4
7067	D M	4 30/5	S 1-1	4.0	2.2
7068	D M	4 30/5	S 1-1	3.9	2.0
7069	D M	4 30/5	S 1-1	3.9	2.1
7090	D M	4 30/5	S 1-1	3.6	2.0
7011	D F	Crit 31/5	S 1-1	4.2	2.0
7012	D F	Crit 31/5	S 1-1	4.5	1.9
7013	D F	Crit 31/5	S 1-1	4.8	2.1
7014	D F	Crit 31/5	S 1-1	5.6	2.1
7015	D F	Crit 31/5	S 1-1	4.5	2.1
7016	D F	Crit 31/5	S 1-1	3.7	2.3
7017	D F	Crit 31/5	S 1-1	4.3	2.1
7018	D F	Crit 31/5	S 1-1	5.3	2.0

D = Dosing Phase

S = Scheduled Animal Room, 1 = Unscheduled Animal Room, N = Scheduled Necropsy, n = Unscheduled Necropsy

APPENDIX 3 contd. Individual Animal Clinical Chemistry Parameters

Animal #	Sex	Group	Day / Week of Phase	Study Site Name	ALB (g/dL)	GLOB (g/dL)
7019	D F	Ctl	31/5	S 1-1	5.2	1.9
7020	D F	Ctl	31/5	S 1-1	4.5	1.3
7031	D F	2	31/5	S 1-1	4.8	2.0
7032	D F	2	31/5	S 1-1	5.2	2.3
7033	D F	2	31/5	S 1-1	4.5	1.9
7034	D F	2	31/5	S 1-1	5.5	2.0
7035	D F	2	31/5	S 1-1	4.5	2.1
7036	D F	2	31/5	S 1-1	3.9	2.2
7037	D F	2	31/5	S 1-1	4.4	1.5
7038	D F	2	31/5	S 1-1	5.4	2.1
7039	D F	2	31/5	S 1-1	4.4	2.1
7040	D F	2	31/5	S 1-1	4.4	2.2
7051	D F	3	31/5	S 1-1	4.6	1.8
7052	D F	3	31/5	S 1-1	4.7	1.8
7053	D F	3	31/5	S 1-1	3.9	2.5
7054	D F	3	31/5	S 1-1	5.3	2.5
7055	D F	3	31/5	S 1-1	4.7	1.5
7056	D F	3	31/5	S 1-1	4.4	2.0
7057	D F	3	31/5	S 1-1	3.6	1.3
7058	D F	3	31/5	S 1-1	3.6	2.1
7059	D F	3	31/5	S 1-1	4.4	2.0
7060	D F	3	31/5	S 1-1	4.2	2.0
7071	D F	4	31/5	S 1-1	4.3	2.2
7072	D F	4	31/5	S 1-1	4.5	2.0

D = Dosing Phase

S = Scheduled Animal Room; U = UnScheduled Animal Room; N = Scheduled Necropsy; u = UnScheduled Necropsy

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APPENDIX 3 contd. Individual Animal Clinical Chemistry Parameters

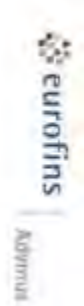
Animal #	Sex	Day /		Sesno- Sessn	ALB (g/dL)	GLDH (g/dL)
		Group	Week			
7073	D F	4	31/5	S 1-1	5.1	2.4
7074	D F	4	31/5	S 1-1	5.1	2.0
7075	D F	4	31/5	S 1-1	4.3	2.1
7076	D F	4	31/5	S 1-1	5.4	2.6
7077	D F	4	31/5	S 1-1	4.9	2.0
7078	D F	4	31/5	S 1-1	4.4	2.3
7079	D F	4	31/5	S 1-1	4.5	2.3
7080	D F	4	31/5	S 1-1	4.4	1.8

D = Dosing Phase

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, n = UnScheduled Necropsy

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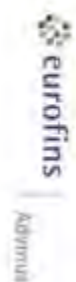


APPENDIX 4. Individual Animal Clinical Analysis of Urine

Animal #	Sex	Dry Group Week	Strain	Study Week	Strain Name	UBIL	UBLO	URET (mg/dL)	USIU (mg/dL)	UBO (DUAL)	pH	SG	UCOL
7001	D M	Cd	305	S 1-1		SMALL	NEGATIVE	15	NEGATIVE	0.2	6.3	1.030	D YEL
7002	D M	Cd	305	S 1-1		SMALL	NEGATIVE	TRACE	NEGATIVE	0.2	6.0	1.030	D YEL
7003	D M	Cd	305	S 1-1		SMALL	NEGATIVE	TRACE	NEGATIVE	0.2	6.1	1.010	D YEL
7004	D M	Cd	305	S 1-1		NEGATIVE	NEGATIVE	TRACE	NEGATIVE	0.2	7.0	1.020	YEL
7005	D M	Cd	305	S 1-1		NEGATIVE	NEGATIVE	15	NEGATIVE	0.2	6.5	1.030	YEL
7006	D M	Cd	305	S 1-1		NEGATIVE	NEGATIVE	15	NEGATIVE	0.2	7.0	1.025	YEL
7007	D M	Cd	305	S 1-1		NEGATIVE	SMALL	TRACE	NEGATIVE	0.2	7.0	1.020	YEL
7008	D M	Cd	305	S 1-1		NEGATIVE	SMALL	TRACE	NEGATIVE	0.2	7.0	1.025	YEL
7009	D M	Cd	305	S 1-1		NEGATIVE	NEGATIVE	15	NEGATIVE	0.2	6.3	1.025	YEL
7010	D M	Cd	305	S 1-1		NEGATIVE	TL	TRACE	NEGATIVE	0.2	7.0	1.010	L YEL
7021	D M	2	305	S 1-1		NEGATIVE	NEGATIVE	TRACE	NEGATIVE	0.2	7.0	1.026	YEL
7022	D M	2	305	S 1-1		SMALL	NEGATIVE	NEGATIVE	NEGATIVE	0.2	5.5	1.030	D YEL
7023	D M	2	305	S 1-1		NEGATIVE	NEGATIVE	15	NEGATIVE	0.2	6.5	1.010	D YEL
7024	D M	2	305	S 1-1		NEGATIVE	NEGATIVE	15	NEGATIVE	0.2	6.3	1.030	YEL
7025	D M	2	305	S 1-1		NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2	7.0	1.020	YEL
7026	D M	2	305	S 1-1		NEGATIVE	TI	TRACE	NEGATIVE	0.2	7.0	1.025	YEL
7027	D M	2	305	S 1-1		NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2	6.5	1.025	YEL
7028	D M	2	305	S 1-1		NEGATIVE	NEGATIVE	15	NEGATIVE	0.2	7.0	1.020	L YEL
7029	D M	2	305	S 1-1		NEGATIVE	NEGATIVE	TRACE	NEGATIVE	0.2	7.0	1.030	YEL
7030	D M	2	305	S 1-1		NEGATIVE	TI	TRACE	NEGATIVE	0.2	6.3	1.030	YEL
7040	D M	3	305	S 1-1		NEGATIVE	TI	TRACE	NEGATIVE	0.2	7.0	1.025	YEL
7042	D M	3	305	S 1-1		SMALL	NEGATIVE	NEGATIVE	NEGATIVE	0.2	6.0	1.030	D YEL
7043	D M	3	305	S 1-1		NEGATIVE	NEGATIVE	TRACE	NEGATIVE	0.2	7.0	1.020	L YEL
7044	D M	3	305	S 1-1		NEGATIVE	NEGATIVE	15	NEGATIVE	0.2	6.3	1.030	YEL

U = Dosing Phase

S = Scheduled Animal Room; U = Unscheduled Animal Room; N = Scheduled Neuroplex; n = Unscheduled Neuroplex

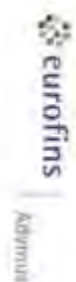


APPENDIX 4 contd. Individual Animal Clinical Analysis of Urine

Animal #	Sex	Day Group Week	Week of Phase	Scm- Scm Norm	UBIL	UBLO	UKBT (mg/dL)	UBLU (mg/dL)	UBO (IU/dL)	pH	SG	UCOL
7045	D M	3	30/5	S (-)	NEGATIVE	TL	NEGATIVE	NEGATIVE	0.2	7.0	1.013	YEL
7046	D M	3	30/5	S (-)	NEGATIVE	SMALL	15	NEGATIVE	0.2	6.5	1.030	YEL
7047	D M	3	30/5	S (-)	NEGATIVE	NEGATIVE	TRACE	NEGATIVE	0.2	7.0	1.000	YEL
7048	D M	3	30/5	S (-)	NEGATIVE	SMALL	15	NEGATIVE	0.2	7.0	1.029	L YEL
7049	D M	3	30/5	S (-)	NEGATIVE	NEGATIVE	TRACE	NEGATIVE	0.2	6.5	1.000	YEL
7050	D M	3	30/5	S (-)	NEGATIVE	NEGATIVE	15	NEGATIVE	0.2	7.0	1.000	YEL
7061	D M	4	30/5	S (-)	NEGATIVE	NEGATIVE	TRACE	NEGATIVE	0.2	6.5	1.025	YEL
7062	D M	4	30/5	S (-)	NEGATIVE	NEGATIVE	15	NEGATIVE	0.2	6.5	1.030	YEL
7063	D M	4	30/5	S (-)	NEGATIVE	MODERATE	NEGATIVE	NEGATIVE	0.2	6.5	1.020	YEL
7064	D M	4	30/5	S (-)	NEGATIVE	NEGATIVE	TRACE	NEGATIVE	0.2	6.5	1.000	YEL
7065	D M	4	30/5	S (-)	NEGATIVE	NEGATIVE	TRACE	NEGATIVE	0.2	6.5	1.000	YEL
7066	D M	4	30/5	S (-)	NEGATIVE	NEGATIVE	15	NEGATIVE	0.2	6.5	1.030	YEL
7067	D M	4	30/5	S (-)	NEGATIVE	NEGATIVE	TRACE	NEGATIVE	0.2	7.0	1.000	YEL
7068	D M	4	30/5	S (-)	NEGATIVE	NEGATIVE	15	NEGATIVE	0.2	7.0	1.025	YEL
7069	D M	4	30/5	S (-)	NEGATIVE	NEGATIVE	15	NEGATIVE	0.2	7.0	1.010	YEL
7070	D M	4	30/5	S (-)	NEGATIVE	TL	TRACE	NEGATIVE	0.2	6.5	1.025	YEL
7013	D F	Int	31/5	S (-)	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2	6.5	1.020	YEL
7012	D F	Cont	31/5	S (-)	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2	6.5	1.030	YEL
7013	D F	Cont	31/5	S (-)	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2	6.0	1.025	YEL
7014	D F	Cont	31/5	S (-)	NEGATIVE	TL	NEGATIVE	NEGATIVE	0.2	7.0	1.000	L YEL
7015	D F	Cont	31/5	S (-)	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2	6.5	1.025	YEL
7016	D F	Cont	31/5	S (-)	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2	6.8	1.010	L YEL
7017	D F	Cont	31/5	S (-)	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2	6.5	1.015	YEL
7018	D F	Cont	31/5	S (-)	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2	6.5	1.010	L YEL

D - Dosing Phase

S - Scheduled Animal Room, U - Unscheduled Animal Room, N - Scheduled Necropsy, u - Unscheduled Necropsy



APPENDIX 4 contd. Individual Animal Clinical Analysis of Urine

Animal #	Sex	Group	Week	Phase	Study Name	URIL	URLO	URFT (mg/dL)	URLU (mg/dL)	URM (EC/dL)	pH	SG	UCOL
7010	D F	Ctrl	315	S 1-1		NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2	6.0	1.023	YEL
7020	D F	Ctrl	315	S 1-1		INS -	INS -	INS -	INS -	INS -	INS -	INS -	INS -
7031	D F	2	315	S 1-1		SMALL	SMALL	NEGATIVE	NEGATIVE	0.2	6.5	1.080	D YEL
7002	D F	2	315	S 1-1		NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2	7.0	1.015	YEL
7033	D F	2	315	S 1-4		INS -	INS -	INS -	INS -	INS -	INS -	INS -	INS -
7034	D F	2	315	S 1-4		SMALL	TI	NEGATIVE	NEGATIVE	0.2	6.3	1.050	D YEL
7035	D F	2	315	S 1-4		INS -	INS -	INS -	INS -	INS -	INS -	INS -	INS -
7036	D F	2	315	S 1-4		SMALL	SMALL	NEGATIVE	NEGATIVE	0.2	6.1	1.030	D YEL
7037	D F	2	315	S 1-4		NEGATIVE	TI	NEGATIVE	NEGATIVE	0.2	6.1	1.021	YEL
7038	D F	2	315	S 1-0		NEGATIVE	SMALL	NEGATIVE	NEGATIVE	0.2	7.2	1.012	YEL
7039	D F	2	315	S 1-3		NEGATIVE	SMALL	NEGATIVE	NEGATIVE	0.2	8.0	1.010	YEL
7040	D F	2	315	S 1-4		NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2	7.0	1.015	L YEL
7051	D F	3	315	S 1-1		NEGATIVE	SMALL	NEGATIVE	NEGATIVE	0.2	7.0	1.020	YEL
7052	D F	3	315	S 1-1		NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2	6.1	1.030	YEL
7053	D F	3	315	S 1-1		NEGATIVE	TI	NEGATIVE	NEGATIVE	0.2	7.0	1.020	YEL
7054	D F	3	315	S 1-1		NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2	6.2	1.025	YEL
7055	D F	3	315	S 1-3		NEGATIVE	TI	NEGATIVE	NEGATIVE	0.2	7.0	1.013	L YEL
7056	D F	3	315	S 1-1		NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2	6.0	1.025	YEL
7057	D F	3	315	S 1-4		SMALL	NEGATIVE	NEGATIVE	NEGATIVE	0.2	6.0	1.050	D YEL
7058	D F	3	315	S 1-1		SMALL	SMALL	NEGATIVE	NEGATIVE	0.2	7.0	1.050	D YEL
7059	D F	3	315	S 1-4		NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2	6.1	1.010	L YEL
7060	D F	3	315	S 1-1		SMALL	NEGATIVE	NEGATIVE	NEGATIVE	0.2	6.0	1.030	D YEL
7071	D F	4	315	S 1-1		NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2	6.1	1.025	YEL
7072	D F	4	315	S 1-4		NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2	6.1	1.025	YEL

D= Dosing Phase

S = Scheduled Animal Room, U = Unscheduled Animal Room, N = Scheduled Necropsy, n = Unscheduled Necropsy.

APPENDIX 4 contd. Individual Animal Clinical Analysis of Urine

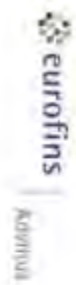
Animal #	Sex	p	Day / Group Week of Phase	Screen- Scan Name	URUL		URLO		URKF (mg/dL)		URFU (mg/dL)		URG (EU/dL)		pH	SG	UCOL
					INS	---	INS	---	INS	---	INS	---	INS	---			
7073	D F	4	31/5	S 1-1	INS	---	INS	---	INS	---	INS	---	INS	---	6.0	1.030	YEL
7074	D F	4	31/5	S 1-1	NEGATIVE	---	NEGATIVE	---	NEGATIVE	---	NEGATIVE	---	NEGATIVE	---	6.0	1.030	YEL
7075	D F	4	31/5	S 1-1	NEGATIVE	---	NEGATIVE	---	NEGATIVE	---	NEGATIVE	---	NEGATIVE	---	6.5	1.030	D YEL
7076	D F	4	31/5	S 1-1	SMALL	---	NEGATIVE	---	NEGATIVE	---	NEGATIVE	---	NEGATIVE	---	6.5	1.030	D YEL
7077	D F	4	31/5	S 1-1	NEGATIVE	---	NEGATIVE	---	NEGATIVE	---	NEGATIVE	---	NEGATIVE	---	6.5	1.030	YEL
7078	D F	4	31/5	S 1-1	NEGATIVE	---	NEGATIVE	---	NEGATIVE	---	NEGATIVE	---	NEGATIVE	---	6.5	1.020	L YEL
7079	D F	4	31/5	S 1-1	SMALL	---	TI	---	NEGATIVE	---	NEGATIVE	---	NEGATIVE	---	6.5	1.030	D YEL
7080	D F	4	31/5	S 1-1	NEGATIVE	---	NEGATIVE	---	NEGATIVE	---	NEGATIVE	---	NEGATIVE	---	6.5	1.030	L YEL

D = Dosing Phase

S = Scheduled Animal Room, U = Unscheduled Animal Room, S = Scheduled Necropsy, u = Unscheduled Necropsy

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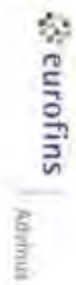


APPENDIX 4 cont'd. Individual Animal Clinical Analysis of Urine

Animal #	Sex	Day / Group / Week / of Phase	Scat# / Scat Name	UCLA	UVOL (ml.)	QUAL	UPRO (mg/dl.)	USed	USedAbK
7001	D M	Ctrl 30.5	S 1-1	CLEAR	5.5	MEDIUM	30	WNL	-
7002	D M	Ctrl 30.5	S 1-1	CLEAR	1.7	DARK	100	WNL	-
7003	D M	Ctrl 30.5	S 1-1	CLEAR	4.0	MEDIUM	30	WNL	-
7004	D M	Ctrl 30.5	S 1-1	CLEAR	4.3	MEDIUM	30	WNL	-
7005	D M	Ctrl 30.5	S 1-1	CLEAR	5.0	MEDIUM	30	WNL	-
7006	D M	Ctrl 30.5	S 1-1	CLEAR	5.4	DARK	30	WNL	-
7007	D M	Ctrl 30.5	S 1-1	CLEAR	9.0	MEDIUM	30	WNL	BACT
7008	D M	Ctrl 30.5	S 1-1	CLEAR	5.0	MEDIUM	30	WNL	-
7009	D M	Ctrl 30.5	S 1-1	CLEAR	7.5	MEDIUM	15	WNL	-
7010	D M	Ctrl 30.5	S 1-1	CLEAR	40.0	LIGHT	0	WNL	-
7021	D M	2 30.5	S 1-1	CLEAR	10.0	LIGHT	0	WNL	-
7022	D M	2 30.5	S 1-1	CLEAR	3.0	DARK	100	WNL	-
7023	D M	2 30.5	S 1-1	CLEAR	4.1	DARK	30	WNL	-
7024	D M	2 30.5	S 1-1	CLEAR	5.0	MEDIUM	30	WNL	-
7025	D M	2 30.5	S 1-1	CLEAR	11.3	LIGHT	15	WNL	-
7026	D M	2 30.5	S 1-1	CLEAR	7.0	DARK	30	WNL	-
7027	D M	2 30.5	S 1-1	CLEAR	16.0	MEDIUM	0	WNL	BACT
7028	D M	2 30.5	S 1-1	CLEAR	9.3	LIGHT	15	WNL	-
7029	D M	2 30.5	S 1-1	CLEAR	21.0	LIGHT	0	WNL	-
7030	D M	2 30.5	S 1-1	CLEAR	4.9	DARK	100	WNL	-
7041	D M	3 30.5	S 1-1	CLEAR	6.5	MEDIUM	30	WNL	-
7042	D M	3 30.5	S 1-1	CLEAR	3.5	DARK	30	WNL	-
7043	D M	3 30.5	S 1-1	CLEAR	27.0	LIGHT	0	WNL	-
7044	D M	3 30.5	S 1-1	CLEAR	6.2	MEDIUM	30	WNL	-

D = Dosing Phase

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, n = UnScheduled Necropsy



APPENDIX 4 contd. Individual Animal Clinical Analysis of Urine

Animal ID	Sex	Day of Group Week of Phase	Semin. Sam Name	UCLA	UVOL (mL)	QUAL	UPRO (mg/dL)	USed	USedA/N
7045	D M	3 30:5	S 1-1	CLEAR	10.0	LIGHT	15	WNL	...
7046	D M	3 30:5	S 1-1	CLEAR	5.0	MEDIUM	15	WNL	...
7047	D M	3 30:5	S 1-1	CLEAR	10.5	LIGHT	15	WNL	...
7048	D M	3 30:5	S 1-1	CLEAR	13.5	LIGHT	15	WNL	...
7049	D M	3 30:5	S 1-1	CLEAR	8.8	MEDIUM	30	WNL	...
7050	D M	3 30:5	S 1-1	CLEAR	12.0	LIGHT	15	WNL	...
7061	D M	4 30:5	S 1-1	CLEAR	9.0	LIGHT	30	WNL	...
7062	D M	4 30:5	S 1-1	CLEAR	8.5	MEDIUM	15	WNL	...
7063	D M	4 30:5	S 1-1	CLEAR	11.0	LIGHT	15	WNL	...
7064	D M	4 30:5	S 1-1	CLEAR	5.4	DARK	30	WNL	...
7065	D M	4 30:5	S 1-1	CLEAR	5.5	MEDIUM	30	WNL	...
7066	D M	4 30:5	S 1-1	CLEAR	6.0	DARK	30	WNL	...
7067	D M	4 30:5	S 1-1	CLEAR	21.0	LIGHT	0	WNL	...
7068	D M	4 30:5	S 1-1	CLEAR	7.0	MEDIUM	30	WNL	...
7069	D M	4 30:5	S 1-1	CLEAR	10.0	LIGHT	0	WNL	...
7070	D M	4 30:5	S 1-1	CLEAR	10.4	LIGHT	15	WNL	...
7011	D F	Ctrl 31:5	S 1-1	CLEAR	5.5	MEDIUM	0	WNL	...
7012	D F	Ctrl 31:5	S 1-1	CLEAR	7.8	LIGHT	0	WNL	...
7013	D F	Ctrl 31:5	S 1-1	CLEAR	5.5	LIGHT	0	WNL	...
7014	D F	Ctrl 31:5	S 1-1	CLEAR	24.0	LIGHT	0	WNL	...
7015	D F	Ctrl 31:5	S 1-1	CLEAR	5.0	DARK	0	WNL	...
7016	D F	Ctrl 31:5	S 1-1	CLEAR	17.0	LIGHT	0	WNL	...
7017	D F	Ctrl 31:5	S 1-1	CLEAR	12.5	LIGHT	0	WNL	...
7018	D F	Ctrl 31:5	S 1-1	CLEAR	12.0	LIGHT	0	WNL	...

D = Dosing Phase

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, n = UnScheduled Necropsy

APPENDIX 4 contd. Individual Animal Clinical Analysis of Urine.

Animal #	Sex	Day / Group Week # of Phase	Semi- Scan Name	UCLA	UVOL (mL)	QUAL	UPRO (mg/dL)	USol	USedA6K
7019	D F	Ctl	31/5	S 1-1	CLEAR	4.5	DARK	15	WNL
7020	D F	Ctl	31/5	S 1-1	INS	INS - L	DARK	INS	WNL
7031	D F	2	31/5	S 1-1	CLEAR	1.5	DARK	100	WNL
7032	D F	2	31/5	S 1-1	CLEAR	9.0	MEDIUM	0	WNL
7033	D F	2	31/5	S 1-1	INS	INS - L	DARK	INS	WNL
7034	D F	2	31/5	S 1-1	CLEAR	2.0	DARK	30	WNL
7035	D F	2	31/5	S 1-1	INS	INS - L	DARK	INS	WNL
7036	D F	2	31/5	S 1-1	CLEAR	1.6	DARK	30	WNL
7037	D F	2	31/5	S 1-1	CLEAR	3.0	DARK	15	WNL
7038	D F	2	31/5	S 1-1	CLEAR	15.0	DARK	0	WNL
7039	D F	2	31/5	S 1-1	CLEAR	8.0	DARK	15	WNL
7040	D F	2	31/5	S 1-1	CLEAR	13.5	LIGHT	0	WNL
7051	D F	3	31/5	S 1-1	CLEAR	6.0	DARK	0	WNL
7052	D F	3	31/5	S 1-1	CLEAR	12.5	LIGHT	0	WNL
7053	D F	3	31/5	S 1-1	CLEAR	3.5	MEDIUM	15	WNL
7054	D F	3	31/5	S 1-1	CLEAR	8.4	MEDIUM	0	WNL
7055	D F	3	31/5	S 1-1	CLEAR	18.0	LIGHT	0	WNL
7056	D F	3	31/5	S 1-1	CLEAR	6.0	MEDIUM	0	WNL
7057	D F	3	31/5	S 1-1	CLEAR	1.5	DARK	30	WNL
7059	D F	3	31/5	S 1-1	CLEAR	3.5	DARK	30	WNL
7059	D F	3	31/5	S 1-1	CLEAR	23.0	LIGHT	0	WNL
7060	D F	3	31/5	S 1-1	CLEAR	1.5	DARK	30	WNL
7071	D F	4	31/5	S 1-1	CLEAR	6.0	MEDIUM	15	WNL
7072	D F	4	31/5	S 1-1	CLEAR	10.5	MEDIUM	0	WNL

D - Dosing Phase

S = Scheduled Animal Room, U = UnScheduled Animal Room, N = Scheduled Necropsy, u = UnScheduled Necropsy.

APPENDIX 4 (cont'd). Individual Animal Clinical Analysis of Urine.

Animal #	Sex	Day / Group / Week # / of Phase	Screen- Score Name	UCLA	UVVL (mL)	QUAL	UPRO (mg/dL)	Used	UsedAbn
7073	D F	4 / 31/5	S 1-1	INS	INS	MEDIUM	INS	WNL	---
7074	D F	4 / 31/5	S 1-1	CLEAR	3.0	MEDIUM	15	WNL	---
7075	D F	4 / 31/5	S 1-1	CLEAR	4.5	MEDIUM	15	WNL	---
7076	D F	4 / 31/5	S 1-1	CLEAR	1.5	MEDIUM	30	WNL	---
7077	D F	4 / 31/5	S 1-1	CLEAR	3.0	DARK	30	WNL	---
7078	D F	4 / 31/5	S 1-1	CLEAR	18.0	LIGHT	0	WNL	---
7079	D F	4 / 31/5	S 1-1	CLEAR	2.5	DARK	30	WNL	---
7080	D F	4 / 31/5	S 1-1	CLEAR	16.0	LIGHT	0	WNL	---

D = Dosing Phase

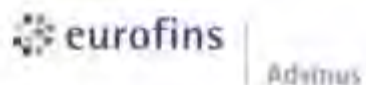
S = Scheduled Animal Room; 1 = UnScheduled Animal Room; N = Scheduled Necropsy; n = UnScheduled Necropsy

 PSL Study No. 51651
 Eurofins Advisory Study Phase No. G18871_PATH/Clinical Pathology Phase Report
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11. ANNEXURES



ANNEXURE 1. GLP Certificate

The summary of GLP accreditations received by the test facility from multiple Monitoring Authorities and the latest GLP certificate issued by the Indian National GLP Compliance Monitoring Authority are given below:

(i) Summary of Accreditations Received by the Test Facility from Multiple GLP Monitoring Authorities

GLP Monitoring Authority	Accreditation received in the year
Germany	1992, 1997, 2001, 2005 and 2010.
Netherlands	1999, 2003, 2007 and 2009.
India	2005, 2008, 2012, 2014 and 2017.

Note:

1. The test facility was inspected / monitored as per the OECD GLP system by the respective Monitoring Authorities stated above, and maintained the accreditations continuously.
2. India accepted the OECD Council invitation and received the Full Adherence status for Mutual Acceptance of Data (MAD) in March 2011, and also became a member of the OECD GLP Working Group. As per the OECD provisions, the Monitoring Authorities in OECD member countries as well as those in Full Adherent countries would inspect test facilities in the respective countries for the purpose of monitoring and accreditation. Accordingly, since 2011, the test facility was inspected only by the Indian National GLP Compliance Monitoring Authority (NGCMA) for monitoring and accreditation.



ANNEXURE 1 contd. GLP Certificate

(i) GLP Certificate – India

**National Good Laboratory Practice Compliance
Monitoring Authority**

Certificate of GLP Compliance



GOVERNMENT OF INDIA
Department of Science and Technology
Ministry of Science and Technology, New Mehrauli Road, New Delhi-110016
www.dst.gov.in/igmas

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ANNEXURE 1 contd. GLP Certificate



GOVERNMENT OF INDIA
Department of Science and Technology
National Good Laboratory Practice (GLP) Compliance Monitoring Authority (NGCMA)

Certificate of GLP Compliance

Based on the inspection and the subsequent follow-up actions

Eurofins Advinus Limited
21&22 Phase II, Peenya Industrial Area
Bengaluru – 560058

is certified capable of conducting the below-mentioned tests/studies in compliance with Organization for Economic Co-operation & Development (OECD) Principles of GLP:

- **Physical-chemical Testing including Five batch analysis**
- **Toxicity Studies**
- **Mutagenicity Studies**
- **Environmental Toxicity Studies on Aquatic & Terrestrial Organisms**
- **Studies on Behaviour in Water, Soil, and Air; Bioaccumulation**
- **Residue Studies**
- **Analytical and Clinical Chemistry Testing**
- **Others**

The specific areas of expertise, types of chemicals and test systems are listed in annexure overleaf.

Validity: November 07, 2017 – November 06, 2020

This certificate is subject to the condition that the test facility complies with the Terms & Conditions of the NGCMA's Document No. GLP-101 and OECD Principles of GLP.

Certificate No. : GLP/C-111/2017
Issue Date : 26-12-2017



Neeraj Sharma
(Dr. Neeraj Sharma)
Head, NGCMA



ANNEXURE 1 contd. GLP Certificate

National GLP Compliance Monitoring Authority (NGCMA)

Annexure to Certificate of GLP Compliance No. GLP/C-111/2017

Areas of Expertise:

Physical-chemical Testing including Five-batch Analysis

Toxicity Studies

- o Acute Toxicity
- o Skin Irritation/ corrosion
- o Eye Irritation
- o Skin Sensitization
- o Dermal Toxicity
- o Inhalation Toxicity
- o Sub-acute/ Sub-chronic Toxicity
- o Chronic Toxicity
- o Reproductive Toxicity
- o Carcinogenicity studies

Mutagenicity Studies

- o Chromosomal Aberration Test (*In-vitro/ In-vivo*)
- o Micronucleus Assay (*In-vitro/ In-vivo*)
- o Bacterial Reverse Mutation Assay (AMES Test)
- o Gene Mutation Test (*In-vitro*)

Environmental Toxicity Studies on Aquatic & Terrestrial Organisms

Studies on Behaviour in Water, Soil, and Air; Bioaccumulation

- o Biodegradability Studies
- o Environmental Fate Studies

Residue Studies

Analytical and Clinical Chemistry Testing

Others

- o Bioanalytical and Toxicokinetics
- o Drug Metabolism and Pharmacokinetics & Tissue Distribution
- o Safety Pharmacology
- o PK and Immunogenicity analysis of Biologics

Types of Chemicals:

Industrial Chemicals, Pharmaceuticals, Veterinary Drugs, Pesticides, Cosmetic Products, Food Additives, Feed Additives, GMDs, Biomaterials, Ophthalmic Devices, Packaging Materials, Nutraceuticals and Medical Devices.

Test Systems:

Rat, Mice, Rabbit, Guinea Pig, Dog, Goat, Chicken, Quail, Pigeon, Hamster, Fresh Water Fish, Daphnia, Algae, Honeybee, Earthworm, *Salmonella typhimurium*, *Escherichia coli*, Mouse Lymphoma Cell line, Chinese Hamster Ovary (CHO) Cell Line, RHE and Human Hepatocellular Carcinoma Cell Line.



[Redacted Signature]
[Redacted Name]
Head, NGCMA

APPENDIX K: ANIMAL NUMBERS, DOSE GROUPS, AND FATES

PRODUCT IDENTIFICATION

Silk Fibroin

Individual Animal Numbers, Dose Groups and Fates
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
1	0 mg/kg/day	Male	7001	1	30	5	05/12/19	8:25	.	Term	Term
			7002	1	30	5	05/12/19	8:25	.	Term	Term
			7003	2	30	5	05/12/19	8:25	.	Term	Term
			7004	2	30	5	05/12/19	8:25	.	Term	Term
			7005	3	30	5	05/12/19	8:25	.	Term	Term
			7006	3	30	5	05/12/19	8:25	.	Term	Term
			7007	4	30	5	05/12/19	8:25	.	Term	Term
			7008	4	30	5	05/12/19	8:25	.	Term	Term
			7009	5	30	5	05/12/19	8:25	.	Term	Term
			7010	5	30	5	05/12/19	8:25	.	Term	Term
1	0 mg/kg/day	Female	7011	6	31	5	06/12/19	8:02	.	Term	Term
			7012	6	31	5	06/12/19	8:02	.	Term	Term
			7013	7	31	5	06/12/19	8:02	.	Term	Term
			7014	7	31	5	06/12/19	8:02	.	Term	Term
			7015	8	31	5	06/12/19	8:02	.	Term	Term
			7016	8	31	5	06/12/19	8:03	.	Term	Term
			7017	9	31	5	06/12/19	8:03	.	Term	Term
			7018	9	31	5	06/12/19	8:03	.	Term	Term
			7019	10	31	5	06/12/19	8:03	.	Term	Term
			7020	10	31	5	06/12/19	8:03	.	Term	Term
2	125 mg/kg/day	Male	7021	11	30	5	05/12/19	8:25	.	Term	Term
			7022	11	30	5	05/12/19	8:26	.	Term	Term
			7023	12	30	5	05/12/19	8:26	.	Term	Term
			7024	12	30	5	05/12/19	8:26	.	Term	Term
			7025	13	30	5	05/12/19	8:26	.	Term	Term
			7026	13	30	5	05/12/19	8:26	.	Term	Term
			7027	14	30	5	05/12/19	8:26	.	Term	Term
			7028	14	30	5	05/12/19	8:26	.	Term	Term
			7029	15	30	5	05/12/19	8:26	.	Term	Term
			7030	15	30	5	05/12/19	8:26	.	Term	Term

Individual Animal Numbers, Dose Groups and Fates
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
2	125 mg/kg/day	Female	7031	16	31	5	06/12/19	8:03	.	Term	Term
			7032	16	31	5	06/12/19	8:03	.	Term	Term
			7033	17	31	5	06/12/19	8:03	.	Term	Term
			7034	17	31	5	06/12/19	8:03	.	Term	Term
			7035	18	31	5	06/12/19	8:03	.	Term	Term
			7036	18	31	5	06/12/19	8:03	.	Term	Term
			7037	19	31	5	06/12/19	8:03	.	Term	Term
			7038	19	31	5	06/12/19	8:03	.	Term	Term
			7039	20	31	5	06/12/19	8:03	.	Term	Term
			7040	20	31	5	06/12/19	8:03	.	Term	Term
3	250 mg/kg/day	Male	7041	21	30	5	05/12/19	8:26	.	Term	Term
			7042	21	30	5	05/12/19	8:26	.	Term	Term
			7043	22	30	5	05/12/19	8:26	.	Term	Term
			7044	22	30	5	05/12/19	8:26	.	Term	Term
			7045	23	30	5	05/12/19	8:26	.	Term	Term
			7046	23	30	5	05/12/19	8:26	.	Term	Term
			7047	24	30	5	05/12/19	8:26	.	Term	Term
			7048	24	30	5	05/12/19	8:27	.	Term	Term
			7049	25	30	5	05/12/19	8:27	.	Term	Term
			7050	25	30	5	05/12/19	8:27	.	Term	Term
3	250 mg/kg/day	Female	7051	26	31	5	06/12/19	8:03	.	Term	Term
			7052	26	31	5	06/12/19	8:03	.	Term	Term
			7053	27	31	5	06/12/19	8:04	.	Term	Term
			7054	27	31	5	06/12/19	8:04	.	Term	Term
			7055	28	31	5	06/12/19	8:04	.	Term	Term
			7056	28	31	5	06/12/19	8:04	.	Term	Term
			7057	29	31	5	06/12/19	8:04	.	Term	Term
			7058	29	31	5	06/12/19	8:04	.	Term	Term
			7059	30	31	5	06/12/19	8:04	.	Term	Term
			7060	30	31	5	06/12/19	8:04	.	Term	Term

Individual Animal Numbers, Dose Groups and Fates
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Group	Dose Level	Sex	Animal	Cage	Removal Day	Removal Week	Removal Date	Removal Time	Time Slot	Removal Symptom	Pathology Reason
4	500 mg/kg/day	Male	7061	31	30	5	05/12/19	8:27	.	Term	Term
			7062	31	30	5	05/12/19	8:27	.	Term	Term
			7063	32	30	5	05/12/19	8:27	.	Term	Term
			7064	32	30	5	05/12/19	8:27	.	Term	Term
			7065	33	30	5	05/12/19	8:27	.	Term	Term
			7066	33	30	5	05/12/19	8:27	.	Term	Term
			7067	34	30	5	05/12/19	8:27	.	Term	Term
			7068	34	30	5	05/12/19	8:27	.	Term	Term
			7069	35	30	5	05/12/19	8:27	.	Term	Term
			7070	35	30	5	05/12/19	8:27	.	Term	Term
4	500 mg/kg/day	Female	7071	36	31	5	06/12/19	8:04	.	Term	Term
			7072	36	31	5	06/12/19	8:04	.	Term	Term
			7073	37	31	5	06/12/19	8:04	.	Term	Term
			7074	37	31	5	06/12/19	8:04	.	Term	Term
			7075	38	31	5	06/12/19	8:04	.	Term	Term
			7076	38	31	5	06/12/19	8:04	.	Term	Term
			7077	39	31	5	06/12/19	8:04	.	Term	Term
			7078	39	31	5	06/12/19	8:04	.	Term	Term
			7079	40	31	5	06/12/19	8:04	.	Term	Term
			7080	40	31	5	06/12/19	8:04	.	Term	Term

APPENDIX L: INDIVIDUAL ANIMAL NECROPSY OBSERVATIONS

PRODUCT IDENTIFICATION

Silk Fibroin

Individual Animal Necropsy Observations
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Animal:	7001	Group:	1	Sex:	Male
		Dose:	0		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7002	Group:	1	Sex:	Male
		Dose:	0		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7003	Group:	1	Sex:	Male
		Dose:	0		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7004	Group:	1	Sex:	Male
		Dose:	0		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7005	Group:	1	Sex:	Male
		Dose:	0		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7006	Group:	1	Sex:	Male
		Dose:	0		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7007	Group:	1	Sex:	Male
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Individual Animal Necropsy Observations
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Dose: 0

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7008 Group: 1 Sex: Male
Dose: 0

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7009 Group: 1 Sex: Male
Dose: 0

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:testes-combined : right; flaccid
epididymides-combined : right; small

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7010 Group: 1 Sex: Male
Dose: 0

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7011 Group: 1 Sex: Female
Dose: 0

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7012 Group: 1 Sex: Female
Dose: 0

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7013 Group: 1 Sex: Female

Individual Animal Necropsy Observations
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Dose: 0

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7014	Group:	1	Sex:	Female
		Dose:	0		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7015	Group:	1	Sex:	Female
		Dose:	0		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7016	Group:	1	Sex:	Female
		Dose:	0		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7017	Group:	1	Sex:	Female
		Dose:	0		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7018	Group:	1	Sex:	Female
		Dose:	0		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7019	Group:	1	Sex:	Female
		Dose:	0		

Individual Animal Necropsy Observations
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7020	Group:	1	Sex:	Female
		Dose:	0		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7021	Group:	2	Sex:	Male
		Dose:	125		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7022	Group:	2	Sex:	Male
		Dose:	125		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7023	Group:	2	Sex:	Male
		Dose:	125		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7024	Group:	2	Sex:	Male
		Dose:	125		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7025	Group:	2	Sex:	Male
		Dose:	125		

Necropsy Date: 12/5/2019

Individual Animal Necropsy Observations
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7026	Group: 2	Sex: Male
	Dose: 125	

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7027	Group: 2	Sex: Male
	Dose: 125	

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7028	Group: 2	Sex: Male
	Dose: 125	

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7029	Group: 2	Sex: Male
	Dose: 125	

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:testes-combined : right; small
testes-combined : flaccid

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7030	Group: 2	Sex: Male
	Dose: 125	

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7031	Group: 2	Sex: Female
	Dose: 125	

Necropsy Date: 12/6/2019

Individual Animal Necropsy Observations
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7032	Group:	2	Sex:	Female
		Dose:	125		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7033	Group:	2	Sex:	Female
		Dose:	125		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7034	Group:	2	Sex:	Female
		Dose:	125		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7035	Group:	2	Sex:	Female
		Dose:	125		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7036	Group:	2	Sex:	Female
		Dose:	125		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7037	Group:	2	Sex:	Female
		Dose:	125		

Necropsy Date: 12/6/2019

Individual Animal Necropsy Observations
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7038	Group:	2	Sex:	Female
		Dose:	125		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7039	Group:	2	Sex:	Female
		Dose:	125		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7040	Group:	2	Sex:	Female
		Dose:	125		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7041	Group:	3	Sex:	Male
		Dose:	250		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7042	Group:	3	Sex:	Male
		Dose:	250		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7043	Group:	3	Sex:	Male
		Dose:	250		

Necropsy Date: 12/5/2019

Individual Animal Necropsy Observations
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7044	Group:	3	Sex:	Male
		Dose:	250		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7045	Group:	3	Sex:	Male
		Dose:	250		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7046	Group:	3	Sex:	Male
		Dose:	250		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7047	Group:	3	Sex:	Male
		Dose:	250		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7048	Group:	3	Sex:	Male
		Dose:	250		

Necropsy Date: 12/5/2019

Last Clinical Observations:

Eschar, Head, Superficial

Gross Pathology Observations [Correlation]:

non correlated finding : no correlated finding [Eschar, Head, Superficial (C)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7049	Group:	3	Sex:	Male
		Dose:	250		

Individual Animal Necropsy Observations
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7050	Group:	3	Sex:	Male
		Dose:	250		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7051	Group:	3	Sex:	Female
		Dose:	250		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7052	Group:	3	Sex:	Female
		Dose:	250		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7053	Group:	3	Sex:	Female
		Dose:	250		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7054	Group:	3	Sex:	Female
		Dose:	250		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7055	Group:	3	Sex:	Female
		Dose:	250		

Necropsy Date: 12/6/2019

Individual Animal Necropsy Observations
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7056	Group:	3	Sex:	Female
		Dose:	250		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7057	Group:	3	Sex:	Female
		Dose:	250		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7058	Group:	3	Sex:	Female
		Dose:	250		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7059	Group:	3	Sex:	Female
		Dose:	250		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7060	Group:	3	Sex:	Female
		Dose:	250		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7061	Group:	4	Sex:	Male
		Dose:	500		

Necropsy Date: 12/5/2019

Individual Animal Necropsy Observations
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7062	Group:	4	Sex:	Male
		Dose:	500		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7063	Group:	4	Sex:	Male
		Dose:	500		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7064	Group:	4	Sex:	Male
		Dose:	500		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7065	Group:	4	Sex:	Male
		Dose:	500		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7066	Group:	4	Sex:	Male
		Dose:	500		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7067	Group:	4	Sex:	Male
		Dose:	500		

Necropsy Date: 12/5/2019

Individual Animal Necropsy Observations
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7068	Group:	4	Sex:	Male
		Dose:	500		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7069	Group:	4	Sex:	Male
		Dose:	500		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7070	Group:	4	Sex:	Male
		Dose:	500		

Necropsy Date: 12/5/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7071	Group:	4	Sex:	Female
		Dose:	500		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7072	Group:	4	Sex:	Female
		Dose:	500		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7073	Group:	4	Sex:	Female
		Dose:	500		

Necropsy Date: 12/6/2019

Individual Animal Necropsy Observations
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats**Gross Pathology Observations [Correlation]:**

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7074	Group:	4	Sex:	Female
		Dose:	500		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7075	Group:	4	Sex:	Female
		Dose:	500		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7076	Group:	4	Sex:	Female
		Dose:	500		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7077	Group:	4	Sex:	Female
		Dose:	500		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7078	Group:	4	Sex:	Female
		Dose:	500		

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal:	7079	Group:	4	Sex:	Female
		Dose:	500		

Necropsy Date: 12/6/2019

Individual Animal Necropsy Observations
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Gross Pathology Observations [Correlation]:

uterus : fluid filled

Any remaining protocol required tissues, which have been examined, have no visible lesions

Animal: 7080

Group: 4

Sex: Female

Dose: 500

Necropsy Date: 12/6/2019

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

APPENDIX M: INDIVIDUAL ANIMAL TERMINAL BODY AND ORGAN WEIGHTS

PRODUCT IDENTIFICATION

Silk Fibroin

Individual Animal Terminal Body and Organ Weights
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	Terminal BW (g)	Adrenal Glands Wt (g)	Brain Wt (g)	Heart Wt (g)	Kidneys Wt (g)	Liver Wt (g)	Spleen Wt (g)
	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31
	7011	233	0.079	1.96	0.86	1.86	7.35
7012	261	0.081	1.96	0.91	1.96	8.27	0.64
7013	228	0.086	2.11	0.96	2.12	7.68	0.61
7014	274	0.089	2.11	1.02	1.97	9.27	0.73
7015	266	0.084	2.02	0.96	1.89	8.79	0.55
7016	275	0.075	2.22	0.97	2.09	10.10	0.64
7017	246	0.092	1.94	0.91	1.98	8.33	0.60
7018	232	0.083	1.84	0.87	1.66	7.77	0.49
7019	253	0.067	1.81	0.91	1.98	8.96	0.50
7020	247	0.077	2.08	0.98	1.85	7.38	0.49
Mean	251.5	0.0813	2.005	0.935	1.936	8.390	0.577
SD	17.3	0.0073	0.128	0.051	0.131	0.894	0.080
N	10	10	10	10	10	10	10

Individual Animal Terminal Body and Organ Weights
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	Thymus Wt (g)	Thyroid-Parathyroid Wt (g)
	Day 31	Day 31
	7011	0.448
7012	0.389	0.018
7013	0.520	0.026
7014	0.477	0.032
7015	0.446	0.022
7016	0.399	0.030
7017	0.382	0.015
7018	0.408	0.017
7019	0.443	0.025
7020	0.633	0.022
Mean	0.4545	0.0226
SD	0.0758	0.0056
N	10	10

Individual Animal Terminal Body and Organ Weights
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female		Day(s) Relative to Start Date					
125 mg/kg/day Group 2	Terminal BW (g)	Adrenal Glands Wt (g)	Brain Wt (g)	Heart Wt (g)	Kidneys Wt (g)	Liver Wt (g)	Spleen Wt (g)
	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31
7031	201	0.067	1.88	0.80	1.55	6.80	0.44
7032	284	0.088	1.96	1.01	2.26	9.27	0.68
7033	244	0.078	2.26	0.93	1.82	8.59	0.44
7034	262	0.086	2.02	0.99	2.19	9.55	0.55
7035	250	0.102	2.17	0.87	1.78	9.21	0.62
7036	220	0.078	2.01	0.79	1.42	6.62	0.56
7037	238	0.087	1.98	0.89	1.83	7.18	0.57
7038	262	0.091	2.02	1.06	1.94	10.39	0.71
7039	291	0.078	1.90	1.28	2.10	9.57	0.69
7040	225	0.074	2.00	0.79	1.58	6.64	0.56
Mean	247.7	0.0829	2.020	0.941	1.847	8.382	0.582
SD	28.2	0.0099	0.115	0.153	0.281	1.430	0.095
N	10	10	10	10	10	10	10

Individual Animal Terminal Body and Organ Weights
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Day(s) Relative to Start Date

125 mg/kg/day Group 2	Thymus Wt (g)	Thyroid-Parathyroid Wt (g)
	Day 31	Day 31
	7031	0.295
7032	0.500	0.021
7033	0.461	0.028
7034	0.359	0.023
7035	0.329	0.025
7036	0.352	0.018
7037	0.403	0.023
7038	0.503	0.037
7039	0.325	0.026
7040	0.318	0.024
Mean	0.3845	0.0257
SD	0.0777	0.0055
N	10	10

Individual Animal Terminal Body and Organ Weights
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female		Day(s) Relative to Start Date					
250 mg/kg/day Group 3	Terminal BW (g)	Adrenal Glands Wt (g)	Brain Wt (g)	Heart Wt (g)	Kidneys Wt (g)	Liver Wt (g)	Spleen Wt (g)
	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31
	7051	259	0.083	1.98	0.92	1.95	8.32
7052	289	0.084	2.10	1.06	2.02	9.19	0.55
7053	280	0.091	2.04	0.97	2.00	8.79	0.60
7054	270	0.068	2.05	0.86	1.87	9.52	0.62
7055	250	0.080	2.02	1.00	1.88	9.78	0.56
7056	218	0.089	2.02	0.87	1.84	8.44	0.46
7057	251	0.069	2.01	0.93	2.03	8.50	0.52
7058	239	0.085	2.08	0.85	1.86	7.85	0.47
7059	252	0.084	2.09	0.99	1.88	8.99	0.51
7060	230	0.075	1.96	0.79	1.87	7.31	0.51
Mean	253.8	0.0808	2.035	0.924	1.920	8.669	0.529
SD	21.9	0.0078	0.046	0.082	0.073	0.750	0.053
N	10	10	10	10	10	10	10

Individual Animal Terminal Body and Organ Weights
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Day(s) Relative to Start Date

250 mg/kg/day Group 3	Thymus Wt (g)	Thyroid-Parathyroid Wt (g)
	Day 31	Day 31
	7051	0.483
7052	0.421	0.022
7053	0.466	0.027
7054	0.425	0.024
7055	0.389	0.026
7056	0.475	0.030
7057	0.453	0.022
7058	0.396	0.023
7059	0.622	0.024
7060	0.302	0.022
Mean	0.4432	0.0243
SD	0.0824	0.0026
N	10	10

Individual Animal Terminal Body and Organ Weights
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Day(s) Relative to Start Date

500 mg/kg/day Group 4	Terminal BW (g)	Adrenal Glands Wt (g)	Brain Wt (g)	Heart Wt (g)	Kidneys Wt (g)	Liver Wt (g)	Spleen Wt (g)
	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31
	7071	267	0.078	1.94	1.02	2.14	9.71
7072	276	0.077	2.29	1.05	1.98	9.57	0.67
7073	229	0.071	2.06	0.81	1.93	7.73	0.60
7074	232	0.078	1.93	0.90	1.67	7.49	0.50
7075	260	0.101	2.13	0.93	1.98	9.07	0.60
7076	256	0.088	1.97	0.92	1.82	8.52	0.72
7077	244	0.088	2.21	0.91	2.19	8.76	0.61
7078	242	0.085	2.07	0.85	1.67	9.12	0.54
7079	287	0.080	2.12	0.94	2.22	9.51	0.58
7080	240	0.065	2.03	0.84	1.67	5.98	0.51
Mean	253.3	0.0811	2.075	0.917	1.927	8.546	0.592
SD	19.2	0.0100	0.116	0.075	0.215	1.171	0.067
N	10	10	10	10	10	10	10

Individual Animal Terminal Body and Organ Weights
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Day(s) Relative to Start Date

500 mg/kg/day Group 4	Thymus Wt (g)	Thyroid-Parathyroid Wt (g)
	Day 31	Day 31
	7071	0.378
7072	0.595	0.027
7073	0.461	0.026
7074	0.380	0.025
7075	0.549	0.025
7076	0.373	0.020
7077	0.451	0.030
7078	0.397	0.028
7079	0.431	0.034
7080	0.411	0.023
Mean	0.4426	0.0264
SD	0.0754	0.0038
N	10	10

APPENDIX N: INDIVIDUAL ANIMAL ORGAN-TO-BODY WEIGHT RATIOS

PRODUCT IDENTIFICATION

Silk Fibroin

Individual Animal Organ-To-Body Weight Ratio
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female		Day(s) Relative to Start Date					
0 mg/kg/day Group 1	Adrenal /TBW (Ratio)	Brain /TBW (Ratio)	Heart /TBW (Ratio)	Kidneys /TBW (Ratio)	Liver /TBW (Ratio)	Spleen /TBW (Ratio)	Thymus /TBW (Ratio)
	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31
7011	0.339	8.41	3.69	7.98	31.55	2.23	1.923
7012	0.310	7.51	3.49	7.51	31.69	2.45	1.490
7013	0.377	9.25	4.21	9.30	33.68	2.68	2.281
7014	0.325	7.70	3.72	7.19	33.83	2.66	1.741
7015	0.316	7.59	3.61	7.11	33.05	2.07	1.677
7016	0.273	8.07	3.53	7.60	36.73	2.33	1.451
7017	0.374	7.89	3.70	8.05	33.86	2.44	1.553
7018	0.358	7.93	3.75	7.16	33.49	2.11	1.759
7019	0.265	7.15	3.60	7.83	35.42	1.98	1.751
7020	0.312	8.42	3.97	7.49	29.88	1.98	2.563
Mean	0.3248	7.994	3.726	7.721	33.317	2.293	1.8188
SD	0.0383	0.592	0.217	0.647	1.957	0.261	0.3537
N	10	10	10	10	10	10	10

Individual Animal Organ-To-Body Weight Ratio
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female	Day(s) Relative to Start Date
0 mg/kg/day Group 1	Thyroid-Parathyroid /TBW (Ratio)
	Day 31
7011	0.8155
7012	0.6897
7013	1.1404
7014	1.1679
7015	0.8271
7016	1.0909
7017	0.6098
7018	0.7328
7019	0.9881
7020	0.8907
Mean	0.89527
SD	0.19509
N	10

Individual Animal Organ-To-Body Weight Ratio
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female		Day(s) Relative to Start Date					
125 mg/kg/day Group 2	Adrenal /TBW (Ratio)	Brain /TBW (Ratio)	Heart /TBW (Ratio)	Kidneys /TBW (Ratio)	Liver /TBW (Ratio)	Spleen /TBW (Ratio)	Thymus /TBW (Ratio)
	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31
	7031	0.333	9.35	3.98	7.71	33.83	2.19
7032	0.310	6.90	3.56	7.96	32.64	2.39	1.761
7033	0.320	9.26	3.81	7.46	35.20	1.80	1.889
7034	0.328	7.71	3.78	8.36	36.45	2.10	1.370
7035	0.408	8.68	3.48	7.12	36.84	2.48	1.316
7036	0.355	9.14	3.59	6.45	30.09	2.55	1.600
7037	0.366	8.32	3.74	7.69	30.17	2.39	1.693
7038	0.347	7.71	4.05	7.40	39.66	2.71	1.920
7039	0.268	6.53	4.40	7.22	32.89	2.37	1.117
7040	0.329	8.89	3.51	7.02	29.51	2.49	1.413
Mean	0.3363	8.249	3.789	7.439	33.728	2.348	1.5547
SD	0.0368	0.999	0.287	0.532	3.333	0.257	0.2623
N	10	10	10	10	10	10	10

Individual Animal Organ-To-Body Weight Ratio
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Day(s) Relative to Start Date

125 mg/kg/day Group 2	Thyroid-Parathyroid /TBW (Ratio)
	Day 31
7031	1.5920
7032	0.7394
7033	1.1475
7034	0.8779
7035	1.0000
7036	0.8182
7037	0.9664
7038	1.4122
7039	0.8935
7040	1.0667
Mean	1.05138
SD	0.26845
N	10

Individual Animal Organ-To-Body Weight Ratio
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female		Day(s) Relative to Start Date					
250 mg/kg/day Group 3	Adrenal /TBW (Ratio)	Brain /TBW (Ratio)	Heart /TBW (Ratio)	Kidneys /TBW (Ratio)	Liver /TBW (Ratio)	Spleen /TBW (Ratio)	Thymus /TBW (Ratio)
	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31
	7051	0.320	7.64	3.55	7.53	32.12	1.89
7052	0.291	7.27	3.67	6.99	31.80	1.90	1.457
7053	0.325	7.29	3.46	7.14	31.39	2.14	1.664
7054	0.252	7.59	3.19	6.93	35.26	2.30	1.574
7055	0.320	8.08	4.00	7.52	39.12	2.24	1.556
7056	0.408	9.27	3.99	8.44	38.72	2.11	2.179
7057	0.275	8.01	3.71	8.09	33.86	2.07	1.805
7058	0.356	8.70	3.56	7.78	32.85	1.97	1.657
7059	0.333	8.29	3.93	7.46	35.67	2.02	2.468
7060	0.326	8.52	3.43	8.13	31.78	2.22	1.313
Mean	0.3206	8.066	3.649	7.601	34.258	2.086	1.7538
SD	0.0433	0.646	0.266	0.508	2.860	0.141	0.3460
N	10	10	10	10	10	10	10

Individual Animal Organ-To-Body Weight Ratio
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female	Day(s) Relative to Start Date
250 mg/kg/day Group 3	Thyroid-Parathyroid /TBW (Ratio)
	Day 31
7051	0.8880
7052	0.7612
7053	0.9643
7054	0.8889
7055	1.0400
7056	1.3761
7057	0.8765
7058	0.9623
7059	0.9524
7060	0.9565
Mean	0.96663
SD	0.16191
N	10

Individual Animal Organ-To-Body Weight Ratio
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female		Day(s) Relative to Start Date					
500 mg/kg/day Group 4	Adrenal /TBW (Ratio)	Brain /TBW (Ratio)	Heart /TBW (Ratio)	Kidneys /TBW (Ratio)	Liver /TBW (Ratio)	Spleen /TBW (Ratio)	Thymus /TBW (Ratio)
	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31
	7071	0.292	7.27	3.82	8.01	36.37	2.21
7072	0.279	8.30	3.80	7.17	34.67	2.43	2.156
7073	0.310	9.00	3.54	8.43	33.76	2.62	2.013
7074	0.336	8.32	3.88	7.20	32.28	2.16	1.638
7075	0.388	8.19	3.58	7.62	34.88	2.31	2.112
7076	0.344	7.70	3.59	7.11	33.28	2.81	1.457
7077	0.361	9.06	3.73	8.98	35.90	2.50	1.848
7078	0.351	8.55	3.51	6.90	37.69	2.23	1.640
7079	0.279	7.39	3.28	7.74	33.14	2.02	1.502
7080	0.271	8.46	3.50	6.96	24.92	2.13	1.713
Mean	0.3211	8.222	3.623	7.611	33.689	2.341	1.7494
SD	0.0406	0.612	0.185	0.687	3.494	0.247	0.2707
N	10	10	10	10	10	10	10

Individual Animal Organ-To-Body Weight Ratio
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female	Day(s) Relative to Start Date
500 mg/kg/day Group 4	Thyroid-Parathyroid /TBW (Ratio)
	Day 31
7071	0.9738
7072	0.9783
7073	1.1354
7074	1.0776
7075	0.9615
7076	0.7813
7077	1.2295
7078	1.1570
7079	1.1847
7080	0.9583
Mean	1.04373
SD	0.13698
N	10

APPENDIX O: INDIVIDUAL ANIMAL ORGAN-TO-BRAIN WEIGHT RATIOS¹

PRODUCT IDENTIFICATION

Silk Fibroin

¹ [organ weight/brain weight]

Individual Animal Organ-To-Brain Weight Ratios
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Day(s) Relative to Start Date

0 mg/kg/day Group 1	Adrenal /BrW (Ratio)	Heart /BrW (Ratio)	Kidneys /BrW (Ratio)	Liver /BrW (Ratio)	Spleen /BrW (Ratio)	Thymus /BrW (Ratio)	Thyroid-Parathyroid /BrW (Ratio)
	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31
7011	0.040	0.44	0.95	3.75	0.27	0.229	0.0010
7012	0.041	0.46	1.00	4.22	0.33	0.198	0.0009
7013	0.041	0.45	1.00	3.64	0.29	0.246	0.0012
7014	0.042	0.48	0.93	4.39	0.35	0.226	0.0015
7015	0.042	0.48	0.94	4.35	0.27	0.221	0.0011
7016	0.034	0.44	0.94	4.55	0.29	0.180	0.0014
7017	0.047	0.47	1.02	4.29	0.31	0.197	0.0008
7018	0.045	0.47	0.90	4.22	0.27	0.222	0.0009
7019	0.037	0.50	1.09	4.95	0.28	0.245	0.0014
7020	0.037	0.47	0.89	3.55	0.24	0.304	0.0011
Mean	0.0407	0.467	0.967	4.192	0.287	0.2268	0.00112
SD	0.0040	0.020	0.062	0.434	0.032	0.0345	0.00024
N	10	10	10	10	10	10	10

Individual Animal Organ-To-Brain Weight Ratios
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Day(s) Relative to Start Date

125 mg/kg/day Group 2	Adrenal /BrW (Ratio)	Heart /BrW (Ratio)	Kidneys /BrW (Ratio)	Liver /BrW (Ratio)	Spleen /BrW (Ratio)	Thymus /BrW (Ratio)	Thyroid-Parathyroid /BrW (Ratio)
	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31
	7031	0.036	0.43	0.82	3.62	0.23	0.157
7032	0.045	0.52	1.15	4.73	0.35	0.255	0.0011
7033	0.035	0.41	0.81	3.80	0.19	0.204	0.0012
7034	0.043	0.49	1.08	4.73	0.27	0.178	0.0011
7035	0.047	0.40	0.82	4.24	0.29	0.152	0.0012
7036	0.039	0.39	0.71	3.29	0.28	0.175	0.0009
7037	0.044	0.45	0.92	3.63	0.29	0.204	0.0012
7038	0.045	0.52	0.96	5.14	0.35	0.249	0.0018
7039	0.041	0.67	1.11	5.04	0.36	0.171	0.0014
7040	0.037	0.40	0.79	3.32	0.28	0.159	0.0012
Mean	0.0410	0.468	0.917	4.154	0.289	0.1903	0.00128
SD	0.0044	0.088	0.153	0.711	0.053	0.0371	0.00029
N	10	10	10	10	10	10	10

Individual Animal Organ-To-Brain Weight Ratios
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Day(s) Relative to Start Date							
250 mg/kg/day Group 3	Adrenal /BrW (Ratio)	Heart /BrW (Ratio)	Kidneys /BrW (Ratio)	Liver /BrW (Ratio)	Spleen /BrW (Ratio)	Thymus /BrW (Ratio)	Thyroid-Parathyroid /BrW (Ratio)
	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31
7051	0.042	0.46	0.98	4.20	0.25	0.244	0.0012
7052	0.040	0.50	0.96	4.38	0.26	0.200	0.0010
7053	0.045	0.48	0.98	4.31	0.29	0.228	0.0013
7054	0.033	0.42	0.91	4.64	0.30	0.207	0.0012
7055	0.040	0.50	0.93	4.84	0.28	0.193	0.0013
7056	0.044	0.43	0.91	4.18	0.23	0.235	0.0015
7057	0.034	0.46	1.01	4.23	0.26	0.225	0.0011
7058	0.041	0.41	0.89	3.77	0.23	0.190	0.0011
7059	0.040	0.47	0.90	4.30	0.24	0.298	0.0011
7060	0.038	0.40	0.95	3.73	0.26	0.154	0.0011
Mean	0.0397	0.454	0.944	4.258	0.260	0.2175	0.00119
SD	0.0037	0.036	0.040	0.339	0.026	0.0386	0.00013
N	10	10	10	10	10	10	10

Individual Animal Organ-To-Brain Weight Ratios
PSL Study Number 51651 - A 28-Day Oral Gavage Toxicity Study in Rats

Sex: Female Day(s) Relative to Start Date							
500 mg/kg/day Group 4	Adrenal /BrW (Ratio)	Heart /BrW (Ratio)	Kidneys /BrW (Ratio)	Liver /BrW (Ratio)	Spleen /BrW (Ratio)	Thymus /BrW (Ratio)	Thyroid-Parathyroid /BrW (Ratio)
	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31	Day 31
7071	0.040	0.53	1.10	5.01	0.30	0.195	0.0013
7072	0.034	0.46	0.86	4.18	0.29	0.260	0.0012
7073	0.034	0.39	0.94	3.75	0.29	0.224	0.0013
7074	0.040	0.47	0.87	3.88	0.26	0.197	0.0013
7075	0.047	0.44	0.93	4.26	0.28	0.258	0.0012
7076	0.045	0.47	0.92	4.32	0.37	0.189	0.0010
7077	0.040	0.41	0.99	3.96	0.28	0.204	0.0014
7078	0.041	0.41	0.81	4.41	0.26	0.192	0.0014
7079	0.038	0.44	1.05	4.49	0.27	0.203	0.0016
7080	0.032	0.41	0.82	2.95	0.25	0.202	0.0011
Mean	0.0391	0.443	0.929	4.120	0.286	0.2124	0.00127
SD	0.0048	0.039	0.096	0.544	0.033	0.0262	0.00016
N	10	10	10	10	10	10	10

APPENDIX P: HISTOPATHOLOGY

PRODUCT IDENTIFICATION

Silk Fibroin

Submitted By:

HSRL
Histo-Scientific Research Laboratories
5930 Main Street
Mount Jackson, VA 22842



PATHOLOGY REPORT

SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS

Product Safety Labs (PSL) Study Number 51651

Prepared by

HSRL
Histo-Scientific Research Laboratories
5930 Main Street
Mount Jackson, VA 22842

Testing Facility

Product Safety Labs
2394 US Highway 130
Dayton, NJ 08810

Sponsor

Cambridge Crops, Inc.
444 Somerville Ave.
Somerville, MA 02143

March 31, 2020

5930 Main Street
Mt. Jackson, VA 22842

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Final Pathology Report
Cambridge Crops, Inc.
PSL Study Number 51651

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Final Pathology Report
Cambridge Corps, Inc.
PSL Study Number 51651

1.0 GLP Compliance Statement- Histopathology Slide Preparation

The histological slide preparation portion of Product Safety Labs Study Number 51651, which was performed at Histo-Scientific Research Laboratories (HSRL), 5930 Main Street, Mount Jackson, VA 22842, was conducted in compliance with U.S. FDA GLP, 21 CFR Part 58, 1987.

[Redacted Signature]

Principal Investigator
Histo-Scientific Research Laboratories (HSRL)

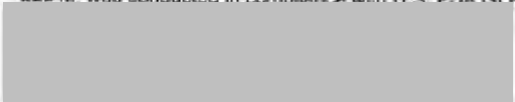
3/21/20
Date

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Final Pathology Report
Cambridge Crops, Inc.
PSL Study Number 51651

2.0 GLP Compliance Statement- Histopathology Evaluation

The histological slide evaluation portion of Product Safety Labs Study Number 51651, which was performed at Histo-Scientific Research Laboratories (HSRL), 5930 Main Street, Mount Jackson, VA 22842, was conducted in compliance with U.S. FDA (21 CFR Part 58, 1987


Principal Investigator
Histo-Scientific Research Laboratories (HSRL)

31 Mar 2020
Date

Final Pathology Report
Cambridge Crops, Inc.
PSL Study Number 51651

3.0 Executive Summary

The objective of this study was to evaluate the potential subchronic toxicity of Silk Fibroin in male and female rats likely to arise from repeated exposure, via oral gavage, over a test period of at least 28 days. A no-observed-adverse-effect-level (NOAEL) was determined.

Methods: According to the protocol, 80 rats (40 male and 40 female) were assigned to four treatment groups. Following the in-life procedures, all animals were euthanized on Day 30/31 and subjected to a gross necropsy. Protocol-specified tissues were collected and forwarded to HSRL. Upon receipt, protocol-required tissues from both the control and high dose groups (Groups 1 and 4, respectively) and gross lesions from all animals were processed, embedded in paraffin, sectioned and stained with hematoxylin and eosin (H&E). The resulting microscopic slides were evaluated by Christine E. Watson, MS, BVMS, MRCVS, DACVP of HSRL. This pathology report by HSRL presents the results of the microscopic evaluation of protocol-required tissues and gross lesions from all animals.

Conclusion: The objective of this study was to evaluate the potential subchronic toxicity of Silk Fibroin in male and female rats likely to arise from repeated exposure, via oral gavage, over a test period of at least 28 days. A no-observed-adverse-effect-level (NOAEL) was determined.

Administration of Silk Fibroin via repeated exposure by oral gavage to control (Group 1) and high-dose (Group 4; 500 mg/kg/day) male and female rats was not associated with mortality. All animals survived to terminal sacrifice (Day 30/31). There were no test substance-related gross or microscopic findings.

Final Pathology Report
Cambridge Crops, Inc.
PSL Study Number 51651

4.0 Introduction

4.1 Protocol

This report presents the histopathology results of a study to evaluate the potential subchronic toxicity of Silk Fibroin administered via oral gavage to rats, PSL Study Number 51651, Cambridge Crops, Inc., Somerville, MA. All in-life procedures and tissue harvests were performed at Product Safety Labs under the direction of Raghavendra Gowda, Ph.D, Study Director. Histology was performed at HSRL and microscopic evaluation was completed by Christine E. Watson, MS, BVMS, MRCVS, DACVP at HSRL.

4.2 Objective

The objective of this study was to evaluate the potential subchronic toxicity of Silk Fibroin in male and female rats likely to arise from repeated exposure, via oral gavage, over a test period of at least 28 days. A no-observed-adverse-effect-level (NOAEL) was determined.

5.0 Methods

5.1 Compliance Statement

The histology and pathology portions of this study performed by HSRL were conducted in compliance with U.S. FDA GLP: 21 CFR Part 58, 1987.

5.2 Study Design

According to the protocol, 80 animals (40 male and 40 female) were enrolled in the study. The study design is further described in Table 1 as follows:

Table 1. Dose Levels

Group	Number Animals/Group (Male/Female)	Oral Gavage Dose of Test Substance (mg/kg/day)	Dose Volume (mL/kg)	Concentration (mg/mL) ^b
1	10/10	0 (Vehicle Control) ^a	10	0
2	10/10	125		12.5
3	10/10	250		25
4	10/10	500		50

^a Distilled Water

^b Appropriate concentrations of the test substance as received in vehicle to achieve the target dose level

5.3 Necropsy

At terminal sacrifice on Day 30/31, all animals were euthanized and subjected to a gross necropsy. Necropsies included examination of the external surface of the body, all orifices, musculoskeletal system, and the cranial, thoracic, abdominal and pelvic cavities, with their associated organs and tissues. At scheduled termination, the following organs were weighed: adrenals (combined), brain, epididymides (combined, males only), heart, kidneys (combined), liver, ovaries with oviducts (combined, females only), spleen, testes (combined, males only), thymus, and uterus (females only). The seminal vesicles with coagulating gland (combined, males only), thyroid/parathyroid, and ventral prostate (males only) were weighed fixed at HSRL. The following organs and tissues from all animals were preserved in 10% NBF:

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accessory genital organs (prostate and seminal vesicles)	nasal turbinates
adrenals	nose
all gross lesions	ovaries
aorta	oviducts
bone (femur)	pancreas
bone marrow (from femur and sternum)	parathyroid
brain – sections including medulla/pons, cerebellar, and cerebral cortex	peripheral nerve (sciatic)
cecum	pharynx
cervix	pituitary gland
colon	rectum
duodenum	salivary glands (sublingual, submandibular, and parotid)
esophagus	skeletal muscle
Harderian gland	skin
heart	spinal cord – 3 levels: cervical, mid-thoracic, and lumbar
ileum with Peyer's patches	spleen
jejunum	sternum
kidneys	stomach
larynx	thymus
liver	thyroid
lungs	trachea
lymph node mandibular	urinary bladder
lymph node mesenteric	uterus
mammary gland	vagina

The epididymides, eyes, optic nerve, and testes were preserved in modified Davidson's fixative and then stored in ethanol.

5.4 Histological Processing

Collected tissues from all animals were forwarded to HSRL where the protocol-required tissues from both the control and high dose groups (Groups 1 and 4, respectively) and gross lesions from all animals were processed, embedded in paraffin, sectioned and stained with hematoxylin and eosin (H&E). Animal information from PSL's Gross Pathology Results was entered into Pristima[®] at HSRL. All microscopic slides were evaluated, and microscopic findings were entered directly into Pristima[®] by Christine E. Watson, MS, BVMS, MRCVS, DACVP of HSRL. Gross to microscopic correlations and the incidence of microscopic findings are presented in the Histopathology Incidence Tables portion of this report.

Within the Histopathology Incidence Tables, the following abbreviations apply:

M=Male
F=Female
1>=Minimal
2>=Mild
3>=Moderate
4>=Marked
5>=Severe

Within the Tissue Accountability Appendix, the following abbreviation applies:

SOPs=Standard Operating Procedures

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6.0 Results

6.1 Animal Mortality

There were no unscheduled death animals among the animals submitted for histopathological evaluation.

6.2 Macroscopic Observations

The gross findings at terminal sacrifice on Day 30/31, were considered incidental, of the nature commonly observed in rats (background findings) and/or were of similar incidence in control and dosed rats and were not considered related to administration of Silk Fibroin.

Animals 7009 and 7029 had macroscopic findings of unilateral (right) small and/or flaccid testes correlated microscopically with testicular atrophy. Animal 7009 had macroscopic findings of small right epididymis that microscopically correlated epididymal atrophy. Females in Groups 1 through 4 with a macroscopic finding of a fluid filled uterus was consistent with normal estrogen cycling of female rats.

6.3 Microscopic Observations

No Silk Fibroin-related microscopic findings were noted in terminal sacrifice animals on Day 30/31. The microscopic findings observed were considered incidental (background findings), of the nature commonly observed in rats, and/or were of similar incidence and severity in the control and dosed animals and were not considered related to the administration of the test substance.

7.0 Conclusion

The objective of this study was to evaluate the potential subchronic toxicity of Silk Fibroin in male and female rats likely to arise from repeated exposure, via oral gavage, over a test period of at least 28 days. A no-observed-adverse-effect-level (NOAEL) was determined.

Administration of Silk Fibroin via repeated exposure by oral gavage to control (Group 1) and high-dose (Group 4; 500 mg/kg/day) male and female rats was not associated with mortality. All animals survived to terminal sacrifice (Day 30/31). There were no test substance-related gross or microscopic findings.

Signature



Study Pathologist

31 Mar 2022
Date

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**Appendix A. Histopathology Incidence Tables (Expanded Summary Report of Histopathology Day
30/31 Animals)**

Expanded Summary Report of Histopathology

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Study: 51651

Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS

Test Article: Silk Fibroin

Rat Sprague-Dawley

Repeat Dose Toxicity/Oral

	Males		
	Dosage Group	Control	1
	Number of Animals:	10	10
	Number Examined:	10	10
	Number Unremarkable:	1	1
Amygd. Acute	Number examined:	10	10
	Number unremarkable:	10	10
Bone Marrow	Number examined:	10	10
	Number unremarkable:	10	10
Bone: Femur	Number examined:	10	10
	Number unremarkable:	10	10
Bone: Sternum	Number examined:	10	10
	Number unremarkable:	10	10
Brain	Number examined:	10	10
	Number unremarkable:	10	10
Epithelium:	Number examined:	10	10
	Number unremarkable:	8	10
ATROPHY	U	1	0
0/60 Finding Incidence	I	0	0
Stem granules:	I	1	0

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Study: 51651

Study Title: SILVETOLIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS

Test Article: SILVETOLIN

Rat Sprague-Dawley

Repeat Dose Toxicity/Oral

	Males		
	Dosage Group	Control	1
	Number of Animals:	10	10
	Number Examined:	10	10
	Number Unremarkable:	1	1
Epithelium	Number examined:	10	10
	Number unremarkable:	0	10
System glandular	Total Finding Incidence	1	3
Esophageus	Number examined:	10	10
	Number unremarkable:	10	10
Eye	Number examined:	10	10
	Number unremarkable:	10	10
Gland Adrenal	Number examined:	10	10
	Number unremarkable:	10	10
Gland Histonea	Number examined:	10	10
	Number unremarkable:	10	10
Gland Mammary	Number examined:	10	10
	Number unremarkable:	10	10

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Study: 51651

Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS

Test Article: Silk Fibroin

Rat/Sprague-Dawley

Repeat Dose Toxicity/Oral

	Males		
	Dosage Group	Control	1
	Number of Animals:	10	10
	Number Examined:	10	10
	Number Unremarkable:	1	1
Gland, Parathyroid	Number examined:	10	9
	Number unremarkable:	10	9
Gland, Pituitary	Number examined:	10	10
	Number unremarkable:	10	10
Gland, Prostate	Number examined:	10	10
	Number unremarkable:	10	9
	HYPERPLASIA	1	1
	Total Finding Incidence:	9	1
Gland, Salivary, Parotid	Number examined:	10	10
	Number unremarkable:	10	10
Gland, Salivary, Sublingual	Number examined:	10	10
	Number unremarkable:	10	9
	INFLAMMATION	1	1
	Total Finding Incidence:	9	1

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Study: 51651

Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS

Test Article: Silk Fibroin

Rat Species: Dawley

Repeat Dose Toxicity: Oral

	Males			
	Dosage Group:	Control	2	4
	Number of Animals:	10	1	10
	Number Examined:	10	1	10
	Number Unremarkable:	1	0	1
Gland, Salivary, Submandibular	Number examined:	10	0	10
	Number unremarkable:	10	0	10
Gland, Thyroid	Number examined:	10	0	10
	Number unremarkable:	10	0	10
Hair:	Number examined:	10	0	10
	Number unremarkable:	9	0	10
INFILTRATE	(+)	1	0	0
Total Finding Incidence:		1	0	0
Kidney	Number examined:	10	0	10
	Number unremarkable:	4	0	2
CYST	(+)	0	0	1
Total Finding Incidence:		0	0	1
INFILTRATE	(+)	0	0	0
Total Finding Incidence:		0	0	0
Large Intestine, Cecum	Number examined:	10	0	10
	Number unremarkable:	10	0	10

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Study: 51651

Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS

Test Article: Silk Fibroin

Rat/Sprague-Dawley

Repeat Dose Toxicity/Oral

	Males		
	Dosage Group	Control	1
	Number of Animals:	10	10
	Number Examined:	10	10
	Number Unremarkable:	1	1
Large Intestine, Colon	Number examined:	10	10
	Number unremarkable:	10	10
Large Intestine, Rectum	Number examined:	10	10
	Number unremarkable:	10	10
Lung	Number examined:	10	10
	Number unremarkable:	10	10
Liver	Number examined:	10	10
	Number unremarkable:	4	4
INFILTRATE	1:	0	0
	Total Finding Incidence:	0	0
Uterus	Number examined:	10	10
	Number unremarkable:	10	10
INFILTRATE	1:	0	0
	Total Finding Incidence:	0	0

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Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS

Test Article: Silk Fibroin

Rat/Sprague-Dawley

Repeat Dose Toxicity/Oral

	Males			
	Dosage Group:	Control	2	4
	Number of Animals:	10	1	10
	Number Examined:	10	1	10
	Number Unremarkable:	1	0	1
Lymph Node, Mandibular	Number examined:	10	0	10
	Number unremarkable:	10	0	10
Lymph Node, Mesenteric	Number examined:	10	0	10
	Number unremarkable:	10	0	10
Muscle, Skeletal	Number examined:	10	0	10
	Number unremarkable:	10	0	10
Nasal Turbinate	Number examined:	10	0	10
	Number unremarkable:	10	0	10
Nerve, Optic	Number examined:	10	0	10
	Number unremarkable:	10	0	10
Nerve, Peripheral (sciatic)	Number examined:	10	0	10
	Number unremarkable:	10	0	10

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Test Article: Silk Fibroin

Rat/Sprague-Dawley

Repeat Dose Toxicity/Oral

	Males		
	Dosage Group	Control	1
	Number of Animals:	10	10
	Number Examined:	10	10
	Number Unremarkable:	1	1
Uterus	Number examined:	10	10
	Number unremarkable:	10	10
Pituitary	Number examined:	10	10
	Number unremarkable:	10	10
Thyroid Gland	Number examined:	10	10
	Number unremarkable:	10	10
Heart	Number examined:	10	10
	Number unremarkable:	10	9
INFLAMMATION	1:	0	2
	fold Finding Incidence:	0	2
Salivary Vesicle with Coagulating Gland	Number examined:	10	10
	Number unremarkable:	10	10
Skin	Number examined:	10	10
	Number unremarkable:	9	9

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Test Article: Silk Fibroin

Rat Sprague-Dawley

Repeat Dose Toxicity/Oral

	Males		
	Dosage Group	Control	1
	Number of Animals:	10	10
	Number Examined:	10	10
	Number Unremarkable:	1	1
Stom	Number examined:	10	10
	Number unremarkable:	9	9
CVST	1:	1	1
	Total Finding Incidence:	1	1
INFILTRATE	1:	0	1
	Total Finding Incidence:	0	1
Small Intestine, Duodenum	Number examined:	10	10
	Number unremarkable:	10	10
Small Intestine, Jejunum	Number examined:	10	10
	Number unremarkable:	10	10
Small Intestine, Ileum	Number examined:	10	10
	Number unremarkable:	10	10
Small Intestine, Cecum	Number examined:	10	10
	Number unremarkable:	10	10

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Test Article: Silk Fibroin

Rat/Sprague-Dawley

Repeat Dose Toxicity/Oral

	Males		
	Dosage Group:	Control	1
	Number of Animals:	10	10
	Number Examined:	10	10
	Number Unremarkable:	1	1
Spinal Cord, Lumbar	Number examined:	10	10
	Number unremarkable:	10	10
Spinal Cord, Midthoracic	Number examined:	10	10
	Number unremarkable:	10	10
Spleen	Number examined:	10	10
	Number unremarkable:	10	10
Stomach	Number examined:	10	10
	Number unremarkable:	10	10
Testes	Number examined:	10	10
	Number unremarkable:	9	10
ACROPHY	1	1	0
Total Finding Incidence	1	1	0
Thymus	Number examined:	10	10
	Number unremarkable:	10	10

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StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS

Test Article: Silk Fibroin

Rat/Sprague-Dawley

Repeat Dose Toxicity/Oral

	Males			
	Dosage Group:	Control	2	4
	Number of Animals:	10	1	10
	Number Examined:	10	1	10
	Number Unremarkable:	1	0	1
Trachea	Number examined:	10	0	10
	Number unremarkable:	10	0	10
Urinary Bladder	Number examined:	10	0	10
	Number unremarkable:	10	0	10

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Test Article: Silk Fibroin

Rat/Sprague-Dawley

Repeat Dose Toxicity/Oral

		Females				
		Dosage Group:	Control	2	3	4
		Number of Animals:	10	3	5	10
		Number Examined:	10	3	5	10
		Number Unremarkable:	4	0	0	4
Artery, Aorta	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	
Bone Marrow	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	
Bone, Femur	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	
Bone, Sternum	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	
Brain	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	
Cervix	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	

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Test Article: Silk Fibroin

Rat/Sprague-Dawley

Repeat Dose Toxicity/Oral

		Females				
		Dosage Group:	Control	2	3	4
		Number of Animals:	10	3	5	10
		Number Examined:	10	3	5	10
		Number Unremarkable:	4	0	0	4
Esophagus	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	
Eye	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	
Gland, Adrenal	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	
Gland, Harderian	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	
Gland, Mammary	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	
Gland, Parathyroid	Number examined:	9	0	0	10	
	Number unremarkable:	9	0	0	10	

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Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS

Test Article: Silk Fibroin

Rat/Sprague-Dawley

Repeat Dose Toxicity/Oral

	Females				
	Dosage Group:	Control	2	3	4
	Number of Animals:	10	3	3	10
	Number Examined:	10	3	3	10
	Number Unremarkable:	4	0	0	4
Gland, Pituitary	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Gland, Salivary, Parotid	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Gland, Salivary, Sublingual	Number examined:	10	0	0	10
	Number unremarkable:	9	0	0	10
INFILTRATE	[-]	1	0	0	0
	Total Finding Incidences:	1	0	0	0
Gland, Salivary, Submandibular	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Gland, Thyroid	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Heart	Number examined:	10	0	0	10
	Number unremarkable:	8	0	0	0

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Test Article: Silk Fibroin

Rat/Sprague-Dawley

Repeat Dose Toxicity/Oral

	Females				
	Dosage Group:	Control	2	3	4
	Number of Animals:	10	3	3	10
	Number Examined:	10	3	3	10
	Number Unremarkable:	4	0	0	4
Heart	Number examined:	10	0	0	10
	Number unremarkable:	8	0	0	8
INFILTRATE	1:	2	0	0	1
	Total Finding Incidence:	2	0	0	1
Kidney	Number examined:	10	0	0	10
	Number unremarkable:	7	0	0	7
INFILTRATE	1:	3	0	0	3
	Total Finding Incidence:	3	0	0	3
Large Intestine: Cecum	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Large Intestine: Colon	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Large Intestine: Rectum	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10

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Study: 51651

Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS

Test Article: Silk Fibroin

Rat/Sprague-Dawley

Repeat Dose Toxicity/Oral

	Females				
	Dosage Group:	Control	2	3	4
	Number of Animals:	10	3	5	10
	Number Examined:	10	3	5	10
	Number Unremarkable:	4	0	0	4
Uterus:	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Liver:	Number examined:	10	0	0	10
	Number unremarkable:	7	0	0	0
ESPIEPLATE	D:	3	0	0	4
	Obs Finding Incidence:	3	0	0	4
Lungs:	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Lymph Node, Mandibular:	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Lymph Node, Mesenteric:	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Muscle, Skeletal:	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10

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Study: 51651

StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS

Test Article: Silk Fibroin

Rat/Sprague-Dawley

Repeat Dose Toxicity/Oral

		Females				
		Dosage Group:	Control	2	3	4
		Number of Animals:	10	3	5	10
		Number Examined:	10	3	5	10
		Number Unremarkable:	4	0	0	4
Nasal Turbinate	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	
Nerve, Optic	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	
Nerve, Peripheral (sciatic)	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	
Nose	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	
Ovary	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	
Oviduct	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	

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Study: 51651

Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS

Test Article: Silk Fibroin

Rat Sprague-Dawley

Repeat Dose Toxicity/Urta

	Females				
	Dosage Group:	Control	2	3	4
	Number of Animals:	10	3	5	10
	Number Examined:	10	3	5	10
	Number Unremarkable:	4	0	0	4
Pancreas	Number examined:	10	0	0	10
	Number unremarkable:	0	0	0	0
INFILTRATE	1:	1	0	0	1
	Total Finding Incidence:	1	0	0	1
Peyer's Patch	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Thyroid	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Skin	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Small Intestine: Duodenum	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Small Intestine: Ileum	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10

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Test Article: Silk Fibroin

Rat/Sprague-Dawley

Repeat Dose Toxicity/Oral

	Females				
	Dosage Group:	Control	2	3	4
	Number of Animals:	10	3	5	10
	Number Examined:	10	3	5	10
	Number Unremarkable:	4	0	0	4
Small Intestine, Jejunum	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Spinal Cord, Cervical	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Spinal Cord, Lumbar	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Spinal Cord, Midthoracic	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Spleen	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10
Stomach	Number examined:	10	0	0	10
	Number unremarkable:	10	0	0	10

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HSRL

Study: 51651

StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS

Test Article: Silk Fibroin

Rat/Sprague-Dawley

Repeat Dose Toxicity/Oral

		Females				
		Dosage Group:	Control	2	3	4
		Number of Animals:	10	3	5	10
		Number Examined:	10	3	5	10
		Number Unremarkable:	4	0	0	4
Thymus	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	
Trachea	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	
Urinary Bladder	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	
Uterus	Number examined:	10	3	5	10	
	Number unremarkable:	10	3	5	10	
Vagina	Number examined:	10	0	0	10	
	Number unremarkable:	10	0	0	10	

Final Pathology Report
Cambridge Crops, Inc.
PSL Study Number 51651

Appendix B. Histopathology Incidence Tables (Individual Data Listing of Gross to Microscopic Correlation)

HSRL		Individual Data Listing of Gross to Microscopic Correlation		Printed: 03/31/2020 08:35:28 AM	
		Study: 51651		Pristima® Version 7.2.0 Build 15	
Rat/Sprague-Dawley		Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS		Repeat Dose Toxicity/Oral	
Gross Observations		Status	Microscopic Observations		
Animal #	Sex	Group			
7009	M	1			
			Correlated	Epididymis, Small, right	Epididymis, ATROPHY, minimal, Unilateral; right
			Correlated	Testes, Flaccid, right	Testes, ATROPHY, minimal, Unilateral; right
7029	M	2			
			Correlated	Testes, Flaccid, noted	Testes, ATROPHY, minimal
			Correlated	Testes, Small, right	Testes, ATROPHY, minimal
7013	F	1			
			Not Correlated	Uterus, Fluid filled, noted	
7014	F	1			
			Not Correlated	Uterus, Fluid filled, noted	
7018	F	1			
			Not Correlated	Uterus, Fluid filled, noted	
7019	F	1			
			Not Correlated	Uterus, Fluid filled, noted	
7032	F	2			
			Not Correlated	Uterus, Fluid filled, noted	
7038	F	2			
			Not Correlated	Uterus, Fluid filled, noted	

Individual Data Listing of Gross to Microscopic Correlation				Printed: 03/31/2020 08:35:28 AM	
HSRL		Study: 51651		Pristima® Version 7.2.0 Build 15	
Rat/Sprague-Dawley			StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS		Repeat Dose Toxicity/Oral
Gross Observations			Status	Microscopic Observations	
Animal #	Sex	Group			
7039	F	2			
			Uterus, Fluid filled, noted	Not Correlated	
7052	F	3			
			Uterus, Fluid filled, noted	Not Correlated	
7053	F	3			
			Uterus, Fluid filled, noted	Not Correlated	
7056	F	3			
			Uterus, Fluid filled, noted	Not Correlated	
7057	F	3			
			Uterus, Fluid filled, noted	Not Correlated	
7060	F	3			
			Uterus, Fluid filled, noted	Not Correlated	
7079	F	4			
			Uterus, Fluid filled, noted	Not Correlated	

Final Pathology Report
Cambridge Crops, Inc.
PSL Study Number 51651

Appendix C. Histopathology Incidence Tables (Individual Gross and Microscopic Observations)

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
Rat/Sprague-Dawley	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Animal #: 7001	Group: 1	Test Article: Silk Fibroin	Day Of Death: Dosing Phase, Day 30	Repeat Dose Toxicity/Oral
	Sex: M		Death Status: Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Epididymis	Within Normal Limits		Sperm granuloma, minimal	
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell	
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Testes	Thymus	Trachea	Urinary Bladder

HSRL
 Individual Gross and Microscopic Observations
 Study: 51651
 Printed: 03/31/2020 08:36:44 AM
 Pristima® Version 7.2.0 Build 15
 StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
 Rat/Sprague-Dawley
 Animal #: 7001
 Test Article: Silk Fibroin
 Repeat Dose Toxicity/Oral
 Group: 1
 Day Of Death: Dosing Phase, Day 30
 Sex: M
 Death Status: Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Continued from previous page ...				
Required tissues not microscopically examined:				
None				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Esophagus	Eye	Gland, Adrenal	Gland, Harderian	Gland, Mammary
Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Large Intestine, Cecum	Large Intestine, Colon
Large Intestine, Rectum	Larynx	Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric
Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)	Nose
Pancreas	Peyer's Patch	Pharynx	Seminal Vesicle with Coagulating Gland	Skin
Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar
Spinal Cord, Midthoracic	Spleen	Stomach	Testes	Thymus
Trachea	Urinary Bladder			

Individual Gross and Microscopic Observations					Printed: 03/31/2020 08:36:44 AM
HSRL					Study: 51651
Rat/Sprague-Dawley					StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
Animal #: 7002	Group: 1	Test Article: Silk Fibroin	Day Of Death: Dosing Phase, Day 30	Repeat Dose Toxicity/Oral	Pristima® Version 7.2.0 Build 15
	Sex: M		Death Status: Terminal sacrifice		
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments		
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell		
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate		
Skin	Within Normal Limits		CYST, minimal /Comments: Follicular cyst		
Tissues grossly within normal limits:					
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain	
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian	
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid	
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch	
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	
Stomach	Testes	Thymus	Trachea	Urinary Bladder	

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7002	Group: 1	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Required tissues not microscopically examined:			Continued from previous page ...	
None				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Lungs	Lymph Node, Mandibular
Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)
Nose	Pancreas	Peyer's Patch	Pharynx	Seminal Vesicle with Coagulating Gland
Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar
Spinal Cord, Midthoracic	Spleen	Stomach	Testes	Thymus
Trachea	Urinary Bladder			

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7003	Group: 1	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Gland, Thyroid	Within Normal Limits		No Abnormalities Detected One of the pair is Missing	
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Testes	Thymus	Trachea	Urinary Bladder

Individual Gross and Microscopic Observations

HSRL Printed: 03/31/2020 08:36:44 AM
Pristima® Version 7.2.0 Build 15
Study: 51651
StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
Test Article: Silk Fibroin **Repeat Dose Toxicity/Oral**
Rat/Sprague-Dawley
Animal #: 7003 **Group:** 1 **Day Of Death:** Dosing Phase, Day 30
Sex: M **Death Status:** Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Continued from previous page ...				
Required tissues not microscopically examined:				
None				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch	Pharynx
Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum
Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach
Testes	Thymus	Trachea	Urinary Bladder	

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7004	Group: 1	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell	
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Testes	Thymus	Trachea	Urinary Bladder
Required tissues not microscopically examined:				
None				

HSRL
 Rat/Sprague-Dawley
 Animal #: 7004

Individual Gross and Microscopic Observations
 Study: 51651
 Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
 Test Article: Silk Fibroin

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 Pristima® Version 7.2.0 Build 15
 Repeat Dose Toxicity/Oral

Group: 1
 Sex: M
 Day Of Death: Dosing Phase, Day 30
 Death Status: Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Continued from previous page ...				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Lungs	Lymph Node, Mandibular
Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)
Nose	Pancreas	Peyer's Patch	Pharynx	Seminal Vesicle with Coagulating Gland
Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum	Spinal Cord, Cervical
Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach	Testes
Thymus	Trachea	Urinary Bladder		

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7005	Group: 1	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Testes	Thymus	Trachea	Urinary Bladder
Required tissues not microscopically examined:				
None				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
Rat/Sprague-Dawley	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Animal #: 7005	Test Article: Silk Fibroin	Group: 1	Day Of Death: Dosing Phase, Day 30	Repeat Dose Toxicity/Oral
	Sex: M		Death Status: Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
			Continued from previous page ...	
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Testes	Thymus	Trachea	Urinary Bladder

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7006	Group: 1	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Testes	Thymus	Trachea	Urinary Bladder
Required tissues not microscopically examined:				
None				

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7006	Group: 1	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
			Continued from previous page ...	
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch	Pharynx
Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum
Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach
Testes	Thymus	Trachea	Urinary Bladder	

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7007	Group: 1	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Testes	Thymus	Trachea	Urinary Bladder
Required tissues not microscopically examined:				
None				

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7007	Group: 1	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
			Continued from previous page ...	
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch	Pharynx
Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum
Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach
Testes	Thymus	Trachea	Urinary Bladder	

Individual Gross and Microscopic Observations					Printed: 03/31/2020 08:36:44 AM	
Study: 51651					Pristima® Version 7.2.0 Build 15	
Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS					Repeat Dose Toxicity/Oral	
Test Article: Silk Fibroin					Day Of Death: Dosing Phase, Day 30	
Rat/Sprague-Dawley					Sex: M	
Animal #: 7008					Group: 1	
					Death Status: Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments			
Gland, Mammary	Within Normal Limits		Tissue Comment: Tissue present for evaluation No Abnormalities Detected			
Heart	Within Normal Limits		INFILTRATE, minimal, focal/multifocal, mixed cell			
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell			
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate			
Tissues grossly within normal limits:						
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain		
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian		
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid		
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney		
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver		
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate		
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch		
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum		
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen		

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7008	Group: 1	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Continued from previous page ...				
Stomach	Testes	Thymus	Trachea	Urinary Bladder
Required tissues not microscopically examined: None				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Large Intestine, Cecum	Large Intestine, Colon
Large Intestine, Rectum	Larynx	Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric
Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)	Nose
Pancreas	Peyer's Patch	Pharynx	Seminal Vesicle with Coagulating Gland	Skin
Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar
Spinal Cord, Midthoracic	Spleen	Stomach	Testes	Thymus
Trachea	Urinary Bladder			

Individual Gross and Microscopic Observations				
HSRL		Study: 51651	Printed: 03/31/2020 08:36:44 AM Pristima® Version 7.2.0 Build 15	
Rat/Sprague-Dawley	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Repeat Dose Toxicity/Oral
Animal #: 7009	Group: 1	Test Article: Silk Fibroin	Day Of Death: Dosing Phase, Day 30	
	Sex: M		Death Status: Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Epididymis	Small, right	Correlated	ATROPHY, minimal, Unilateral; right	
Gland, Mammary	Within Normal Limits		Tissue Comment: Tissue present for evaluation No Abnormalities Detected	
Testes	Flaccid, right	Correlated	ATROPHY, minimal, Unilateral; right	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Esophagus	Eye	Gland, Adrenal	Gland, Harderian	Gland, Mammary
Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch	Pharynx
Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum
Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach
Thymus	Trachea	Urinary Bladder		

Individual Gross and Microscopic Observations

HSRL Printed: 03/31/2020 08:36:44 AM
Pristima® Version 7.2.0 Build 15
Study: 51651
StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
Test Article: Silk Fibroin **Repeat Dose Toxicity/Oral**
Rat/Sprague-Dawley
Animal #: 7009 **Group:** 1 **Day Of Death:** Dosing Phase, Day 30
Sex: M **Death Status:** Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments
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Continued from previous page ...

Required tissues not microscopically examined:
None

Tissues microscopically examined and within normal limits:

Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Esophagus	Eye	Gland, Adrenal	Gland, Harderian	Gland, Mammary
Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch	Pharynx
Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum
Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach
Thymus	Trachea	Urinary Bladder		

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7010	Group: 1	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Testes	Thymus	Trachea	Urinary Bladder
Required tissues not microscopically examined:				
None				

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7010	Group: 1	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
			Continued from previous page ...	
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch	Pharynx
Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum
Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach
Testes	Thymus	Trachea	Urinary Bladder	

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
Rat/Sprague-Dawley	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Animal #: 7011	Group: 1	Test Article: Silk Fibroin	Day Of Death: Dosing Phase, Day 31	Repeat Dose Toxicity/Oral
	Sex: F		Death Status: Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Gland, Parathyroid	Within Normal Limits		Missing	
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7011	Group: 1	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Required tissues not microscopically examined:			Continued from previous page ...	
Gland, Parathyroid				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual	Gland, Salivary, Submandibular
Gland, Thyroid	Heart	Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum
Larynx	Liver	Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric
Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)	Nose
Ovary	Oviduct	Pancreas	Peyer's Patch	Pharynx
Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum	Spinal Cord, Cervical
Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach	Thymus
Trachea	Urinary Bladder	Uterus	Vagina	

Individual Gross and Microscopic Observations					Printed: 03/31/2020 08:36:44 AM
HSRL					Prisma® Version 7.2.0 Build 15
Study: 51651					
Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS					
Rat/Sprague-Dawley	Test Article: Silk Fibroin			Repeat Dose Toxicity/Oral	
Animal #: 7012	Group: 1	Day Of Death: Dosing Phase, Day 31			
Sex: F		Death Status: Terminal sacrifice			
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments		
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate		
Tissues grossly within normal limits:					
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain	
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian	
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual	
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum	
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs	
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas	
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	
Stomach	Thymus	Trachea	Urinary Bladder	Uterus	
Vagina					
Required tissues not microscopically examined:					
None					

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7012	Group: 1	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
			Continued from previous page ...	
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Lungs	Lymph Node, Mandibular
Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)
Nose	Ovary	Oviduct	Pancreas	Peyer's Patch
Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum
Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach
Thymus	Trachea	Urinary Bladder	Uterus	Vagina

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7013	Group: 1	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Uterus	Fluid filled, noted	Not Correlated	No Abnormalities Detected	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Vagina
Required tissues not microscopically examined:				
None				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7013	Group: 1	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Continued from previous page ...				
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				

Individual Gross and Microscopic Observations				Printed: 03/31/2020 08:36:44 AM
HSRL	Study: 51651			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Repeat Dose Toxicity/Oral
Animal #: 7014	Group: 1	Test Article: Silk Fibroin	Day Of Death: Dosing Phase, Day 31	
	Sex: F		Death Status: Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Uterus	Fluid filled, noted	Not Correlated	No Abnormalities Detected	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Vagina
Required tissues not microscopically examined:				
None				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7014	Group: 1	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Continued from previous page ...				
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7015	Group: 1	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Gland, Mammary	Within Normal Limits		Tissue Comment: Tissue present for evaluation No Abnormalities Detected	
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7015	Group: 1	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Required tissues not microscopically examined:			Continued from previous page ...	
None				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Lungs	Lymph Node, Mandibular
Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)
Nose	Ovary	Oviduct	Pancreas	Peyer's Patch
Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum
Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach
Thymus	Trachea	Urinary Bladder	Uterus	Vagina

Individual Gross and Microscopic Observations				
HSRL				Printed: 03/31/2020 08:36:44 AM
				Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS	Test Article: Silk Fibroin	Day Of Death: Dosing Phase, Day 31	Repeat Dose Toxicity/Oral
Animal #: 7016	Group: 1	Sex: F	Death Status: Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Gland, Salivary, Sublingual	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell	
Heart	Within Normal Limits		INFILTRATE, minimal, mixed cell	
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				

Individual Gross and Microscopic Observations

HSRL Printed: 03/31/2020 08:36:44 AM
Pristima® Version 7.2.0 Build 15
Study: 51651
StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
Test Article: Silk Fibroin **Repeat Dose Toxicity/Oral**
Rat/Sprague-Dawley
Animal #: 7016 **Group:** 1 **Day Of Death:** Dosing Phase, Day 31
Sex: F **Death Status:** Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments
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Continued from previous page ...

Required tissues not microscopically examined:
None

Tissues microscopically examined and within normal limits:

Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Submandibular
Gland, Thyroid	Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx
Liver	Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal
Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Ovary
Oviduct	Pancreas	Peyer's Patch	Pharynx	Skin
Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar
Spinal Cord, Midthoracic	Spleen	Stomach	Thymus	Trachea
Urinary Bladder	Uterus	Vagina		

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7017	Group: 1	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Heart	Within Normal Limits		INFILTRATE, minimal, mixed cell	
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell	
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				

Individual Gross and Microscopic Observations

HSRL Printed: 03/31/2020 08:36:44 AM
Pristima® Version 7.2.0 Build 15
Study: 51651
StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
Test Article: Silk Fibroin **Repeat Dose Toxicity/Oral**
Rat/Sprague-Dawley
Animal #: 7017 **Group:** 1 **Day Of Death:** Dosing Phase, Day 31
Sex: F **Death Status:** Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments
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Continued from previous page ...

Required tissues not microscopically examined:
None

Tissues microscopically examined and within normal limits:

Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum
Larynx	Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal
Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Ovary
Oviduct	Pancreas	Peyer's Patch	Pharynx	Skin
Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar
Spinal Cord, Midthoracic	Spleen	Stomach	Thymus	Trachea
Urinary Bladder	Uterus	Vagina		

Individual Gross and Microscopic Observations					Printed: 03/31/2020 08:36:44 AM	
HSRL					Pristima® Version 7.2.0 Build 15	
StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS						
Rat/Sprague-Dawley					Test Article: Silk Fibroin	
Animal #: 7018					Repeat Dose Toxicity/Oral	
Group: 1					Day Of Death: Dosing Phase, Day 31	
Sex: F					Death Status: Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments			
Gland, Pituitary	Within Normal Limits		Tissue Comment:No neurohypophysis present No Abnormalities Detected			
Uterus	Fluid filled, noted	Not Correlated	No Abnormalities Detected			
Tissues grossly within normal limits:						
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain		
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian		
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual		
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum		
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs		
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic		
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas		
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum		
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen		
Stomach	Thymus	Trachea	Urinary Bladder	Vagina		
Required tissues not microscopically examined:						
None						

HSRL
 Rat/Sprague-Dawley
 Animal #: 7018

Individual Gross and Microscopic Observations
 Study: 51651
 Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
 Test Article: Silk Fibroin

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 Pristima® Version 7.2.0 Build 15
 Repeat Dose Toxicity/Oral

Group: 1
 Sex: F
 Day Of Death: Dosing Phase, Day 31
 Death Status: Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Continued from previous page ...				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				

Individual Gross and Microscopic Observations				Printed: 03/31/2020 08:36:44 AM	
HSRL		Study: 51651		Pristima® Version 7.2.0 Build 15	
Rat/Sprague-Dawley		StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS		Repeat Dose Toxicity/Oral	
Animal #: 7019	Group: 1	Test Article: Silk Fibroin	Day Of Death: Dosing Phase, Day 31		
	Sex: F		Death Status: Terminal sacrifice		
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments		
Gland, Pituitary	Within Normal Limits		Tissue Comment:No neurohypophysis in section No Abnormalities Detected		
Pancreas	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell		
Uterus	Fluid filled, noted	Not Correlated	No Abnormalities Detected		
Tissues grossly within normal limits:					
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain	
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian	
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual	
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum	
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs	
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas	
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	
Stomach	Thymus	Trachea	Urinary Bladder	Vagina	

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7019	Group: 1	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Required tissues not microscopically examined:			Continued from previous page ...	
None				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Peyer's Patch
Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum
Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach
Thymus	Trachea	Urinary Bladder	Uterus	Vagina

Individual Gross and Microscopic Observations					Printed: 03/31/2020 08:36:44 AM
HSRL					Prisma® Version 7.2.0 Build 15
Study: 51651					
Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS					
Rat/Sprague-Dawley					Repeat Dose Toxicity/Oral
Animal #: 7020					
Group: 1					
Sex: F					
Day Of Death: Dosing Phase, Day 31					
Death Status: Terminal sacrifice					
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments		
Gland, Pituitary	Within Normal Limits		Tissue Comment: No neurohypophysis in section No Abnormalities Detected		
Tissues grossly within normal limits:					
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain	
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian	
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual	
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum	
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs	
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas	
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	
Stomach	Thymus	Trachea	Urinary Bladder	Uterus	
Vagina					
Required tissues not microscopically examined:					
None					

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:36:44 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7020	Group: 1	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Continued from previous page ...				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				

Individual Gross and Microscopic Observations			
HSRL		Study: 51651	Printed: 03/31/2020 08:37:57 AM
	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS		Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral
Animal #: 7029	Group: 2	Day Of Death: Dosing Phase, Day 30	
	Sex: M	Death Status: Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments
Testes	Flaccid, noted Small, right	Correlated Correlated	ATROPHY, minimal ATROPHY, minimal
Tissues grossly within normal limits: There are no such tissues			
Required tissues not microscopically examined: None			
Tissues microscopically examined and within normal limits: There are no such tissues			

Individual Gross and Microscopic Observations

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Study: 51651
Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
Test Article: Silk Fibroin **Repeat Dose Toxicity/Oral**
Rat/Sprague-Dawley
Animal #: 7032 **Group:** 2 **Day Of Death:** Dosing Phase, Day 31
Sex: F **Death Status:** Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments
Uterus	Fluid filled, noted	Not Correlated	No Abnormalities Detected

Tissues grossly within normal limits:
There are no such tissues

Required tissues not microscopically examined:
None

Tissues microscopically examined and within normal limits:
Uterus

Individual Gross and Microscopic Observations

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Study: 51651
Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
Test Article: Silk Fibroin **Repeat Dose Toxicity/Oral**
Rat/Sprague-Dawley
Animal #: 7038 **Group:** 2 **Day Of Death:** Dosing Phase, Day 31
Sex: F **Death Status:** Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments
Uterus	Fluid filled, noted	Not Correlated	No Abnormalities Detected

Tissues grossly within normal limits:
 There are no such tissues

Required tissues not microscopically examined:
 None

Tissues microscopically examined and within normal limits:
 Uterus

Individual Gross and Microscopic Observations

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Pristima® Version 7.2.0 Build 15
Study: 51651
Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
Rat/Sprague-Dawley **Test Article:** Silk Fibroin **Repeat Dose Toxicity/Oral**
Animal #: 7039 **Group:** 2 **Day Of Death:** Dosing Phase, Day 31
Sex: F **Death Status:** Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments
Uterus	Fluid filled, noted	Not Correlated	No Abnormalities Detected

Tissues grossly within normal limits:
There are no such tissues

Required tissues not microscopically examined:
None

Tissues microscopically examined and within normal limits:
Uterus

Individual Gross and Microscopic Observations

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Pristima® Version 7.2.0 Build 15
Study: 51651
Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
Animal #: 7052 **Group:** 3 **Test Article:** Silk Fibroin **Day Of Death:** Dosing Phase, Day 31 **Repeat Dose Toxicity/Oral**
Sex: F **Death Status:** Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments
Uterus	Fluid filled, noted	Not Correlated	No Abnormalities Detected

Tissues grossly within normal limits:
There are no such tissues

Required tissues not microscopically examined:
None

Tissues microscopically examined and within normal limits:
Uterus

Individual Gross and Microscopic Observations

HSRL Printed: 03/31/2020 08:38:56 AM
Pristima® Version 7.2.0 Build 15
Study: 51651
Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
Test Article: Silk Fibroin **Repeat Dose Toxicity/Oral**
Rat/Sprague-Dawley
Animal #: 7053 **Group:** 3 **Day Of Death:** Dosing Phase, Day 31
Sex: F **Death Status:** Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments
Uterus	Fluid filled, noted	Not Correlated	No Abnormalities Detected

Tissues grossly within normal limits:
There are no such tissues

Required tissues not microscopically examined:
None

Tissues microscopically examined and within normal limits:
Uterus

Individual Gross and Microscopic Observations

HSRL
Study: 51651
Printed: 03/31/2020 08:38:56 AM
Pristima® Version 7.2.0 Build 15

Rat/Sprague-Dawley
Animal #: 7056
Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
Test Article: Silk Fibroin
Repeat Dose Toxicity/Oral

Group: 3
Sex: F
Day Of Death: Dosing Phase, Day 31
Death Status: Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments
Uterus	Fluid filled, noted	Not Correlated	No Abnormalities Detected

Tissues grossly within normal limits:
There are no such tissues

Required tissues not microscopically examined:
None

Tissues microscopically examined and within normal limits:
Uterus

Individual Gross and Microscopic Observations

HSRL Printed: 03/31/2020 08:38:56 AM
Pristima® Version 7.2.0 Build 15
Study: 51651
Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
Animal #: 7057 **Group:** 3 **Test Article:** Silk Fibroin **Day Of Death:** Dosing Phase, Day 31 **Repeat Dose Toxicity/Oral**
Sex: F **Death Status:** Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments
Uterus	Fluid filled, noted	Not Correlated	No Abnormalities Detected

Tissues grossly within normal limits:
There are no such tissues

Required tissues not microscopically examined:
None

Tissues microscopically examined and within normal limits:
Uterus

Individual Gross and Microscopic Observations

HSRL Printed: 03/31/2020 08:38:56 AM
Pristima® Version 7.2.0 Build 15
Study: 51651
Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
Rat/Sprague-Dawley **Test Article:** Silk Fibroin **Repeat Dose Toxicity/Oral**
Animal #: 7060 **Group:** 3 **Day Of Death:** Dosing Phase, Day 31
Sex: F **Death Status:** Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments
Uterus	Fluid filled, noted	Not Correlated	No Abnormalities Detected

Tissues grossly within normal limits:
There are no such tissues

Required tissues not microscopically examined:
None

Tissues microscopically examined and within normal limits:
Uterus

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
Rat/Sprague-Dawley	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Animal #: 7061	Group: 4	Test Article: Silk Fibroin	Day Of Death: Dosing Phase, Day 30	Repeat Dose Toxicity/Oral
	Sex: M		Death Status: Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell	
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate	
Skin	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Testes	Thymus	Trachea	Urinary Bladder

Individual Gross and Microscopic Observations				Printed: 03/31/2020 08:42:39 AM
HSRL	Study: 51651			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Repeat Dose Toxicity/Oral
Animal #: 7061	Group: 4	Test Article: Silk Fibroin	Day Of Death: Dosing Phase, Day 30	
	Sex: M		Death Status: Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Required tissues not microscopically examined:				Continued from previous page ...
None				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Lungs	Lymph Node, Mandibular
Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)
Nose	Pancreas	Peyer's Patch	Pharynx	Seminal Vesicle with Coagulating Gland
Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar
Spinal Cord, Midthoracic	Spleen	Stomach	Testes	Thymus
Trachea	Urinary Bladder			

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7062	Group: 4	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Testes	Thymus	Trachea	Urinary Bladder
Required tissues not microscopically examined:				
None				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7062	Group: 4	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Continued from previous page ...				
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Testes	Thymus	Trachea	Urinary Bladder

Individual Gross and Microscopic Observations					Printed: 03/31/2020 08:42:39 AM
HSRL					Prisma® Version 7.2.0 Build 15
Study: 51651					
Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS					
Rat/Sprague-Dawley					Repeat Dose Toxicity/Oral
Animal #: 7063					
Group: 4					
Sex: M					
Day Of Death: Dosing Phase, Day 30					
Death Status: Terminal sacrifice					
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments		
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate		
Lungs	Within Normal Limits		INFILTRATE, minimal, focal/multifocal, Peribronchiolar, eosinophils		
Tissues grossly within normal limits:					
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain	
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian	
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid	
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch	
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	
Stomach	Testes	Thymus	Trachea	Urinary Bladder	

Individual Gross and Microscopic Observations					Printed: 03/31/2020 08:42:39 AM
HSRL					Study: 51651
Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS					Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin			Repeat Dose Toxicity/Oral	
Animal #: 7063	Group: 4	Day Of Death: Dosing Phase, Day 30			
	Sex: M	Death Status: Terminal sacrifice			
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments		
Required tissues not microscopically examined:					Continued from previous page ...
None					
Tissues microscopically examined and within normal limits:					
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain	
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian	
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid	
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Lymph Node, Mandibular	
Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)	
Nose	Pancreas	Peyer's Patch	Pharynx	Seminal Vesicle with Coagulating Gland	
Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum	Spinal Cord, Cervical	
Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach	Testes	
Thymus	Trachea	Urinary Bladder			

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7064	Group: 4	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Gland, Mammary	Within Normal Limits		Tissue Comment: Tissue present for evaluation No Abnormalities Detected	
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell	
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate	
Pharynx	Within Normal Limits		INFLAMMATION, minimal /Comments: Pyogranulomatous; lamina propria	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7064	Group: 4	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Continued from previous page ...				
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Testes	Thymus	Trachea	Urinary Bladder
Required tissues not microscopically examined: None				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Lungs	Lymph Node, Mandibular
Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)
Nose	Pancreas	Peyer's Patch	Seminal Vesicle with Coagulating Gland	Skin
Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar
Spinal Cord, Midthoracic	Spleen	Stomach	Testes	Thymus

Individual Gross and Microscopic Observations		Printed: 03/31/2020 08:42:39 AM
HSRL	Study: 51651	Pristima® Version 7.2.0 Build 15
	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS	
Rat/Sprague-Dawley	Test Article: Silk Fibroin	Repeat Dose Toxicity/Oral
Animal #: 7064	Group: 4	Day Of Death: Dosing Phase, Day 30
	Sex: M	Death Status: Terminal sacrifice
Tissue	Gross Observations/Comments	Status
		Microscopic Observations/Comments
		Continued from previous page ...
Trachea	Urinary Bladder	

Individual Gross and Microscopic Observations					Printed: 03/31/2020 08:42:39 AM
Study: 51651					Pristima® Version 7.2.0 Build 15
Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS					
Test Article: Silk Fibroin					Repeat Dose Toxicity/Oral
Rat/Sprague-Dawley					
Animal #: 7065					
Group: 4					Day Of Death: Dosing Phase, Day 30
Sex: M					Death Status: Terminal sacrifice
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments		
Gland, Prostate	Within Normal Limits		HYPERPLASIA, minimal		
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell		
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate		
Pharynx	Within Normal Limits		INFLAMMATION, minimal /Comments: Foreign body granuloma; hair present		
Skin	Within Normal Limits		Tissue Comment: No epidermis in section No Abnormalities Detected		
Tissues grossly within normal limits:					
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain	
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian	
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid	
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch	

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
Rat/Sprague-Dawley	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Animal #: 7065	Group: 4	Test Article: Silk Fibroin	Day Of Death: Dosing Phase, Day 30	Repeat Dose Toxicity/Oral
	Sex: M		Death Status: Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
			Continued from previous page ...	
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Testes	Thymus	Trachea	Urinary Bladder
Required tissues not microscopically examined: None				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Large Intestine, Cecum	Large Intestine, Colon
Large Intestine, Rectum	Larynx	Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric
Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)	Nose
Pancreas	Peyer's Patch	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum
Small Intestine, Ileum	Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic

Individual Gross and Microscopic Observations		Printed: 03/31/2020 08:42:39 AM	
HSRL	Study: 51651	Pristima® Version 7.2.0 Build 15	
Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			
Rat/Sprague-Dawley	Test Article: Silk Fibroin	Repeat Dose Toxicity/Oral	
Animal #: 7065	Group: 4	Day Of Death: Dosing Phase, Day 30	
	Sex: M	Death Status: Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments
Continued from previous page ...			
Spleen	Stomach	Testes	Thymus
Urinary Bladder			Trachea

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7066	Group: 4	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell	
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Testes	Thymus	Trachea	Urinary Bladder
Required tissues not microscopically examined:				
None				

HSRL
 Rat/Sprague-Dawley
 Animal #: 7066

Individual Gross and Microscopic Observations
 Study: 51651
 Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
 Test Article: Silk Fibroin

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 Pristima® Version 7.2.0 Build 15
 Repeat Dose Toxicity/Oral

Group: 4
 Sex: M
 Day Of Death: Dosing Phase, Day 30
 Death Status: Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Continued from previous page ...				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Lungs	Lymph Node, Mandibular
Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)
Nose	Pancreas	Peyer's Patch	Pharynx	Seminal Vesicle with Coagulating Gland
Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum	Spinal Cord, Cervical
Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach	Testes
Thymus	Trachea	Urinary Bladder		

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7067	Group: 4	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Gland, Salivary, Sublingual	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell	
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Testes	Thymus	Trachea	Urinary Bladder
Required tissues not microscopically examined:				
None				

HSRL
 Rat/Sprague-Dawley
 Animal #: 7067

Individual Gross and Microscopic Observations
 Study: 51651
 Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
 Test Article: Silk Fibroin

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 Pristima® Version 7.2.0 Build 15
 Repeat Dose Toxicity/Oral

Group: 4
 Sex: M
 Day Of Death: Dosing Phase, Day 30
 Death Status: Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Continued from previous page ...				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Large Intestine, Cecum	Large Intestine, Colon
Large Intestine, Rectum	Larynx	Liver	Lungs	Lymph Node, Mandibular
Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)
Nose	Pancreas	Peyer's Patch	Pharynx	Seminal Vesicle with Coagulating Gland
Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum	Spinal Cord, Cervical
Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach	Testes
Thymus	Trachea	Urinary Bladder		

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7068	Group: 4	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Kidney	Within Normal Limits		CYST, minimal INFILTRATE, minimal, mononuclear cell	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Testes	Thymus	Trachea	Urinary Bladder
Required tissues not microscopically examined:				
None				

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7068	Group: 4	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
			Continued from previous page ...	
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch	Pharynx
Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum
Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach
Testes	Thymus	Trachea	Urinary Bladder	

Individual Gross and Microscopic Observations					Printed: 03/31/2020 08:42:39 AM	
HSRL		Study: 51651			Pristima® Version 7.2.0 Build 15	
Rat/Sprague-Dawley		StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Repeat Dose Toxicity/Oral	
Animal #: 7069		Test Article: Silk Fibroin		Day Of Death: Dosing Phase, Day 30		
Group: 4		Sex: M		Death Status: Terminal sacrifice		
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments			
Gland, Parathyroid	Within Normal Limits		Missing			
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell			
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate			
Tissues grossly within normal limits:						
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain		
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian		
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid		
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney		
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver		
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate		
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch		
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum		
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen		
Stomach	Testes	Thymus	Trachea	Urinary Bladder		

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7069	Group: 4	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Required tissues not microscopically examined:			Continued from previous page ...	
Gland, Parathyroid				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Large Intestine, Cecum	Large Intestine, Colon
Large Intestine, Rectum	Larynx	Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric
Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)	Nose
Pancreas	Peyer's Patch	Pharynx	Seminal Vesicle with Coagulating Gland	Skin
Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar
Spinal Cord, Midthoracic	Spleen	Stomach	Testes	Thymus
Trachea	Urinary Bladder			

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7070	Group: 4	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney
Large Intestine, Cecum	Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver
Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate
Nerve, Optic	Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch
Pharynx	Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Testes	Thymus	Trachea	Urinary Bladder
Required tissues not microscopically examined:				
None				

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7070	Group: 4	Day Of Death:	Dosing Phase, Day 30	
	Sex: M	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
			Continued from previous page ...	
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Epididymis	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Prostate	Gland, Salivary, Parotid
Gland, Salivary, Sublingual	Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Pancreas	Peyer's Patch	Pharynx
Seminal Vesicle with Coagulating Gland	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum
Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach
Testes	Thymus	Trachea	Urinary Bladder	

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7071	Group: 4	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				
Required tissues not microscopically examined:				
None				

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7071	Group: 4	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
			Continued from previous page ...	
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7072	Group: 4	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				
Required tissues not microscopically examined:				
None				

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7072	Group: 4	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
			Continued from previous page ...	
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7073	Group: 4	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				
Required tissues not microscopically examined:				
None				

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7073	Group: 4	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
			Continued from previous page ...	
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Large Intestine, Cecum	Large Intestine, Colon
Large Intestine, Rectum	Larynx	Liver	Lungs	Lymph Node, Mandibular
Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)
Nose	Ovary	Oviduct	Pancreas	Peyer's Patch
Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum
Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach
Thymus	Trachea	Urinary Bladder	Uterus	Vagina

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7074	Group: 4	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Pancreas	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				
Required tissues not microscopically examined:				
None				

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7074	Group: 4	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Tissues microscopically examined and within normal limits:			Continued from previous page ...	
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Peyer's Patch
Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum
Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach
Thymus	Trachea	Urinary Bladder	Uterus	Vagina

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7075	Group: 4	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell	
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				

HSRL
 Rat/Sprague-Dawley
 Animal #: 7075

Individual Gross and Microscopic Observations
 Study: 51651
 Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
 Test Article: Silk Fibroin

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 Pristima® Version 7.2.0 Build 15
 Repeat Dose Toxicity/Oral

Group: 4
 Sex: F
 Day Of Death: Dosing Phase, Day 31
 Death Status: Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Continued from previous page ...				
Required tissues not microscopically examined:				
None				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Large Intestine, Cecum	Large Intestine, Colon
Large Intestine, Rectum	Larynx	Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric
Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)	Nose
Ovary	Oviduct	Pancreas	Peyer's Patch	Pharynx
Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum	Spinal Cord, Cervical
Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach	Thymus
Trachea	Urinary Bladder	Uterus	Vagina	

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7076	Group: 4	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Heart	Within Normal Limits		INFILTRATE, minimal, mixed cell	
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				

HSRL
 Individual Gross and Microscopic Observations
 Study: 51651
 Printed: 03/31/2020 08:42:39 AM
 Pristima® Version 7.2.0 Build 15
 Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
 Rat/Sprague-Dawley
 Animal #: 7076
 Test Article: Silk Fibroin
 Group: 4
 Sex: F
 Day Of Death: Dosing Phase, Day 31
 Repeat Dose Toxicity/Oral
 Death Status: Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Continued from previous page ...				
Required tissues not microscopically examined:				
None				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Kidney	Large Intestine, Cecum	Large Intestine, Colon
Large Intestine, Rectum	Larynx	Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric
Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)	Nose
Ovary	Oviduct	Pancreas	Peyer's Patch	Pharynx
Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum	Spinal Cord, Cervical
Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach	Thymus
Trachea	Urinary Bladder	Uterus	Vagina	

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7077	Group: 4	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				
Required tissues not microscopically examined:				
None				

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7077	Group: 4	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
			Continued from previous page ...	
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7078	Group: 4	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Kidney	Within Normal Limits		INFILTRATE, minimal, mononuclear cell	
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				

HSRL
 Rat/Sprague-Dawley
 Animal #: 7078

Individual Gross and Microscopic Observations
 Study: 51651
 Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
 Test Article: Silk Fibroin

Printed: 03/31/2020 08:42:39 AM
 Pristima® Version 7.2.0 Build 15

Group: 4
 Sex: F
 Day Of Death: Dosing Phase, Day 31
 Death Status: Terminal sacrifice
 Repeat Dose Toxicity/Oral

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Continued from previous page ...				
Required tissues not microscopically examined:				
None				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Large Intestine, Cecum	Large Intestine, Colon
Large Intestine, Rectum	Larynx	Lungs	Lymph Node, Mandibular	Lymph Node, Mesenteric
Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)	Nose
Ovary	Oviduct	Pancreas	Peyer's Patch	Pharynx
Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum	Spinal Cord, Cervical
Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach	Thymus
Trachea	Urinary Bladder	Uterus	Vagina	

Individual Gross and Microscopic Observations				Printed: 03/31/2020 08:42:39 AM Pristima® Version 7.2.0 Build 15	
HSRL	Study: 51651			Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS	
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral		
Animal #: 7079	Group: 4	Sex: F	Day Of Death: Dosing Phase, Day 31	Death Status: Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments		
Gland, Pituitary	Within Normal Limits		Tissue Comment: No neurohypophysis in section No Abnormalities Detected		
Uterus	Fluid filled, noted	Not Correlated	No Abnormalities Detected		
Tissues grossly within normal limits:					
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain	
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian	
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual	
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum	
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs	
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas	
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	
Stomach	Thymus	Trachea	Urinary Bladder	Vagina	
Required tissues not microscopically examined: None					

HSRL
Rat/Sprague-Dawley
Animal #: 7079

Individual Gross and Microscopic Observations
Study: 51651
Study Title: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS
Test Article: Silk Fibroin

Printed: 03/31/2020 08:42:39 AM
Pristima® Version 7.2.0 Build 15
Repeat Dose Toxicity/Oral

Group: 4
Sex: F
Day Of Death: Dosing Phase, Day 31
Death Status: Terminal sacrifice

Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Continued from previous page ...				
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7080	Group: 4	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
Liver	Within Normal Limits		INFILTRATE, minimal, Mononuclear cell infiltrate	
Tissues grossly within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Liver	Lungs
Lymph Node, Mandibular	Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic
Nerve, Peripheral (sciatic)	Nose	Ovary	Oviduct	Pancreas
Peyer's Patch	Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum
Small Intestine, Jejunum	Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen
Stomach	Thymus	Trachea	Urinary Bladder	Uterus
Vagina				
Required tissues not microscopically examined:				
None				

Individual Gross and Microscopic Observations				
HSRL	Study: 51651			Printed: 03/31/2020 08:42:39 AM
	StudyTitle: SILK FIBROIN: A 28-DAY ORAL GAVAGE TOXICITY STUDY IN RATS			Pristima® Version 7.2.0 Build 15
Rat/Sprague-Dawley	Test Article: Silk Fibroin		Repeat Dose Toxicity/Oral	
Animal #: 7080	Group: 4	Day Of Death:	Dosing Phase, Day 31	
	Sex: F	Death Status:	Terminal sacrifice	
Tissue	Gross Observations/Comments	Status	Microscopic Observations/Comments	
			Continued from previous page ...	
Tissues microscopically examined and within normal limits:				
Artery, Aorta	Bone Marrow	Bone, Femur	Bone, Sternum	Brain
Cervix	Esophagus	Eye	Gland, Adrenal	Gland, Harderian
Gland, Mammary	Gland, Parathyroid	Gland, Pituitary	Gland, Salivary, Parotid	Gland, Salivary, Sublingual
Gland, Salivary, Submandibular	Gland, Thyroid	Heart	Kidney	Large Intestine, Cecum
Large Intestine, Colon	Large Intestine, Rectum	Larynx	Lungs	Lymph Node, Mandibular
Lymph Node, Mesenteric	Muscle, Skeletal	Nasal Turbinate	Nerve, Optic	Nerve, Peripheral (sciatic)
Nose	Ovary	Oviduct	Pancreas	Peyer's Patch
Pharynx	Skin	Small Intestine, Duodenum	Small Intestine, Ileum	Small Intestine, Jejunum
Spinal Cord, Cervical	Spinal Cord, Lumbar	Spinal Cord, Midthoracic	Spleen	Stomach
Thymus	Trachea	Urinary Bladder	Uterus	Vagina

Final Pathology Report
Cambridge Crops, Inc.
PSL Study Number 51651

Appendix D. Tissue Accountability

Appendix D.
Tissue AccountabilityCambridge Crops, Inc.
PSL Study Number 51651

Animal	Tissue	Tissue Accountability Statement
7003	Gland, Thyroid One-of-Pair	Tissue verified as missing from the wet tissues received. A second technician verified the tissue as missing from wets at the time of trimming.
7069	Gland, Parathyroid	Recut and/or retrim slides are not required for this tissue since HSRL SOPs require step sections on the original slide.
7011	Gland, Parathyroid	Recut and/or retrim slides are not required for this tissue since HSRL SOPs require step sections on the original slide.

Final Pathology Report
Cambridge Crops, Inc.
PSL Study Number 51651

Appendix E. Quality Assurance Statement

HSRL HistoScientific Research Laboratories

QUALITY ASSURANCE STATEMENT

Study Title: Silk Fibroin: A 28-Day Oral Gavage Toxicity Study in Rats

Client Study Number: 51651

This histopathology project has been inspected and audited by the HSRL Quality Assurance Unit (QAU) as required by the Good Laboratory Practice (GLP) regulations disseminated by the U.S. Food and Drug Administration (FDA, 21 CFR 58).

<u>Area Inspected</u>		<u>Dates</u>		
		<u>Inspection¹</u>	<u>Reported²</u>	<u>Reported³</u>
Critical Phase:	Embedding	30DEC19	30DEC19	30DEC19
Data Review		09-10JAN20	14JAN20	14JAN20
Pathology Report:	Draft	20JAN20	21JAN20	21JAN20
	Final	31MAR20	31MAR20	31MAR20

All the results/conclusions of the pathology report accurately reflect the raw data.

¹ Date(s) of inspection

² Date(s) inspections reported to HSRL Laboratory Director/Test Site Management, Principal Investigator/HSRL Study Pathologist

³ Date(s) inspections reported to Study Director, Test Facility Management, and Lead QA (if appropriate)


Quality Assurance Auditor

31MAR20
Date

APPENDIX H
FOOD CONSUMPTION DERIVATION FROM
NHANES 2013-2016

Intended for
Cambridge Crops

Date
March 21, 2020

ESTIMATION OF FOOD INTAKE FOR USE IN ESTIMATING POSSIBLE FIBROIN INTAKE

CONTENTS

1.	Introduction	2
2.	Source of Data	3
3.	Categorization of the NHANES Food Codes	4
4.	Generation of the consumption data	6
5.	References	7

1. INTRODUCTION

Estimates of potential intake of fibroin when used as a coating for food products were determined by estimating the intake of the associated food products and combining that with information on the application rate of fibroin to the food (mg fibroin applied/g food). Ramboll has performed calculations which estimate the consumption amounts of specific food products that could be covered by fibroin. Data reported by the Centers for Disease Control and Prevention (CDC) in the National Health and Nutrition Examination Surveys (NHANES) for 2013-2014 and 2015-2016 (CDC 2019a, 2019b) were used to make these calculations. With the consumption data and the average estimates for the application rate of fibroin, Ramboll calculated the potential intake of fibroin.

2. SOURCE OF DATA

NHANES is a multiyear program designed to assess the health and nutritional status of the civilian, non-institutionalized¹ adults and children in the United States. The NHANES program combines interviews on demographics, socioeconomic, dietary and health-related questions with an examination program that consists of medical, dental, and physiological measurements. In the NHANES dietary section, a trained dietary interviewer collects detailed information about the food and beverages consumed by the respondents on the previous day – from midnight to midnight. A second dietary recall interview is administered by phone 3 to 10 days after the first interview and is scheduled to occur on a different day of the week than the first interview. For NHANES 2013-2014, a total of 8,661 individuals provided complete dietary intakes for the first interview and 7,574 of these individuals provided a complete day 2 dietary intake recall. For NHANES 2015-2016, a total of 8,506 individuals gave complete dietary intakes for the first interview and 7,027 of these provided complete dietary intakes for the second interview. These two sets of dietary data (NHANES 2013-2014 and NHANES 2015-2016) were combined for this analysis along with the physiological data of body weight in kilograms (kg). Since multiple surveys were used, the population weights assigned to these data were adjusted so that the combination was still a nationally representative sample of dietary intake. When combining two sets of NHANES data (such as 2013-2014 and 2015-2016) the weights that provide national representation must be divided by 2, as specified by the CDC in their documentation of the NHANES data (CDC 2018).

To determine the grams of specific products in the food that was eaten by the NHANES survey participants, data from the United States Department of Agriculture's Food and Nutrient Data base for Dietary Studies (FNNDS) were used (USDA 2016, 2018). A new version of this database is released with each 2-year NHANES dietary data set. The FNNDS databases contain recipes which break down the food items identified in the NHANES data into ingredients by amount. The percentage of specific ingredients in the recipes can then be used to more accurately determine the amount of food consumed in a specific category being considered. For example, the recipes for fruit pies can supply the percentage of the pie that is actually fruit, and that percentage can be used to determine the grams of fruit consumption out of the total grams of fruit pie consumed.

¹ NHANES does not include persons in supervised care or custody in institutional settings, and also excludes active-duty military personnel, active-duty family members living overseas and any other U.S. citizens residing outside the 50 states and District of Columbia.

3. CATEGORIZATION OF THE NHANES FOOD CODES

The categorization of the potential foods was completed within a combined list of the NHANES 2013-14 and 2015-16 food codes. The selected foods of interest are detailed in Table H1, indicating categories and subcategories of food. All NHANES food codes not assigned to a food category of interest were excluded.

The 9,514 food items from NHANES are all categorized into one of the categories. In the case that the food item contains only ingredients that are part of the food category, this was taken into account by coding. If only part of the food item belongs to a category, the category is split. This indicates that the FNNDS recipes were used to determine what percentage of the food item should be placed in the categories listed in split columns.

To determine the applicable ingredients, a complete list of the standard reference (SR) codes for the ingredients in food was generated, compiled into Microsoft Excel, and specific SR codes which belonged to the desired categories were selected from within the food's listed ingredients. During the procedure of the SAS analysis of the survey data, two output files were generated; one output contained the records for foods that could not be matched to selected SR codes (none were generated for this analysis) and the other contained all the NHANES foods codes that needed to be split into ingredients and the percentages of the categorized ingredients as determined from the recipes.

Table H1: Categories of Food to Consider			
Category Description	Category	Sub-Category	Sub-Category Description
Whole Meat	1	A	Beef
	1	B	Chicken
	1	C	Pork
	1	D	Turkey
	1	E	Other (Lamb, Goat, Veal, Rabbit, Ostrich)
	1	F	Frozen Meats
	1	G	Meat Mixtures or NFS
Ground Meat	2	A	Beef
	2	B	Chicken
	2	C	Pork
	2	D	Turkey
	2	E	Other (Lamb, Goat, Veal, Rabbit, Ostrich)
	2	F	Mixed/Grouped Meats
Processed Meat	3	A	Predominantly beef
	3	B	Predominantly chicken
	3	C	Predominantly pork
	3	D	Predominantly turkey
	3	E	Other (Lamb, Goat, Veal, Rabbit, Ostrich)
	3	F	Mixed/Grouped Meats
Fish	4	A	Fish Fillet
	4	B	Shellfish (Assumed peeled)
	4	C	Seafood eaten raw
Fruits	5	A	Fruits with Edible Peels
	5	B	Fruit Salads where fruit could be unpeeled
Vegetables	6	A	With Edible peels
	6	B	Snackable form
Cheese	7	A	Sliced
	7	B	Pizza cheese topping
Processed Foods/Candy	8	A	Hard Candy
	8	B	Candy Bars

4. GENERATION OF THE CONSUMPTION DATA

On an individual basis, the amount of each food category consumed by a participant in the NHANES survey was determined for each day of the survey. Totals within categories and overall were calculated on an individual basis as well. The amount of food consumed was then averaged over the two days of the survey (if two days of data existed for that individual), and finally divided by the individual's body weight to obtain a food consumption per category in g/kg of body weight/day.

Survey statistics procedures were used for the calculations of the statistics reported (average, median and 95th percentile) for amounts of food consumed in each category. These procedures use the sampling design and weighting methodology supplied by the CDC in the calculations. The "weights" assigned to each individual participating in the survey reflect the amount of the overall United States population that a specific person participating in the survey represents. The application of these weights in estimating potential intake provides values that reflect the entire United States civilian non-institutionalized population.

Survey procedures in SAS version 9.4 were used to determine the estimated average, median and 95th percentile of amounts of food consumed in the United States population. Further detailed calculations are considered work product and available upon request. A summary of information is shown in **Table H2**.

Table H2: Summary of consumption by food category, NHANES 2013-2016*						
Category	Grams per day			Grams / kg·bw / day		
	Average	Median	95%-tile	Average	Median	95%-tile
Whole Meat	55.79	32.03	200.34	0.84	0.44	3.01
Ground Meat	17.52	0.0	109.70	0.26	0.0	1.56
Processed Meat	35.26	17.49	129.58	0.58	0.25	2.26
Fish	14.21	0.0	97.45	0.20	0.0	0.20
Fruits	50.79	0.0	213.48	0.98	0.0	0.98
Vegetables	83.83	50.00	288.98	1.26	0.71	1.26
Cheese	18.11	10.47	67.70	0.29	0.13	0.29
Processed Foods/Candy	6.48	0.0	34.93	0.12	0.0	0.64
Total	281.96	243.29	623.61	4.56	3.57	11.58
*Sample size = 16,210 for grams per day, 16,085 for grams/kg·bw/day. Differences in counts are due to lack of body weight data for specific individuals who had dietary data. Abbreviations: kg = kilogram(s), bw = body weight						

5. REFERENCES

CDC. 2018. National Health and Nutrition Examination Survey: Analytic Guidelines, 2011-2014 and 2015-2016. United States Department of Health and Human Services, Centers for Disease Control and Prevention. Available at: <https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx#analytic-guidelines>

CDC. 2019a. National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: United States Department of Health and Human Services, Centers for Disease Control and Prevention, 2013-2016. Available at: <https://wwwn.cdc.gov/nchs/nhanes/ContinuousNhanes/Default.aspx?BeginYear=2015>

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APPENDIX I
MORI SILK *IN VITRO* DIGESTIBILITY STUDY IN
HUMAN SIMULATED GASTRIC FLUID

STUDY TITLE

Silk Fibroin: *in vitro* digestibility study in human simulated gastric fluid (pH 2.0)
at 10 units per µg test protein

AUTHORS



STUDY COMPLETED ON

12 February 2020

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LABORATORY STUDY ID

20200212 – REG – Silk Fibroin Digestion

Statement of No Data Confidentiality

No claim of confidentiality is made for any information contained in this document. I acknowledge that information not designated as within the scope of FIFRA Section 10(d)(1)(A), (B), or (C) and which pertains to a registered pesticide is not entitled to confidential treatment and may be released to the public, subject to the provisions regarding disclosure to multinational entities under FIFRA section 10(g).

Company

Company Agent:



Cambridge Crops, Inc.

March 18, 2020

Date

These Data May Be Considered Confidential In Countries Outside The United States.

GLP Compliance Statement

This study was not conducted and reported in compliance with the requirements of the Good Laboratory Practice Standards (40 CFR Part 160) of the Code of Federal Regulations of the United States of America. However, raw data and bioinformatics comparisons were archived in PDF format and remain at Cambridge Crops, Inc.

Applicant/Sponsor



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Author:
Name:



Title: General Counsel, Cambridge Crops, Inc.

Date: March 18, 2020

Expert Review Statement

I assisted the Cambridge Crops team with the design of the study outlined in this report. Together, we worked on developing the protocols based off of the Ofori-Anti *et al.* (2008) publication. I did not conduct the study in my laboratory. I did observe the results and was given a chance to view the SDS-PAGE gel as shown in the Figures in Section 8. I have reviewed this paper and agree with the conclusions made by the Cambridge Crops team.

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Records Retention: All study specific raw data and a copy of the final report will be retained at Cambridge Crops, Inc.

Signature of Final Report Approval:

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03/18/2020
Date

SUMMARY

The silk fibroin protein used in this study was produced and supplied by Cambridge Crops, Inc. of Somerville, MA. The protein is derived from silkworm (*Bombyx mori*) cocoons and is comprised of three chains: the light chain, heavy chain (UniProt P05790), and glycoprotein P25. The silk fibroin test material used in this study was provided in its solid, powdered form.

The silk fibroin was subjected to digestion based on the protocol in Ofori-Anti *et al.* (2008)¹ with minor modifications. The time to reach 90% digestion of the protein by pepsin was estimated as the first sample time having less than 10% residual protein compared a non-digested sample. A limit of detection study was performed prior to digestion to ensure that 10% residual protein was detectable using SDS-PAGE and Coomassie blue staining. Due to the methods used during processing, the silk fibroin used in these studies appears as smear on SDS-PAGE. Pepsin was diluted in simulated gastric fluid (SGF) with an adjusted pH to 2.0. The pepsin solution was tested for proteolytic activity by digestion of silk fibroin within 24 hours of each assay day. The mass ratio of pepsin to silk fibroin preparation was adjusted to achieve 10 units of pepsin activity per microgram of total protein in solution. Digestions were performed at 37°C under timed conditions. Samples of the digestion mixtures were removed and neutralized at various time points from 2 minutes seconds to 60 minutes and samples of each were electrophoresed in SDS-PAGE and stained with Coomassie blue to evaluate digestion completeness.

The results of this study demonstrated that silk fibroin protein is rapidly digested in pepsin at pH 2.0 at a ratio of 10 units pepsin per microgram silk fibroin. The SDS-PAGE Coomassie blue gel staining method demonstrated that over 90% of the silk fibroin protein was digested in less than two minutes.

No degradation bands were found to result from digestion of the silk fibroin. Therefore, our conclusion is that silk fibroin is rapidly digested at a ratio of 10 units pepsin per microgram silk fibroin in pepsin at pH 2 and that no pepsin-stable fragments were identified in the assay. Based on Codex (2003) guidelines for the allergenicity assessment, there is no added concern of risk based on stability of silk fibroin in pepsin.

¹ Ofori-Anti, A.O., Ariyaratna, H., Chen, L., Lee, H.L., Pramod, S.N., Goodman, R.E. (2008). Establishing objective detection limits for the pepsin digestion assay used in the assessment of genetically modified foods. *Reg. Toxicol. Pharmacol.* 52:94-103.

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1. Introduction

Cambridge Crops, Inc. of Somerville, MA has developed a shelf-life extension technology using silk fibroin derived from the cocoons of *Bombyx mori* as the primary ingredient. Cambridge Crops performed tests in order to determine whether there is a risk of food allergy associated with the consumption of the protein. This report describes the rationale, test methods, and results pertaining to an *in vitro* digestion assay intended to provide data indicative of potential risks of food safety.

The *Codex Alimentarius* Commission guidelines for assessing the allergenicity (2003) recommends assessing the introduced protein for stability in pepsin at acidic pH using standard conditions as an assay to help evaluate whether the introduced protein is likely to either increase the rate of sensitization or increase the likelihood of eliciting an allergic response in food allergic consumers. The pepsin stability assay is one study in a weight of evidence approach intended to assess the potential allergenicity (Codex, 2003). The test method for the assessment was first described by Astwood *et al.* (1996). The assay is not meant to predict whether a given protein will always be digested in the stomach of the human consumer, but the assay does provide a simple *in vitro* correlation to evaluate protein digestibility. Investigation of proteins that have been tested suggest a marked positive predictive value that food allergens causing systemic reactions are relatively stable in the assay, while non-allergenic food proteins are typically digested relatively quickly (Bannon *et al.*, 2002). Purified porcine pepsin has been used to evaluate the stability of several food allergens and non-allergenic proteins in a multi-laboratory study that demonstrated the rigor and reproducibility in nine laboratories (Thomas *et al.*, 2004). Porcine pepsin is an aspartic endopeptidase with broad substrate specificity. Pepsin is optimally active between pH 1.2 and 2.0, but markedly less active at pH 3.5 and irreversibly denatured at pH 7.0 (Collins and Fine, 1981; Crevieu-Gabriel *et al.*, 1999). The assay is performed under standard conditions of 10 units of pepsin activity per microgram of test protein. The pure porcine pepsin protein used in this assay was purchased from VWR International, product 10791-836 (Lot # 18J2056015).

The digestion was performed at 37°C and samples are removed at specific times and the activity of pepsin is quenched by neutralization with carbonate buffer and LDS loading buffer, then heating to more than 85°C for 10 minutes. The timed digestion samples are separated by SDS-PAGE and stained with Coomassie blue to evaluate the extent of digestion. A review of the digestibility assay by Bannon *et al.* (2002) and by Thomas *et al.* (2004) indicates that most of the non-allergenic food proteins that have been tested are digested in around 30 seconds, while many major food allergens are stable, or produce pepsin-stable fragments that are visible for eight to 60 minutes in this assay.

Assay parameters used in this study included verification of pepsin activity, established limit of detection of the protein in the stained gel (at 10% total stainable protein) and use of an objective measurement of the time of digestion required to reach 90% digestion as described by Ofori-Anti *et al.* (2008). The activity of the pepsin in SGF was tested on each day of assay based on digestion of bovine serum albumin (BSA), as described by VWR, to ensure that it is within a tolerance interval reported by VWR for that lot of enzyme. The results of our activity assay fell within the acceptance criterion of the VWR certified activity at 1,000 activity units per mg of pepsin. A second important criterion included in our standard operating procedure (SOP) is an objective measured level of residual test protein (silk fibroin in this case) that must be reached in determining

the time of digestion. We defined the time of digestion required to achieve 90% reduction in stained band intensity as the time-point when the residual is less than or equal to 10% of the amount of test protein in the initial sample. To accomplish this, a serial dilution of test protein is run on the same SDS-PAGE and Coomassie blue staining system as the digested samples and are analyzed to evaluate a limit of detection (LOD). The LOD must be lower than 10% to perform the digestion assay. Details and results of the study are reported here.

2. Materials

2.1 Test Substance

The test substance for this study was silk fibroin isolated from the cocoons of the silkworm, *Bombyx mori*. The sample was manufactured by Cambridge Crops' production run 17-0202-042-P65.

2.2 Control Substance

The control substance for this study was bovine serum albumin (BSA), purchased from Prospec Bio (Catalog # PRO-422). BSA was used to confirm the pepsin activity indicated by the manufacturer (Difco™ Pepsin manufactured by BD Biosciences; Catalog # 215110; CAS Number 9001-75-6; purchased from VWR International).

2.3 Reference Substance

There was no reference substance used for this study. Analytical reference standards (e.g. molecular weight markers) used in this study were documented in the data and are described in this report.

2.4 Critical Analytical Reagents

- Pepsin (VWR International, Cat.# 10791-836, Lot# 18J2056015)
- SGF without pepsin: 35 mM HCl, 123 mM NaCl (adjusted to pH = 2)
- SGF with pepsin: 105 mg/mL pepsin dissolved in SGF (1.05×10^6 U/mL)
- Bovine serum albumin (BSA)
- Pepsin quenching solution: 0.7 M Na₂CO₃ (pH = 11)
- NuPAGE LDS Sample Buffer (4x) (Invitrogen, Cat.# NP0007, Lot# 2020067)
- PageRuler Prestained NIR Protein Ladder (ThermoFisher, Cat.# 26635, Lot# 00810782)
- NuPAGE 3-8% Tris-Acetate Protein Gels (Invitrogen, Cat.# EA0375BOX, Lot# 19072371)
- MOPS SDS Running Buffer (20x) (G Biosciences, Cat.# 786-926, Lot# 190511)
- InstantBlue Protein Stain (Expedeon, Cat.# ISB1L)

3. Test System

The test system for this study was an *in vitro* digestion model using pepsin in simulated gastric fluid (SGF). Standard Operating Procedures (SOPs) for preparation of the SGF, determination of the detection limit assay, pepsin activity assay, digestion assay, SDS-PAGE and gel staining are on record in the laboratory. The SGF preparation and digestion procedures were based on the methods described by Thomas *et al.* (2004) as modified by Ofori-Anti *et al.*, (2008).

The pepsin activity assay was based on the method described by Sigma Aldrich for determining the activity of pepsin. An appropriate mass of pepsin powder was dissolved in prepared SGF, pH 2.0 to provide 2 mg/ml. Acidified bovine serum albumin (2% mass to volume) was prepared and digestions to evaluate the labeled pepsin activity were performed in triplicate.

The amount of pepsin powder used to prepare SGF was calculated from the specific activity labeled on the product as 10,000 units /mg solid pepsin product. The assay was designed for fixed volumes and a fixed amount of test protein, so the amount of pepsin diluted in SGF is adjusted to provide the appropriate ratio of 10 units of pepsin activity per microgram test protein. Pepsin stock is dissolved in SGF at a concentration of 105 mg/mL (1.05×10^6 U/mL). In addition, a silk fibroin stock was made at 42 mg/mL in SGF. The digestion reaction mixture was made by mixing 1.43 mL silk fibroin stock solution and 570 μ L pepsin stock solution. This achieves the desired ratio of 10 units pepsin per microgram silk fibroin protein in 2 mL. The reaction mixture is placed in a preheated incubator at 37 °C and gently agitated at 120 RPM for the duration of the experiment.

Once the test protein solution was placed in the incubator (37 °C), 200 μ L aliquots were withdrawn at predetermined times (t = 0, 2, 5, 10, 20, 30, 60 min.) and added to test tubes containing a mixture of 70 μ L 0.7 M Na₂CO₃ (pH = 11) and 70 μ L 5x LDS buffer, for a total of 340 μ L. Upon addition of the test solution to the denaturing reagents (LDS buffer and Na₂CO₃), the samples are immediately heated in a water bath to 95 °C for 5 min. in order to halt digestion. Samples were allowed to cool to room temperature before running on SDS-PAGE at 350 μ g/well.

All samples from a single digestion were applied to wells of the same SDS-PAGE gel along with molecular weight markers, undigested test protein equivalent to the initial undigested test protein sample (t = 0 and 60 min.), and pepsin alone (t = 0 and 60 min.) to assess pepsin stability throughout the duration of the assay.

Samples were separated by electrophoresis, stained with InstantBlue Protein Stain, and images were captured using a Canon PowerShot SX540 camera. The stability of the protein was defined as the time required to achieve 90% digestion, which was estimated based on the shortest time-digested sample with a band intensity equal to, or less than the 10% undigested well in the LOD assay. Proteins with more than 10% stainable full-length protein band remaining at 60 minutes were considered stable. Proteins reduced to < 10% stainable band at 5 to 30 minutes were considered of intermediate stability. Proteins reduced to < 10% stainable band by 2 minutes were considered labile (rapidly digested).

3.1 Justification for Selection of the Test System

In vitro digestion models are used commonly to assess the digestibility of ingested substances. Previous studies have used this simple, *in vitro* assay to evaluate potential risk of food allergy, and demonstrated that stability in pepsin is a risk factor for food allergy, which might be related to initial sensitization or to elicitation once the individual is sensitized (Astwood *et al.*, 1996 and del Val *et al.*, 1999). The FAO/WHO (2001) suggested conducting the pepsin digestion assay at pH 1.2 and pH 2.0. In this analysis, digestion was performed at pH 2.0 as a conservative approach as some authors have claimed a lack of predictive value for the digestion assay in pepsin at pH 1.2 (Fu *et al.*, 2002; Yagami *et al.*, 2000). However, Bannon *et al.* (2002) reviewed a broad range of published representative pepsin digestion studies and found a strong positive predictive value when comparing the stability of allergenic and non-allergenic dietary proteins. As defined by Codex (2003), this assay measures the resistance of a test protein to proteolysis in a test tube system. It is not meant to be a stand-alone determinant in evaluating the potential allergenicity of proteins and is not intended to predict the fate of proteins in the digestive tract of consumers. The results are to be judged in a weight of evidence approach which should also include history of safe use, sequence identity matches to known allergens, and abundance of the protein in food material.

3.2 Experimental Controls

Controls in this study were meant to ensure assay reliability and include:

- Measurement of the activity of pepsin in SGF
- Evaluation of the sensitivity of the staining properties of the test protein from serially diluted samples via SDS-PAGE
- Inclusion of samples of pepsin without test protein at t = 0 and 60 min. to determine whether any stainable protein bands observed in digestion samples with test protein are from the test protein, contaminants in pepsin, or from pepsin autocatalysis
- Inclusion of protein in SGF without pepsin at times zero and over 60 minutes to evaluate the effect of acid and heat alone.

4. Detailed Study Methods

This study evaluated the stability of silk fibroin, derived from the cocoons of *Bombyx mori*, in pepsin in SGF at pH = 2. Several control steps were performed to ensure study validity. A detailed description of the study is presented here. Laboratory records and protocols are on file at Cambridge Crops, Inc. in Somerville, MA and may be made available upon request.

4.1 Verification of Detection System and Sensitivity

A dilution series of test sample was prepared with sample quantities loaded in SDS-PAGE gel using 4x LDS buffer, covering a range from 100% total protein per well (350 µg) to 1% total protein per well (3.5 µg). Following electrophoresis, the gels were stained with InstantBlue (Coomassie) for at least 2 hours. The gels were washed with deionized water three times until the background was clear. The image was captured using Canon PowerShot SX540 camera.

4.2 Preparation of SGF Plus Pepsin

The simulated gastric fluid (SGF) was prepared by mixing 1.75 mL 1.0 M HCL with 48.25 mL diH₂O and then adding 359.4 mg NaCl. This achieves a final SGF solution concentration of 35 mM HCl and 123 mM NaCl. The activity of pepsin purchased from VWR International was verified to be 10,000 U/mg. A stock pepsin solution was prepared by adding 1.05 g pepsin to 20 mL SGF. This achieves a final pepsin stock concentration of 105 mg/mL (1.05×10^6 U/mL). After thoroughly dissolved and mixed, the pepsin solutions were stored at 4°C and assayed for activity and used within 24 hours.

4.3 Pepsin Activity Assay

The activity of pepsin was verified with Bovine Serum Albumin (“BSA”) to ensure the activity units claimed by the vendor. This product has a labeled activity of 10,000 units per mg of solid material. Enzymatic activity assay protocol from Sigma Aldrich was followed (3.4.23.1, <https://www.sigmaaldrich.com/technical-documents/protocols/biology/enzymatic-assay-of-pepsin.html>). The SGF plus pepsin was freshly prepared and stored at 4°C before use. The procedure was performed as follows:

4.3.1 A solution of 25% bovine serum albumin was prepared by 25 mg/mL BSA in SGF.

4.3.2 1 mL of BSA solution (2%) was aliquoted into 4 tubes to achieve final concentrations of 2 tubes at 20 mg/mL and 2 tubes at 40 mg/mL.

4.3.3 350 µL of pepsin quenching solution (carbonate buffer) and 70 µL 5x LDS reducing buffer were added to each tube described in **4.6.1**.

4.3.4 Digestion and control samples were prepared:

4.3.4.1 200 µL pepsin stock solution is added to each solution in 4.3.2. The mixture was immediately placed in a preheated incubator (37°C) and agitated at 120 RPM to start the digestion of test sample. 200 µL aliquots from this sample were added to tubes.

4.3.4.2 200 µL pepsin stock was added to 1 mL SGF. The mixture was immediately placed in a preheated incubator (37°C) and agitated at 120 RPM to start the digestion of test sample. 200 µL aliquots from this sample were added to tubes labeled P0 and P30 at t=0 and t=30 min., respectively.

4.3.4.3 The absorbance at 280 nm was measured on a spectrophotometer (Spectramax-100). The activity units of pepsin per mL were calculated as the mean net absorbance ($A_{280 \text{ nm BSA}} - A_{280 \text{ controls}}$) multiplied by a conversion factor of 1,000 to yield units of activity per mg of solid pepsin.

4.4 Control Protein Digestions (BSA).

Bovine serum albumin (BSA) digestion assays were tested as control proteins to verify the appropriate activity of the test system.

4.5 Protein Digestion

Silk fibroin protein powder was stored at 4° C until immediately before use in the following digestion assay.

4.5.1 Sample Tube Preparation: 1.5 mL centrifuge tubes were labeled at P0, P60, D0, D2, D5, D10, D20, D30, D60, F0, F60.

4.5.2 70 µL of pepsin quenching solution (carbonate buffer) and 70 µL 5x LDS reducing buffer were added to each tube described in **4.6.1**.

4.5.3 Digestion and control samples were prepared:

4.5.3.1 1.43 mL (equivalent to 60 mg) fibroin stock solution was added to 570 µL pepsin stock solution. The mixture was immediately placed in a preheated incubator (37°C) and agitated at 120 RPM to start the digestion of test sample. 200 µL aliquots from this sample will be added to tubes labeled D0, D2, D5, D10, D20, D30, D60 (e.g. D2 at 2 min., D30 at 30 min).

4.5.3.2 1 mL pepsin stock was added to 1 mL SGF. The mixture was immediately placed in a preheated incubator (37°C) and agitated at 120 RPM to start the digestion of test sample. 200 µL aliquots from this sample will be added to tubes labeled P0 and P60 at t=0 and t=60 min., respectively.

4.5.3.3 1.43 mL (equivalent to 60 mg) fibroin stock solution is added to 570 µL pepsin stock solution. The mixture was immediately placed in a preheated incubator (37°C) and agitated at 120 RPM to start the digestion of test sample. 200 µL aliquots from this sample will be added to tubes labeled F0 and F60 at t=0 and t=60 min., respectively.

4.5.4. Upon addition of the sample aliquots to the quenching solution, samples were vortexed and heated in a water bath to 95°C for 5 min. in order to halt digestion. Samples were allowed to cool to room temperature before running on SDS-PAGE at 350 µg/well.

4.6 SDS-PAGE Gel

All samples on any one gel were from a single digestion experiment. NuPAGE 3-8% Tris-Acetate Protein gels were used with NuPAGE MOPS SDS Running Buffer.

4.6.1 20 µL of each sample was loaded per well, with a final protein load of 350 µg/well.

4.6.2 5 µL of PageRuler Prestained NIR Protein Ladder is loaded to the outermost wells

4.6.3 Electrophoresis was accomplished at a constant 120 V for 1.5 hrs.

4.6.4 Gels were stained for a minimum of 2 hours in InstantBlue (Coomassie), as detailed by the supplier, Expedeon.

4.7 Image Analysis

The de-stained gels were visualized by placing the gel on a lightbox (Porta-Trace, Cat.# LYSB00U6KPXAG) and capturing an image with a Canon PowerShot SX540 camera. The raw image was saved as an archival file.

5. Results & Discussion

5.1 Limit of Detection

The stained gel of the dilution series of total protein (Figure 1) demonstrated a clear pattern of stepwise reduced intensity of stained bands with each step in the dilution series. The minimum amount of protein that was detectable was 10 µg, equivalent to roughly 3% of the highest concentration (350 µg).

5.2 Pepsin Activity

The certified activity of the lot of pepsin from VWR International used in this study was labeled as 10,000 units per mg solid.

5.3 Control Substance Digestion Results

Stained gels of digestion tests of BSA (Figure 2) demonstrated that at both ratio of 10 units and 1 unit of pepsin activity per activity per 1 µg of test protein, BSA was digested rapidly within the SGF plus pepsin test system with more than 10% visually stainable full-length protein band remaining at 30 minutes. These results with 1 and 10 units with BSA are consistent with results from previous tests (Ofori-Anti, A.O. 2008), which demonstrates the reproducibility of this SGF plus pepsin test system.

5.4 Silk Fibroin Protein Digestion Results

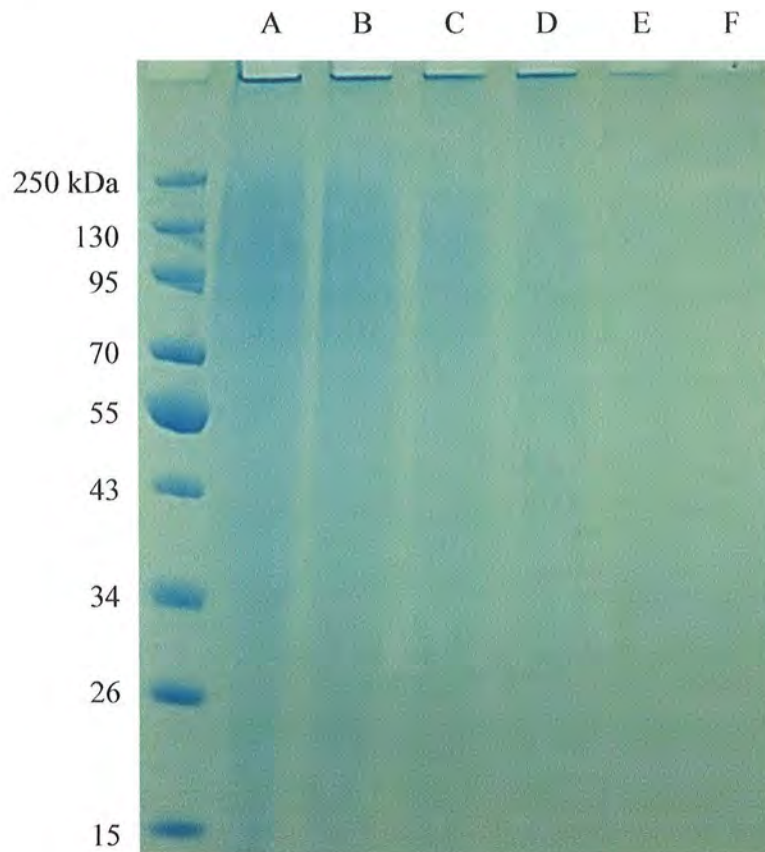
Digestion of the test protein, silk fibroin, was conducted at pH 2 at the ratio of 10 units pepsin per 1 µg test protein (Figure 3). A stained gel of this digestion experiment demonstrated that silk fibroin was stable in acid alone but was rapidly digested by pepsin in under 2 minutes (Lane B) to below the detectable band intensity of the 3% undigested protein from the LOD assay (Figure 1, Lane E).

6. Conclusions

The results of this study demonstrated that the silk fibroin test protein was rapidly digested after incubation in SGF plus pepsin at 37°C at a ratio of 10 units pepsin per 1 µg test protein within 2 minutes based on InstantBlue Coomassie staining detection.

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8. Figures**Figure 1**

InstantBlue Coomassie stained SDS-PAGE gel showing serial dilution of silk fibroin starting from 100% total protein used in digestion.

Lane	Description	Protein Content
A	100% total protein	350 µg silk fibroin
B	57% total protein	200 µg silk fibroin
C	29% total protein	100 µg silk fibroin
D	14% total protein	50 µg silk fibroin
E	3% total protein	10 µg silk fibroin
F	1% total protein	3.5 µg fibroin

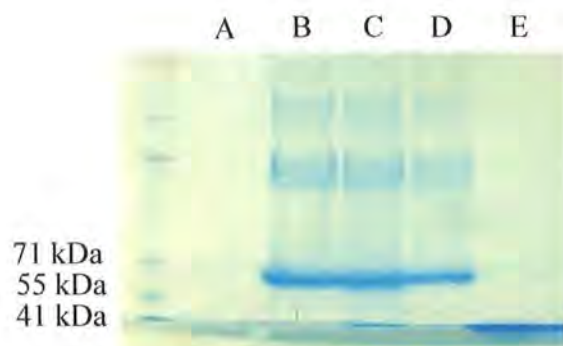


Figure 2

InstantBlue Coomassie stained SDS-PAGE gel showing the digestion of bovine serum albumin (BSA) in simulated gastric fluid at the ratio of 10 units per μg protein (pH 2.0) to measure pepsin activity. BSA was loaded at 1.47 μg per lane.

Lane	Description	Incubation time
A	Experimental control (BSA 1 mg/ml)	0 min
B	BSA in SGF (2%)	0 min
C	BSA+pepsin quenched	0 min
D	BSA (1%)+pepsin (quenched)	0 min
E	BSA + pepsin	30 min

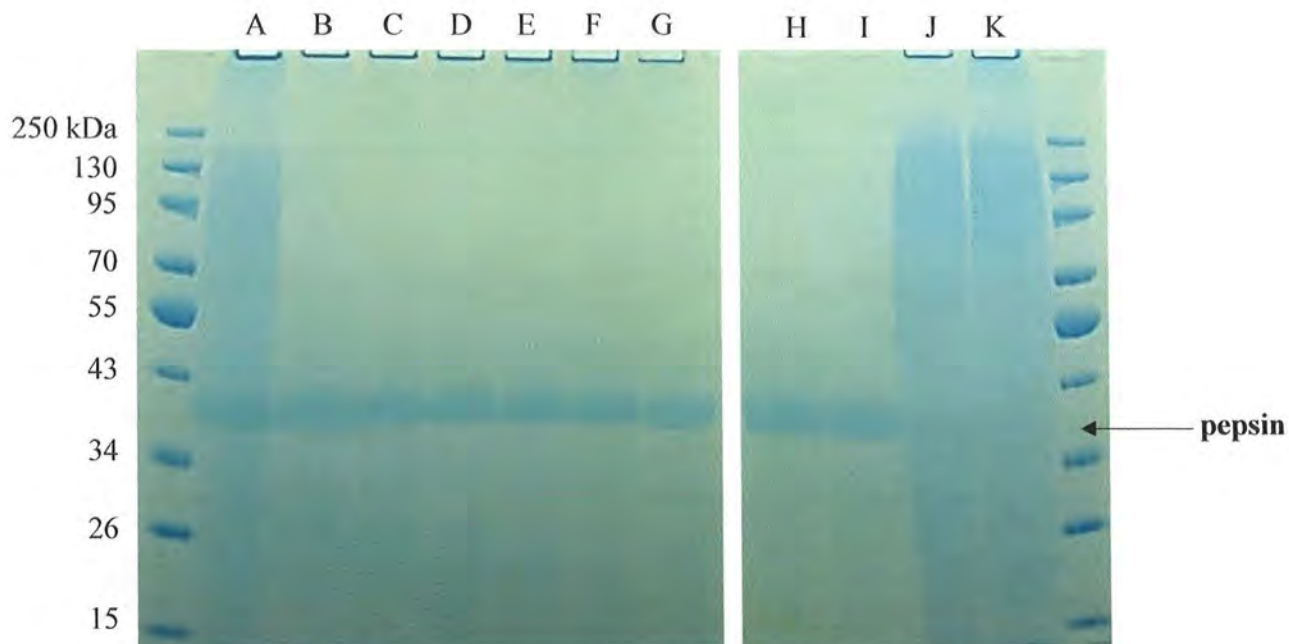


Figure 3

InstantBlue Coomassie stained SDS-PAGE gel showing the digestion of silk fibroin in simulated gastric fluid at the ratio of 10 units per 1 μ g protein (pH 2.0). Silk fibroin was loaded at 350 μ g per lane.

Lane	Description	Incubation time
A	Silk fibroin plus pepsin in SGF	0 min.
B	Silk fibroin plus pepsin in SGF	2 min.
C	Silk fibroin plus pepsin in SGF	5 min.
D	silk fibroin plus pepsin in SGF	10 min.
E	Silk fibroin plus pepsin in SGF	20 min.
F	Silk Fibroin plus pepsin in SGF	30 min.
G	Silk fibroin plus pepsin in SGF	60 min.
H	Control: Pepsin in SGF	0 min.
I	Control: Pepsin in SGF	60 min.
J	Control: Silk fibroin in SGF	0 min.
K	Control: Silk fibroin in SGF	60 min.

From: [Eischeid, Anne](#)
To: [West-Barnette, Shayla](#)
Subject: FW: Cease to Evaluate Request GRN 930
Date: Wednesday, March 24, 2021 11:38:38 AM

Hi Shayla,

Please see below. Notifier wants to know if they can review the cease to evaluate letter before it is issued: can they? I have not yet responded and will wait until you confirm so I can let them know.

Thanks,
Anne

From: Laith Abu-Taleb <laith@mori.com>
Sent: Monday, March 22, 2021 7:33 PM
To: Eischeid, Anne <Anne.Eischeid@fda.hhs.gov>
Cc: Joseph V Rodricks <JRodricks@ramboll.com>; Pelonis, Evangelia C. <pelonis@khlaw.com>; Gavin P Thompson <gthompson@ramboll.com>; Cassie Huang <CHUANG@ramboll.com>; Adam Behrens <adam@mori.com>
Subject: [EXTERNAL] Cease to Evaluate Request

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Dr. Eischeid,

We hope this message finds you doing well.

This email follows up on the discussion we had with you and your team on February 16. Based on this discussion we have decided to request that FDA cease to evaluate GRAS Notice 930, which was filed on July 10, 2020. We are making the request based on our understanding that FDA, after reviewing the information in the GRAS Notice, agrees there is no safety concern with silk fibroin.

That said, we understand that the FDA would prefer that we submit a new and revised GRAS Notice for silk fibroin after certain safety information is published in a peer reviewed scientific journal. To that end, we thank you for your discussion with us on types of peer-reviewed journals that are acceptable.

We are happy to report that the Journal of Food and Chemical Toxicology accepted our article "Toxicological assessment and food allergy of silk fibroin derived from *Bombyx mori* cocoons" for publication on March 8. (*Yigit, S. et al., Toxicological assessment and food allergy of silk fibroin derived from *Bombyx mori* cocoons. Food and Chemical Toxicology, 112117. <https://doi.org/10.1016/j.fct.2021.112117>, 2021).*

Thus, we will be submitting a new and updated GRAS Notice for silk fibroin soon with

reference to this published article. We understand that the publication, in addition to our reported scientific talks given to the food-safety community, will fully address the general recognition and public availability concerns expressed by the Agency. On February 16, 2021, we also discussed a request by FDA to update the exposure estimate to make it more precise regarding which product categories were associated with the highest use level. This updated exposure estimate will also be included in the new GRAS Notice. Finally, the new GRAS Notice will also include the additional information that has already been submitted to FDA in the amendment dated November 18, 2020. This information was submitted in response to questions from FDA raised in calls dated September 15, 2020 and October 29, 2020.

It is our understanding that the cease to evaluate letter will note that FDA does not find any specific safety issues with silk fibroin for its intended use but has two remaining concerns with GRN 930: (1) certain safety information was not yet publicly available to achieve general recognition of safety at the time of submittal and (2) the exposure estimate needs to be updated to address which product categories are intended to be used at the highest levels of use. If at all possible, we would appreciate an opportunity to see a copy of the cease to evaluate letter before it is issued.

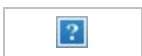
Once again, we sincerely thank you for your time. Looking forward to speaking with you again shortly.

Best regards,
Laith

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