

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

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INTRODUCTION

The commercial grade finished product of SC-18862, a dipeptide ester sweetening agent, may contain from 0-2% of a conversion product, SC-19192. This conversion product is also produced from SC-18862 spontaneously under various laboratory conditions. The human population consuming SC-18862 would also be exposed to varying concentrations of SC-19192. Hence, the preclinical testing of SC-19192 for its potential toxicity was performed. In this toxicity study SC-19192 was administered to young albino rats of both sexes orally in the diet for 115 consecutive weeks. It was the intent of the study to evaluate the safety and tumorigenic potential of SC-19192, and to induce and define such adverse effects as might occur only at prodigious multiples of the estimated daily human intake.

METHODS

Material evaluated.

SC-19192 is a fine white powder with the chemical name 5-benzyl-3, 6-dioxo-2-piperazine-acetic acid. Twelve lots [1R A6906, 4R Drog IV-236B,

2R Drogst IV-232A, 2R Drogst IV-232B, 4R Drogst IV-236A, 3R A-7273, 3R IV-233B, 2R IV-232C, 2R A-7274, 6R JDR 5-30A (A9805), 5R JD 5-18A (A9129), 7R JDR 5-30B (A9829)] were used throughout this study.

Animals, housing and diet.

Three hundred and sixty weanling albino rats, 180 of each sex, of the Charles River CD strain were employed. They were housed individually in suspended wire mesh cages, acclimated to the laboratory environment for one week and placed on treatment at the age of four weeks. The basal diet consisted of Rockland Rat/Mouse Diet (complete), Teklad, Inc. for the first 62 weeks and thereafter Purina Rat Chow, from Ralston Purina Co., St. Louis, was employed. Powdered basal diet with or without the test compound added was fed throughout the study. Chlorinated tap water was available ad libitum. Animal quarters were air-conditioned with thermostats set to maintain room temperature at 72°F continuously; artificial fluorescent lighting was provided for a 12 hour continuous daily photoperiod.

Experimental design.

Animals were separated according to sex and assigned individual cages by the complete randomization design¹. For technical convenience, six groups per sex of 30 rats each were employed; initiation of treatment for the 12 housing sections was staggered over a 2 week period. Each group was further subdivided into dosage groups of 12 control and six treated animals as follows:

Treatment Group	Dosage g/kg/day	Multiples of Estimated Daily Human Dose*	No. of Rats Per Group		Total Rats 6 Groups
			M	F	
Control	0	--	12	12	144
Low	0.75	100	6	6	72
Medium	1.5	200	6	6	72
High	3.0	400	6	6	72

* Based on estimated maximum daily human intake of 7.5 mg/kg orally (assumes 25% decomposition of 30 mg/kg/day intake of SC-18862 to a 27 kg human).

Statistical procedures.

The calculations at each measured time period were based on a treatment group size of six. In cases where there were missing values, the treatment group mean was substituted. An exception to this is the analysis of body weight, food consumption, and autopsy data where data from all survivors was used in the calculations. The data base per group varies with the attrition rate. The mean values are shown in the tables. Each treatment mean was compared to the control mean. The statistically significant differences were determined by use of the calculated Least Significant Difference.^{1a} This statistic is based on the Student's t-value and the pooled mean square (pooled over treatment groups). In cases where the difference between a treatment mean and control mean, disregarding the sign, is greater than the Least Significant Difference, the difference is statistically significant at the 5% level. These cases are designated by asterisks in the tables.

Tumor incidence was evaluated by the method of Sachs^{1b} life table technique and the adjusted tumor index was tested for significance using Chi square.

All statistical analyses were performed by Dr. J. Dutt and staff, Mathematical and Statistical Services Department, G. D. Searle & Co.

Administration of test material.

Treated groups were fed diets prepared by incorporating SC-19192 into the basal diet on a w/w basis with thorough dry mixing in a Hobart Model VCM-40 mixer. Fresh diets were prepared weekly for the first four weeks, once every two weeks for the next 12 weeks and once each month thereafter.

Fresh diet was continuously available in individual feeder jars. Group dosage calculations were made from group mean body weight and group mean food consumption determinations performed periodically. Food spillage by individual animals was recorded at these intervals and food consumption data from the rats that spilled was not used for dosage calculations.

Physical examinations and observations.

Animals were observed daily for survival. General posture, locomotion, behavior, level of motor activity and external appearance of pelage, teeth and body orifices were evaluated prior to the initiation of compound administration and concurrent with the body weight measurement during the study. Individual body weights were recorded weekly for the first four weeks, once every two weeks for the next 8 weeks and once every four weeks thereafter. Ophthalmoscopic exams (direct and/or indirect) were performed by Dr. E. Youkilis. All rats were examined initially prior to treatment and again at periodic intervals during the study.

Clinical laboratory procedures.

Hematologic, clinical chemical and urinalysis examinations were performed periodically on one group of 48 rats, containing 6 males and 6 females from each dosage group. Blood specimens were collected from unfasted ether-anesthetized rats via the jugular vein at all intervals. The same rats were employed for all clinical laboratory examinations throughout the study; in cases where an animal employed for clinical lab workup died during the study, another rat randomly chosen from a corresponding group was substituted.

Hematology. Tubes containing sodium EDTA or sodium citrate were employed for the hematology or coagulation parameters, respectively. The following parameters were measured at treatment days 42, 92, 189, 364, 547 and 734.

<u>Parameter</u>	<u>Method</u>
Hematocrit	Micro method ²
Hemoglobin	Cyanmethemoglobin ³
Total RBC Count	Coulter Counter ⁴
Total WBC Count	Coulter Counter ⁴
Differential WBC Count	Smear ⁵
Prothrombin Time	Quick ⁶

Clinical chemistry. Determination of the following parameters was made on serum separated from blood after clotting:

<u>Parameter</u>	<u>Treatment Interval (Days)</u>	<u>Method</u>
Glutamic pyruvic transaminase	42,92,189,364,547,734	Russel & Cotlove ⁷
Glutamic oxaloacetic transaminase	42,92,189,364,547,734	Russel & Cotlove ⁷
Alkaline phosphatase	42,92,189,364,547,734	McComb & Borvers ⁸
Total bilirubin	42,92,189,364,547,734	Jendrassik and Grof ⁹
Glucose	42,92,189,364,547,734	Frings <u>et al</u> ¹⁰
Blood (serum) urea nitrogen	42,92,189,364	Marsk <u>et al</u> ¹¹
Total cholesterol	42,92,189,364,734	Levine <u>et al</u> ¹²
L-phenylalanine	42,92,189,364,547,734	Hill <u>et al</u> ¹³
Sodium	734	Willis ¹⁴
Potassium	734	Willis ¹⁴
Calcium	734	Pylrus <u>et al</u> ¹⁵
Protein electro- phoresis	734	Cellulose acetate ¹⁶

Urinalysis. Urine specimens were collected on treatment days 42, 92, 190, 364, 547 and 734 from unfasted rats housed individually in metabolism cages for 2-4 hours. The parameters were measured as listed on the next page:

<u>Parameter</u>	<u>Method</u>
Specific gravity	Total solids meter
pH	Bili-Labstix (Ames)
Occult blood	Bili-Labstix (Ames)
Protein	Bili-Labstix (Ames)
Glucose ⁺	Bili-Labstix (Ames)
Ketones ⁺	Bili-Labstix (Ames)
Bilirubin	Bili-Labstix (Ames)
Microscopic on spun sediment	Light microscopy
Urobilinogen ⁺⁺	Urobilistix (Ames)
Phenylketones	Phenistix (Ames)

⁺ Not measured on treatment day 547.

⁺⁺ Not measured on treatment days 92, 734.

Postmortem examination procedures.

Rats found dead during the study were autopsied immediately whenever possible. In cases where the necropsy could not be performed promptly, the thoracic and abdominal cavities of dead rats were opened and the entire animal was immersed in neutral buffered formalin fixative for subsequent gross examination and dissection.

At study termination all survivors (unfasted) were selected at random, anesthetized with ether, and exsanguinated via the abdominal aorta. Animals killed in extremis and by design were immediately autopsied, and entire organs or representative tissue blocks from stomach, small (duodenum, jejunum) and large intestine, lung, heart, liver, kidney, spleen, pancreas, pituitary, thyroid-parathyroid, adrenal, ovary, uterus, vagina, testis, ventral and

dorsal prostate, seminal vesicle, mammary gland, urinary bladder, lymph node (mesenteric), nerve (brachial plexus), brain, spinal cord, bone with marrow (rib junction), bone marrow smear, salivary gland (submax.), and eye (right) were removed following gross examination. Underlined organs were weighed fresh only in animals killed by design or in extremis; organs from animals found dead were not weighed. Tissues were submitted for processing unless severely autolyzed.

Pituitary and eye were fixed in Zenker's acetic solution; all other tissues were fixed in cold neutral buffered formalin. Representative blocks of the above fixed tissues from control and treated groups were embedded in paraffin, sectioned and stained with hematoxylin-eosin.

Tissue specimen selection for microscopic evaluation:

Stomach - One sagittal section encompassing forestomach, fundus and pylorus.

Liver - One section each from left and right lateral lobe.

Lung - One section from right middle lobe.

Kidney - One transverse section from each kidney.

Heart - One section through the mid-ventricles.

Ovary and Testis - One section from each organ, bilaterally.

Mammary gland - One section from right 4th and 5th glands.

Brain - Seven coronal sections representing all major neuro-anatomic areas of the brain were evaluated. The fixed brain was cut in five coronal slices measuring approximately 4 mm in thickness which were numbered 1 through 5, and embedded in paraffin. Two microscopic sections each were cut at different levels from block 3 (optic chiasma) and block 5 (midportion of cerebellum with trapezoid body); one section each was cut from blocks 1, 2 and 4.

Urinary bladder - Fixed urinary bladder was bisected longitudinally and both hemispheres were embedded in one paraffin block. Two sections at different levels (4 levels in all) were examined.

One representative section was examined microscopically from each of the other organs listed. In addition, each usual or unusual lesion observed grossly was processed for microscopic evaluation.

All tissues examined microscopically are listed in Table 10.

Additionally, tissue blocks from heart, liver, kidney and adrenal of survivors were frozen in liquid nitrogen and stored at -94°F for subsequent processing, if indicated. Air dried smears of femoral marrow in fetal calf serum were stained with Romanowsky stain and stored for subsequent use if needed to supplement marrow sections.

RESULTS

Physical and behavioral signs.

Throughout the study, there was no evidence of a compound effect with regard to physical appearance and behavior among the rats at any treatment level.

Signs of aging commonly observed in laboratory rats of the Charles River strain occurred at a low or moderate incidence during the first year and with gradually increasing frequency during the second year of the study. These signs were noted at a comparable rate in both treated groups as well as in the control group; they included hunched appearance, roughening of the fur coat, desquamation of the tail, sores on all parts of the body, particularly on the tail, localized alopecia on extremities and body, stains on the fur coat or urine stains on the abdominal fur seen more commonly in males than in females, and soft feces. During the second year, the number of animals showing respiratory signs, characterized by labored respiration, wheezing, etc., increased at a comparable rate in all treated groups, as well as in the control group.

An unidentified infectious disease spread among the animals between 12 and 14 weeks of treatment. Control and treated animals were affected with equal frequency and severity. Many of the affected animals exhibited a swollen neck, primarily related to enlargement of the submaxillary glands. Eyes of affected animals were bulging, appeared red, and exhibited moderate lacrimation. The above symptoms were suggestive of a virus infection of the salivary and Harderian glands, sialodacryoadenitis similar to that described by Innes and Stanton (1961)¹⁷. All affected animals recovered within two weeks.

Another unidentified infectious disease occurred in high incidence between 48 and 52 weeks of treatment. Again, the control and treated rats were affected with equal frequency and severity. Many animals in all groups were morbid. Affected animals exhibited anorexia, loss in weight, labored respiration and dyspnea. Non-survivors exhibited moderate to severe pneumonia, histologically. To prevent further loss of animals, all morbid rats were injected IM with 20,000 units of potassium penicillin G (Pfizerpen, Pfizer, Inc.) daily for 4-8 days. This empirical measure reduced the lethality and morbidity among animals. All affected animals surviving recovered in about two weeks. Over a period of two weeks, a total of 17 animals (8 control; 3 low dose; 4 medium dose and 2 high dose animals) died.

Survival rate. Survival data are presented in Table 1.

No detrimental compound-induced effect on the survival rate was observed in any of the groups throughout the treatment period. However, a significant increase in survival rate was observed in the medium and high dose groups at some intervals, as indicated in Table 1.

Ophthalmoscopic examination. Individual ophthalmoscopic findings are presented in the Appendix. A summary of these findings is listed in Table 2.

Ophthalmoscopic examinations performed periodically on all surviving rats revealed no evidence of any compound-related alterations in any of the treated groups. In general the ophthalmoscopic findings observed in this study are consistent with "expected" changes as a result of the aging process. The nature, incidence and severity of lesions observed are comparable between the control and all treated groups.

Table 1

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Survival Data

Weeks of Treatment	MALES								FEMALES							
	Incident+				%				Incident+				%			
	C	L	M	H	C	L	M	H	C	L	M	H	C	L	M	H
40	72/72	36/36	36/36	36/36	100	100	100	100	71/72	35/36	36/36	36/36	99	97	100	100
46	70/72	36/36	36/36	36/36	97	100	100	100	71/72	35/36	36/36	36/36	99	97	100	100
52	65/72	33/36	33/36	35/36	90	100	100	97	71/72	35/36	34/36	35/36	99	97	94	97
60	64/72	33/36	31/36	35/36	89	92	86	97	71/72	34/36	34/36	35/36	99	94	94	97
68	63/72	33/36	31/36	35/36	86	92	86	97	71/72	33/36	34/36	35/36	99	92	94	97
76	59/72	32/36	31/36	35/36	82	89	86	97*	69/72	32/36	34/36	34/36	96	89	94	94
84	54/72	31/36	29/36	33/36	75	86	81	92	63/72	31/36	34/36	33/36	88	86	94	92
88	52/72	28/36	29/36	32/36	72	78	81	89	60/72	31/36	33/36	32/36	83	86	92	89
92	47/72	26/36	29/36	27/36	65	72	81	75	57/72	29/36	28/36	31/36	79	81	78	86
96	42/72	26/36	28/36	25/36	58	72	78	69	53/72	28/36	28/36	29/36	74	78	69	81
100	35/72	23/36	26/36	24/36	49	64	72*	67	43/72	25/36	25/36	27/36	60	69	69	75
104	33/72	22/36	26/36	21/36	46	61	72*	58	37/72	23/36	23/36	26/36	51	64	64	72
108	26/72	19/36	23/36	20/36	36	53	64*	56	37/72	20/36	21/36	25/36	51	56	58	69
115	19/72	16/36	19/36	18/36	26	44	53*	50	25/72	15/36	16/36	21/36	35	42	44	58*

+No. survivors/no. animals on study.

*Mean differs significantly from control ($p < 0.05$).

Table 2

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Ophthalmoscopic Findings

Diagnosis	Treatment Group and Weeks of Treatment															
	Control				Low Dose				Medium Dose				High Dose			
	27-31	52	76-79	97-98	27-31	52	76-79	97-98	27-31	52	76-79	97-98	27-31	52	76-79	97-98
MALES																
Corneal Haziness																
Bilateral		1/65		4/35				1/23	2/33			2/26	1/36	2/35		3/24
Left only		2/65		3/35	2/33			1/23	1/33			1/26	1/36	1/35		1/24
Right only								2/23	1/33			1/26		1/35		1/24
Corneal Scar																
Bilateral				1/35												
Left only				2/35								1/26				
Right only		1/65						1/23								
Iris: Anterior																
synechiae (L)												1/26				
Iris: Iris filament																
Adherent to cornea														1/35		1/24
Lens: Cortical opacity																
Bilateral								1/23								
Left only	1/72	2/65		3/35				1/23				2/26				2/24
Right only				2/35				2/23				1/26				1/24
Lens: Y sutures																
Bilateral				2/35				2/23				1/26				1/24
Right only								1/23								
Lens Posterior																
Subcapsular opacity																
Bilateral					1/33			1/23	1/33			1/26				
Right only				2/35										1/35		2/24
Left only	2/65											1/26		1/35		
Eye: Palpebral													1/36	1/35		
hyperemia																

Table 2 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Ophthalmoscopic Findings

Diagnosis	Treatment Group and Weeks of Treatment											
	Control			Low Dose			Medium Dose			High Dose		
	27-31	52	76-79	97-98	27-31	52	76-79	97-98	27-31	52	76-79	97-98
<u>MALES (cont.)</u>												
Eye: Chromodacryorrhea (L)		1/65		1/35								1/24
Eye: Palpebral inflammation												
Bilateral										1/36	1/35	
Left only										1/36		
<u>FEMALES</u>												
Corneal Haziness												
Bilateral	1/71	2/71		2/43		1/35			2/34	1/25	1/36	2/35
Left only		1/71		3/43								
Right only	3/71	3/71	1/69	3/43		1/35		2/25	1/34			1/27
Corneal Scar (L)												
Left only				1/43								
Iris: Synechiae (R)									1/34			1/27
Iritis									1/34			
Lens: Cortical opacity												
Bilateral				1/43								1/27
Right only				2/43				3/25				4/27
Left only				2/43				1/25				1/27
Lens: Y sutures (Bil.)				4/43			2/25			4/25		3/27
Lens: Subcapsular opacity												
Left only	1/71	1/71		1/43					2/34	2/34		
Right only									2/34		1/35	1/35

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Ophthalmoscopic Findings

[illegible]

Growth, food and compound consumption.

Group mean body weight, weight gain, food and compound consumption are presented in Tables 3 and 4 and Figures 1 and 2. A summary of statistically significant changes in the absolute body weight data, food intake data, and the concentration of SC-19192 in the diet are presented in Tables 2A, 2B and 4A, respectively.

Fluctuations in body weight gain were observed in the low and medium dose male groups during the first 84 days (12 weeks) of the study. Statistically significant decreases in absolute body weight mean values were observed in two of eight measurement intervals at the low dose, and three of eight measurement intervals at the medium dose level during this period. A statistically significant effect was not consistently present, however, at these dose levels. A statistically significant reduction was consistently present throughout this period in the high dose male group. By contrast, absolute body weights were unremarkable at all dose levels in the female groups during this same time interval.

Later in the study, notable alterations in body weight were apparent in other treated groups. A consistent statistically significant decrease in absolute body weight was observed in both low and medium dose male groups from treatment day 168 through 448, but was not present prior to or following this interval. In the females no consistent body weight changes were present at any time in the low dose group, but a statistically significant reduction was consistently present from treatment day 168 to day 558 in the medium dose group. Such an effect was absent prior to and after this interval, however. The high dose female group exhibited a significant decrease in body weight from treatment day 112 throughout the remainder of the study.

The changes in body weight gain (% change/week), in general, appear to be comparable in the control and treated groups of both sexes; although significant fluctuations (both increases and decreases) in weight gain were randomly observed in the treated groups throughout the study, no particular trend was apparent.

Significant changes, either increases or decreases, in absolute (g/day) or relative (g/kg/day) food intake were sporadically observed in all treated groups. No consistent pattern was apparent in any group prior to 196 days of treatment. From that point on, in the high dose male group only, food intake was consistently and significantly increased until day 644 (Table 2B). This consistent effect was not present in any other treated group, however.

Group mean values (g/kg/day) for compound ingestion (Table 4) over the entire 115 week treatment period were within roughly 10% of the proposed doses of 0.75, 1.5 and 3.0 g/kg/day of SC-19192. However, wide fluctuations in compound intake were observed in all the groups at various times during the study. This is to be expected when compound is administered through the diet, and animals are randomly distributed in a large number (12) of separate housing groups.

The concentration of SC-19192 in the diet of the treated groups was varied to achieve a relatively constant predetermined intake of compound per unit of body weight. SC-19192 concentration in the diet of various treated groups was relatively low (0.4-3.6%) during the first 3-4 months of the study. During that period, statistically significant differences in absolute body weight between treated and control groups were minimal and infrequent. Hence, during the early part of the study (up to 112 days), when the animals were growing and the concentration of SC-19192 in the diet was relatively low, the

caloric content of the various treated and control diets was most comparable. Under these conditions the absolute body weight of rats from treated groups was not affected particularly adversely.

In the latter part of the study, the SC-19192 concentration in the diets of the medium and high dose groups reached levels of 3.9 and 7.9%, respectively. However, with the exception of the high dose male group, the total food intake (absolute and relative) of control and all treated groups remained equivalent. Assuming that the SC-19192 dietary component is partially available as calorogenic material, it is apparent that each treated group received proportionately less calories per unit of diet than did the control group. In other words, diets were not isocaloric; the caloric value varied both among the various treated groups and also between treated and control groups. Since this study was oriented toward evaluation of tumorigenic potential rather than nutritional properties, and a paired-fed control group was not present, definitive conclusions regarding nutritional effects cannot be drawn. It would appear that food efficiency may be altered in the high dose male and female groups throughout much or all of the study. The significantly lower body weights observed sporadically or periodically at low or medium dose levels may well reflect a decreased caloric intake, however, rather than representing a direct effect of SC-19192.

Table 2A

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Summary of Presence and Direction of All Statistically Significant
Changes in Absolute Body Weights

Treatment Group	Days of Treatment																
	7	14	21	28	42	56	70	84	112	140	168	196	224	252	280	308	336
Males																	
Low	-	-	-	↓	↓	-	-	-	-	-	↓	↓	↓	↓	↓	↓	-
Medium	-	↓	↓	↓	-	-	-	-	↓	-	↓	↓	↓	↓	↓	↓	↓
High	-	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓
Females																	
Low	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medium	-	-	-	-	-	-	-	-	-	-	↓	↓	↓	↓	↓	↓	↓
High	-	-	-	-	-	-	-	-	↓	↓	↓	↓	↓	↓	↓	↓	↓

Treatment Group	Days of Treatment															
	364	392	420	448	476	504	532	560	588	616	644	672	700	728	756	784
Males																
Low	↓	↓	↓	↓	↓	-	-	-	-	-	-	-	-	-	-	-
Medium	↓	↓	↓	↓	-	-	-	-	-	-	-	-	-	-	-	-
High	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	-	-	-
Females																
Low	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	↓
Medium	↓	↓	↓	↓	↓	↓	↓	↓	↓	-	-	-	-	↓	-	-
High	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓	↓

- = Indicates the absence of a statistically significant change.

↑ or ↓ = Indicates the presence and direction of a statistically significant change.

Table 2B

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Summary of Presence and Direction of All Statistically Significant
Changes in Food Intake (gm/kg/day)

Treatment Group	Days of Treatment																
	0-7	7-14	14-21	21-28	28-42	42-56	56-70	70-84	84-112	112-140	140-168	168-196	196-224	224-252	252-280	280-308	308-336
Low	↑	↑	↑	-	↑	-	-	-	-	-	↑	-	-	-	-	-	↑
	↑	↑	-	-	↑	-	-	-	-	-	↑	-	-	↑	-	-	↑
	↑	↑	-	↑	↑	↑	↑	-	↑	-	↑	↑	↑	↑	↑	↑	↑
Males																	
Low	-	↑	-	-	↑	↑	-	-	↑	-	-	-	-	-	↑	↑	-
	-	↑	-	-	↑	↑	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	↑	↑	-	-	-	-	-	-	-	-	-	-	-
Females																	
Low	-	↑	-	-	↑	↑	-	-	↑	-	-	-	-	-	-	-	-
	-	↑	-	-	↑	↑	-	-	-	-	-	-	-	-	-	-	-
	-	-	-	-	↑	↑	-	-	-	-	-	-	-	-	-	-	-
Males																	
Treatment Group	336-364	364-392	392-420	420-448	448-476	476-504	504-532	532-560	560-588	588-616	616-644	644-672	672-700	700-728	728-756	756-784	784-805
	-	↑	-	-	-	↑	↑	↑	↑	-	-	-	-	-	-	-	-
	-	↑	-	-	-	↑	↑	↑	↑	-	-	-	-	↑	↑	-	-
Low	-	↑	-	-	-	↑	↑	↑	↑	-	-	-	-	-	-	-	-
	-	↑	-	-	-	↑	↑	↑	↑	-	-	-	-	↑	↑	-	-
	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	-	-	-	↑	↑	-
Females																	
Low	-	-	-	↑	-	-	-	-	-	-	-	-	-	-	-	-	-
	-	↑	↑	↑	-	↑	↑	↑	↑	↑	-	-	-	-	-	-	-
	-	-	↑	↑	↑	↑	↑	↑	↑	↑	↑	-	-	↑	↑	↑	-

- = Indicates the absence of a statistically significant change.

↑ or + = Indicates the presence and direction of a statistically significant change.

Table 3

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#098873

B O D Y W E I G H T A N D W E I G H T G A I N

MEAN VALUES⁺

TREATMENT GROUP	DAYS OF TREATMENT AND INTERVENING PERIODS						
	0	7	14	21	28	42	56
B O D Y W E I G H T (GRAMS)							
M A L E S							
CONTROL	91.2	136.7	181.7	224.5	280.4	354.0	400.3
LOW	89.5	133.8	175.4	215.5	267.5*	343.7*	398.4
MEDIUM	91.3	135.0	174.6*	213.7*	266.5*	344.9	395.8
HIGH	90.5	133.3	168.7*	209.8*	265.9*	337.5*	382.9*
						419.4*	446.5*
						470.7	461.7
						494.7	459.0
						510.2	488.4*
						494.7	463.7*
						539.0	521.9
						523.6	490.4*
F E M A L E S							
CONTROL	89.7	125.3	150.5	164.8	186.5	213.8	234.1
LOW	92.8	129.5	151.8	166.4	185.8	211.9	233.4
MEDIUM	90.5	126.9	149.6	165.9	187.0	211.0	231.8
HIGH	87.1	122.1	148.5	161.7	184.5	210.9	229.2
						247.7	260.0
						278.1	260.7
						273.5	256.0
						271.1	255.7
						265.5*	278.9*
M A L E S							
W E I G H T G A I N (% CHANGE/WEEK)							
CONTROL	53.47	35.11	22.80	25.71	13.66	6.45	5.28
LOW	52.99	33.01	22.67	24.75	15.07	7.82*	4.29*
MEDIUM	50.85	31.45	21.80	25.81	15.37	7.20	4.43*
HIGH	50.46	29.05*	23.69	27.92	14.03	6.61	4.76
						3.25	3.42
						2.11	1.79
						1.58*	1.80
						0.99*	1.42
F E M A L E S							
CONTROL	42.35	21.62	9.50	13.70	7.64	4.61	2.97
LOW	42.59	18.41	9.81	12.46	7.25	4.94	3.17
MEDIUM	42.98	19.39	10.88	13.05	6.63*	4.84	2.67
HIGH	43.24	22.79	9.01	14.53	7.38	4.21	3.80*
						2.50	2.61
						1.77	1.23*
						1.61	1.49
						0.96*	1.29

*Mean differs significantly from control ($p < 0.05$).

+Mean based on number of surviving animals.

Table 3 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAY: PT#0988573

B O D Y W E I G H T A N D W E I G H T G A I N

MEAN VALUES[†]

TREATMENT GROUP	DAYS OF TREATMENT AND INTERVENING PERIODS						
	140	168	196	224	252	280	308
B O D Y W E I G H T (GRAMS)							
M A L E S							
CONTROL	539.0	563.0	584.1	604.7	612.0	621.1	633.5
LOW	523.6	538.0*	559.0*	576.3*	586.8*	591.3*	599.7*
MEDIUM	521.9	543.5*	556.5*	573.6*	584.1*	591.7*	592.5*
HIGH	490.4*	499.9*	509.3*	513.3*	520.8*	524.3*	524.4*
							634.3
							611.2
							596.9*
							600.1*
							503.2
							513.7*
							512.9*
							642.2
							611.6*
							608.5*
							512.9*
F E M A L E S							
CONTROL	294.2	301.6	310.9	321.7	328.9	340.1	348.5
LOW	291.1	298.6	307.1	318.7	328.4	332.7	336.0
MEDIUM	286.8	291.1*	299.3*	309.0*	315.8*	320.2*	321.6*
HIGH	278.9*	280.0*	286.5*	293.3*	299.7*	304.5*	303.1*
							305.0*
							352.4
							344.9
							326.7*
							324.1*
							302.2*
							353.2
							342.3
							354.2
							337.8*
							303.2*
M A L E S							
W E I G H T G A I N (% CHANGE/WEEK)							
CONTROL	1.11	0.95	0.89	0.30	0.39	0.52	0.03
LOW	0.68*	0.98	0.79	0.48	0.22	0.37	0.48*
MEDIUM	1.06	0.62*	0.77	0.46	0.33	0.07*	0.15
HIGH	0.50*	0.45*	0.21*	0.39	0.16	0.05*	-0.57*
							-0.41
							-0.33
							-0.68
							-0.05
							0.37
							0.49
F E M A L E S							
CONTROL	0.63	0.78	0.88	0.56	0.84	0.62	0.28
LOW	0.66	0.72	0.93	0.77	0.58	0.24	0.66
MEDIUM	0.39	0.70	0.85	0.55	0.36*	0.12*	0.40
HIGH	0.11*	0.60	0.59	0.54	0.42*	-0.13*	0.30
							-0.25
							0.94
							1.13
							1.08*
							0.11

*Mean differs significantly from control (p < 0.05).

†Mean based on number of surviving animals.

Table 3 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0986573

B O D Y W E I G H T A N D W E I G H T G A I N

MEAN VALUES[†]

TREATMENT GROUP	DAYS OF TREATMENT AND INTERVENING PERIODS					B O D Y W E I G H T (GRAMS)				
	392	420	448	476	504	532	560	588	616	
M A L E S										
CONTROL	642.2	649.8	655.3	647.2	636.5	629.9	644.2	647.4	641.6	
LOW	611.6*	612.9*	614.2*	609.2*	608.9	604.0	614.0	616.9	626.6	
MEDIUM	608.5*	613.2*	618.6*	619.1	621.0	620.9	629.8	646.3	645.9	
HIGH	512.9*	517.2*	520.9*	536.0*	531.8*	538.7*	536.6*	546.4*	540.8*	
F E M A L E S										
CONTROL	366.2	377.7	385.0	394.7	397.4	402.1	421.9	422.9	415.9	
LOW	354.2	365.0	373.8	376.7	387.5	392.8	402.2	419.9	420.8	
MEDIUM	337.8*	345.2*	355.4*	360.0*	360.6*	368.2*	372.1*	388.2*	398.4	
HIGH	303.2*	313.3*	314.6*	326.1*	331.2*	336.2*	343.4*	352.3*	352.4*	
M A L E S										
CONTROL	0.26	0.25	-0.38	-0.53	-0.53	0.08	-0.20	-0.27		
LOW	0.06	0.06	-0.19	-0.07	-0.26	0.02	0.10	-0.06		
MEDIUM	-0.05	0.21	0.02	0.07*	-0.02	0.12	0.66*	-0.02		
HIGH	0.23	0.18	0.73*	-0.19	0.30*	-0.08	0.12	-0.26		
F E M A L E S										
CONTROL	0.78	0.47	0.62	0.14	-0.02	1.01	0.45	-0.47		
LOW	0.76	0.61	0.14*	0.48	0.33	0.63	0.90	0.12		
MEDIUM	0.53	0.74	0.32	0.05	0.54*	0.26*	1.05	0.01		
HIGH	0.84	0.10*	0.90	0.41	0.26	0.56	0.49	-0.26		

*Mean differs significantly from control ($p < 0.05$).

†Mean based on number of surviving animals.

Table 3 (cont.)

SC-19192: 115 WEEK ORAL TJMORIGENICITY STUDY - RAT; PT#0988573

B O D Y W E I G H T A N D W E I G H T G A I N

MEAN VALUES[†]

TREATMENT GROUP	DAYS OF TREATMENT AND INTERVENING PERIODS					AVERAGES 0-805	
	616	644	672	700	728	756	805
M A L E S							
B O D Y W E I G H T (GRAMS)							
CONTROL	641.6	621.9	613.8	595.4	594.4	596.6	570.2
LOW	626.6	614.4	600.5	596.3	574.3	573.6	537.4
MEDIUM	645.9	630.9	613.5	607.2	595.7	585.2	550.6
HIGH	540.8*	556.7*	562.2*	541.3*	550.2	542.5	536.9
M A L E S							
CONTROL	415.8	421.7	417.5	423.2	441.7	448.6	453.4
LOW	420.8	421.0	411.5	408.2	404.5	406.0	391.6*
MEDIUM	398.4	408.7	406.4	390.8	393.0*	402.4	408.8
HIGH	352.4*	350.6*	346.1*	338.3*	343.1*	340.6*	331.2*
M A L E S							
W E I G H T G A I N (% CHANGE/WEEK)							
CONTROL	-0.98	-0.91	-1.40	-0.66	-1.21	-1.56	-1.09
LOW	-0.70	-0.62	-0.97	-0.62	-0.63	-1.67	-1.18
MEDIUM	-0.57	-0.64	-0.65	-0.79	-0.80	-1.22	-1.36
HIGH	-0.51	-0.26	-0.99	-0.11	-0.37	-0.72	-1.75
F E M A L E S							
CONTROL	0.04	-0.25	-0.41	0.30	0.43	-1.10	-0.04
LOW	-0.19	-0.66	-0.84	-0.13	-0.15	-0.83	-0.16
MEDIUM	0.76	0.03	-1.00	-0.29	-0.26	-0.44	0.34
HIGH	-0.17	-0.38	-0.62	0.32	-0.14	-0.53	0.63
F E M A L E S							
CONTROL							1.44
LOW							1.36
MEDIUM							1.38
HIGH							1.32

*Mean differs significantly from control ($p < 0.05$).

†Mean based on number of surviving animals.

SC-19192 115 WEEK ORAL TUMORIGENICITY STUDY- RAT
PT 0988573
FIGURE 1
MALE BODY WEIGHTS

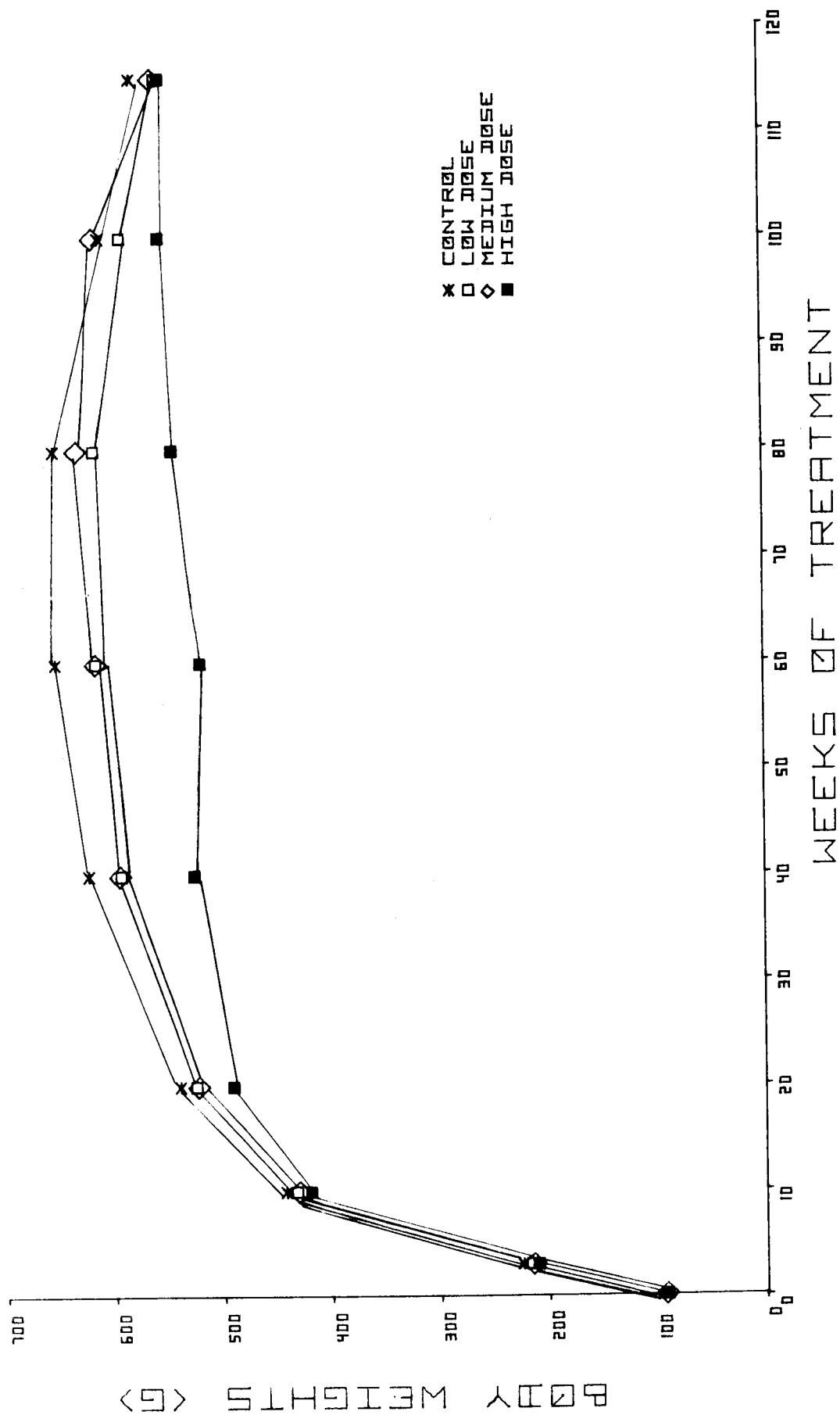


FIGURE 2
 SC-19192 115 WEEK ORAL TUMORIGENICITY STUDY-RAT
 PT 0988573
 FEMALE BODY WEIGHTS

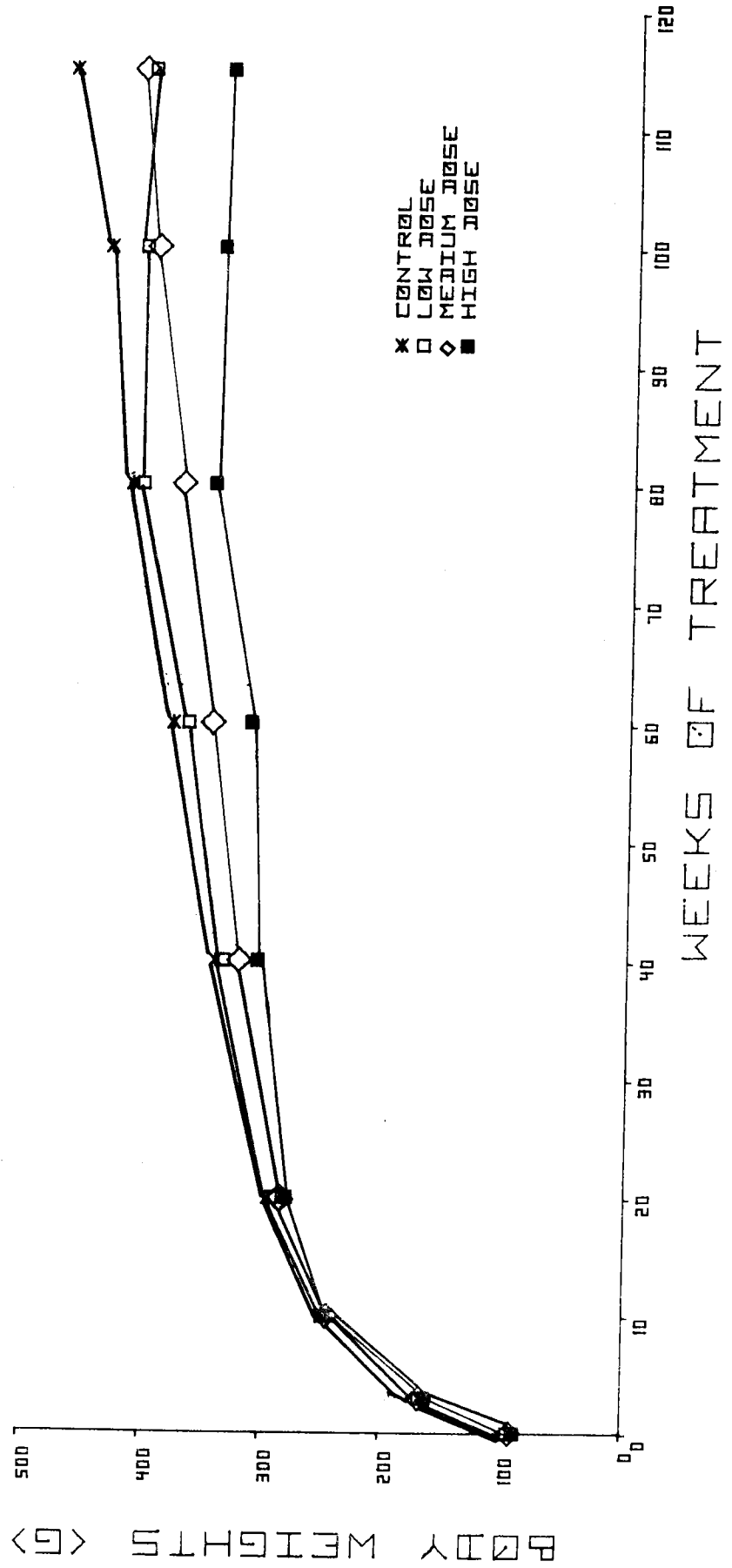


Table 4

52-191321 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: P100911S73

FOOD INTAKE AND DOSE

MEAN VALUES[†]

TREATMENT GROUP	INTERVALS BETWEEN DAYS OF TREATMENT										
	0-7	7-14	14-21	21-28	28-42	42-56	56-70	70-84	84-112	112-140	140-160
	F O O D I N T A K E (GRAMS/DAY)										
M A L E S											
CONTROL	16.2	21.3	20.2	25.2	26.8	27.4	27.0	26.7	26.7	23.7	26.9
LOW	21.2 *	15.9 *	20.9	24.9	27.4	26.1 *	26.5	26.3	25.3 *	23.3	25.8 *
MEDIUM	21.6 *	15.0 *	20.5	24.6	28.2 *	25.5 *	25.9 *	26.5	25.0 *	22.9	26.0
HIGH	20.9 *	15.2 *	20.0	25.3	27.3	24.2 *	26.2	25.9	24.0 *	23.0	24.4 *
F E M A L E S											
CONTROL	20.7	15.7	19.8	19.1	20.8	20.6	21.0	20.2	20.5	18.3	19.8
LOW	27.4 *	12.3 *	20.0	18.9	20.2	19.2 *	20.3	20.2	18.9 *	17.6	19.0 *
MEDIUM	27.8 *	12.4 *	20.2	18.4	20.3	19.2 *	19.7 *	20.0	19.3 *	17.9	19.1 *
HIGH	25.8	13.1 *	19.7	18.7	20.5	19.0 *	19.7 *	19.4	19.0 *	17.0 *	18.2 *
M A L E S											
CONTROL	145.1	134.3	100.4	100.5	84.5	72.6	64.0	58.6	54.6	45.3	48.7
LOW	194.8 *	103.7 *	107.7 *	103.3	90.4 *	70.6	64.2	59.5	53.2	46.5	48.5
MEDIUM	195.5 *	104.7 *	105.8	104.3	92.5 *	68.8 *	65.5	59.6	54.2	46.1	49.0
HIGH	191.3 *	101.7 *	106.8	106.9 *	91.2 *	69.0 *	67.3 *	61.2 *	53.5	48.4 *	48.8
F E M A L E S											
CONTROL	197.6	112.8	125.8	108.4	104.2	92.1	86.8	79.9	76.4	64.3	66.8
LOW	250.9	87.1 *	125.8	108.4	101.6	86.0 *	84.7	79.7	71.0 *	62.5	65.1
MEDIUM	262.4	89.4 *	128.0	104.6	102.5	87.2 *	83.1	80.7	73.2	64.1	65.7
HIGH	251.4	95.9	127.2	108.3	103.4	87.5 *	82.9	77.8	73.3	62.6	65.4
M A L E S											
LOW	920.8	490.3	806.8	774.2	677.9	754.6	551.7	666.0	712.5	645.0	791.3
MEDIUM	1839.7	985.7	1583.8	1562.1	1386.9	1475.3	1106.0	1355.7	1378.2	1280.4	1563.1
HIGH	3567.6	1896.0	3201.2	3203.6	2734.8	2966.5	2345.7	2825.5	2765.2	2594.5	3051.6
F E M A L E S											
LOW	937.3	328.9	942.3	812.5	762.4	809.0	668.1	737.8	683.0	660.4	827.6
MEDIUM	1953.3	665.7	1916.1	1566.4	1536.9	1634.1	1250.5	1440.5	1462.5	1353.1	1602.3
HIGH	3362.3	1417.6	3812.4	3246.1	3102.3	3098.3	2470.6	2862.2	2891.6	2537.0	3164.2

*Mean differs significantly from control ($p < 0.05$).

†Mean based on number of surviving animals.

Table 4 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAI; PI#0988S73

FOOD INTAKE AND DOSAGE

MEAN VALUES[†]

TREATMENT GROUP	INTERVALS BETWEEN DAYS OF TREATMENT					308-335	336-364	364-392
	140-168	168-196	196-224	224-252	252-280	280-308		
	FOOD INTAKE (GRAMS/DAY)							
M A L E S								
CONTROL	26.9	27.1	26.3	25.9	25.8	25.7	24.5	24.6
LOW	25.8 *	26.8	25.6	24.7 *	24.6 *	24.2 *	23.7	24.4
MEDIUM	26.1	26.4	25.8	25.4	24.9	23.8 *	23.6	24.6
HIGH	24.4 *	24.8 *	24.3 *	23.2 *	23.4 *	22.5 *	20.9 *	23.3 *
F E M A L E S								
CONTROL	19.8	20.0	20.4	19.8	20.2	20.0	19.5	19.3
LOW	19.0 *	19.5	19.2 *	18.9	19.1 *	18.0 *	18.7	18.7
MEDIUM	19.1 *	19.4	19.3 *	18.5 *	18.9 *	18.8 *	18.5 *	18.9
HIGH	18.2 *	18.9 *	18.2 *	18.4 *	17.9 *	17.9 *	17.2 *	16.6 *
	FOOD INTAKE (GRAMS/KG/DAY)							
M A L E S								
CONTROL	48.7	47.2	44.4	42.5	41.9	40.9	38.5	38.6
LOW	48.5	49.7 *	45.3	43.9	41.5	40.9	39.2	41.1 *
MEDIUM	49.0	49.4 *	45.5	44.3 *	42.7	40.8	40.0	41.0 *
HIGH	49.8	50.0 *	46.8 *	44.8 *	45.3 *	43.4 *	40.6 *	45.4 *
F E M A L E S								
CONTROL	66.8	65.3	64.0	60.9	60.8	58.6	55.6	53.7
LOW	65.1	64.2	61.2	58.3	57.5 *	54.3 *	54.9	54.4
MEDIUM	65.7	66.1	63.8	59.4	60.0	58.6	56.6	57.3 *
HIGH	65.4	66.9	62.8	62.4	59.3	59.1	56.9	55.4
	DOSAGE (MG/KG/DAY)							
M A L E S								
LOW	791.3	792.7	722.6	714.8	691.8	713.6	743.2	757.5
MEDIUM	1563.1	1544.7	1452.6	1414.6	1424.5	1406.9	1491.3	1512.1
HIGH	3051.6	3062.8	3050.5	2798.8	2951.5	2959.4	2912.5	3241.2
F E M A L E S								
LOW	827.6	729.5	740.2	693.8	743.5	717.0	755.9	728.1
MEDIUM	1602.3	1480.3	1494.6	1391.8	1462.8	1490.8	1502.4	1481.5
HIGH	3164.2	3136.1	2990.6	2877.8	3014.6	2928.2	2941.8	2849.1

*Mean differs significantly from control (p < 0.05).

†Mean based on number of surviving animals.

Table 4 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988573

F O O D I N T A K E A N D D O S A G E											
M E A N V A L U E S ⁺											
TREATMENT GROUP	INTERVALS BETWEEN DAYS OF TREATMENT										
	364-392	392-420	420-448	448-476	476-504	504-532	532-560	560-588	588-616		
F O O D I N T A K E (GRAMS/DAY)											
M A L E S											
CONTROL	24.6	25.8	26.1	25.9	24.3	25.1	25.0	23.8	23.9		
LOW	24.4	23.6*	24.5*	25.0	24.9	24.9	24.8	24.3	24.2		
MEDIUM	24.6	23.7*	24.8*	24.9	25.2	25.8	25.2	25.5*	24.5		
HIGH	23.3*	22.6*	23.8*	23.3*	23.7	25.4	24.0	24.1	24.2		
F E M A L E S											
CONTROL	19.3	20.6	21.4	21.5	20.8	21.1	17.6	20.3	20.1		
LOW	19.7	19.3*	21.7	20.0*	21.1	20.8	16.9	20.9	20.0		
MEDIUM	18.9	20.2	21.7	20.4*	20.7	20.8	16.7	20.4	20.2		
HIGH	15.6*	17.7*	18.5*	19.2*	19.0*	19.8*	16.0	19.0*	17.9*		
F O O D I N T A K E (GRAMS/KG/DAY)											
M A L E S											
CONTROL	38.6	39.8	40.1	39.7	38.0	38.7	39.6	37.2	37.7		
LOW	41.1*	38.5	40.7	41.3	41.0*	41.9*	40.8	39.8*	38.7		
MEDIUM	41.0*	38.3	40.9	40.4	41.0*	41.5*	40.1	40.0*	37.9		
HIGH	45.4*	44.1*	44.8*	44.3*	43.7*	46.5*	44.2*	43.0*	42.0*		
F E M A L E S											
CONTROL	53.7	54.5	55.5	55.9	52.9	52.3	42.3	47.6	46.1		
LOW	54.4	54.2	59.4*	53.7	54.8	53.2	42.7	50.8	48.2		
MEDIUM	57.3	59.2*	62.4*	57.6	57.6*	58.2*	45.7	55.0*	51.2*		
HIGH	55.4	57.7*	59.2*	60.0*	57.9*	59.1*	47.0	54.5*	51.0*		
D O S A G E (MG/KG/DAY)											
M A L E S											
LOW	757.5	734.0	746.9	726.7	769.0	764.3	746.6	732.2	716.3		
MEDIUM	1512.1	1435.9	1502.1	1424.6	1540.7	1495.4	1453.7	1455.4	1387.9		
HIGH	3241.2	3239.7	3198.9	2605.0	2914.3	3074.0	2931.4	2862.1	2797.5		
F E M A L E S											
LOW	728.1	745.7	824.7	710.4	687.7	650.8	529.7	625.1	593.7		
MEDIUM	1481.5	1575.2	1671.1	1403.6	1393.3	1421.9	1151.3	1347.7	1257.5		
HIGH	2849.1	3034.5	3169.7	2949.7	2946.0	2763.7	2234.3	2551.9	2393.0		

*Mean differs significantly from control ($p < 0.05$).

+Mean based on number of surviving animals.

Table 4 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988573

FOOD INTAKE AND DOSAGE										
MEAN VALUES†										
TREATMENT GROUP	INTERVALS BETWEEN DAYS OF TREATMENT						756-784	784-805	AVERAGES 0-805	
	588-616	616-644	644-672	672-700	700-728	728-756				
FOOD INTAKE (GRAMS/DAY)										
MALES										
	23.9	24.7	23.5	23.6	24.4	24.7	22.8	22.7	24.96	
	24.2	24.6	24.1	24.6	24.7	24.0	21.9	22.2	24.50	
	24.5	24.4	23.3	23.6	23.0	21.8*	21.8	22.3	24.38	
HIGH	24.2	24.7	23.4	23.6	23.6	22.4*	23.8	23.0	23.56	
FEMALES										
	20.1	20.6	20.2	21.2	20.2	19.6	21.2	22.0	20.19	
	20.0	19.9	18.6*	19.3*	20.3	19.2	18.4*	21.6	19.45	
	20.2	20.4	19.8	19.7	18.8	18.6	20.2	21.4	19.52	
HIGH	17.9*	18.5*	17.5*	18.9*	18.5	18.3	19.0	19.6	18.38	
FOOD INTAKE (GRAMS/KG/DAY)										
MALES										
	37.7	39.2	38.1	40.0	42.6	41.1	38.7	40.2	46.02	
	38.7	40.5	40.3	39.9	41.4	41.2	39.5	41.2	47.23	
	37.9	38.2	37.4	38.2	38.0*	36.9*	39.1	41.3	46.76	
HIGH	42.0*	43.2*	40.7	41.2	42.7	39.2	43.8*	43.8	49.27	
FEMALES										
	46.1	49.4	48.3	51.4	46.2	45.1	48.9	50.5	60.36	
	48.2	47.6	44.7	47.0	49.7	47.2	46.1	52.0	59.76	
	51.2*	50.3	48.9	51.3	49.0	48.7	48.2	50.7	62.19	
HIGH	51.0	53.1	50.5	55.8	54.5*	53.9*	56.6*	57.3	63.26	
DOSAGE (MG/KG/DAY)										
MALES										
	716.3	752.4	671.8	714.0	715.1	707.5	679.8	699.6	725.10	
	1387.9	1403.4	1477.4	1414.0	1374.6	1306.3	1259.8	1442.2	1431.80	
	2797.5	2886.2	2714.8	2817.7	2973.6	2679.0	2991.1	3034.2	2911.76	
FEMALES										
	593.7	592.1	637.2	734.8	813.6	772.5	747.0	855.2	716.13	
	1257.5	1235.5	1221.2	1302.0	1258.6	1275.8	1259.1	1368.4	1408.60	
	2393.0	2494.7	2926.5	3234.3	3343.1	3304.6	3346.7	3320.7	2933.93	

*Mean differs significantly from control ($p < 0.05$).

†Mean based on number of surviving animals.

Table 4A

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Concentration of SC-19192 in the Basal Diet (g/kg)

Treatment Group	Days of Treatment												
	0-14	15-42	43-56	57-70	71-84	85-112	113-140	141-168	169-196	197-224	225-252	253-280	281-308
Low Medium High	Males												
	4.8	7.6	10.8	8.7	11.3	13.6	14.1	16.6	16.2	16.2	16.6	16.9	17.8
	9.5	15.2	21.9	17.2	23.3	26.1	28.6	33.0	32.3	33.0	33.0	34.5	35.7
Low Medium High	Females												
	3.8	7.6	9.5	8.0	9.4	9.7	10.7	12.9	11.5	12.2	12.1	13.1	13.2
	7.5	15.2	19.1	15.3	18.2	20.4	21.6	25.0	22.9	24.0	24.0	25.0	26.1
Low Medium High	Females												
	15.0	30.9	36.7	30.7	37.0	41.1	42.3	50.9	49.2	50.0	48.4	53.6	52.2

Treatment Group	Days of Treatment												
	309-336	337-364	365-392	393-420	421-448	449-476	477-504	505-532	533-560	561-588	589-616	617-644	
Low Medium High	Males												
	19.1	19.4	18.8	19.5	18.7	17.9	19.1	18.6	18.7	18.8	18.9	18.9	
	38.0	38.8	38.3	39.0	38.2	36.6	39.0	37.4	37.6	37.8	38.0	38.1	
Low Medium High	Females												
	75.0	77.3	76.9	79.4	76.9	62.5	71.4	70.9	71.1	71.3	71.4	71.6	
	13.4	14.0	13.6	14.0	14.1	13.4	12.7	12.4	12.4	12.5	12.5	12.5	
Low Medium High	Females												
	26.3	27.3	27.6	27.3	27.5	25.0	24.8	25.0	25.1	25.1	25.2	25.2	
	54.3	54.6	54.3	55.6	56.6	51.7	53.6	49.1	49.1	49.2	49.2	49.3	

Treatment Group	Days of Treatment												
	645-672	673-700	701-728	729-756	757-784	785-805							
Low Medium High	Males												
	17.0	18.2	17.6	17.5	17.5	17.3							
	41.1	38.4	37.6	36.7	33.3	36.2							
Low Medium High	Females												
	71.4	73.3	74.9	73.4	73.4	74.4							
	14.5	15.9	16.6	16.6	16.5	16.7							
Low Medium High	Females												
	25.6	26.0	26.4	26.8	26.8	27.8							
	61.5	61.5	65.4	65.3	62.9	61.5							

Clinical laboratory findings.

A summary of statistically significant changes in the clinical laboratory data are presented in Table 4B.

Hematology. Group mean values of hematology parameters evaluated are presented in Tables 5, 6 and 6A. Values for individual rats are tabulated in the Appendix. No biologically meaningful variation attributable to compound administration was observed in the parameters measured. Occasionally some of the treated groups showed inconsistent significant deviations from the control group in some parameters; but all of these are considered to be chance deviations and do not have any biological significance.

Clinical chemistry. Group mean clinical chemistry values are presented in Table 7; individual values are tabulated in the Appendix. No compound-related significant variations were observed in the blood chemistry profiles measured except possibly serum total cholesterol. The serum cholesterol in the low and medium dose males was unremarkable throughout the study; however, in the low and medium dose females significant deviations in cholesterol values were observed, but these values were within the normal range. The significant values in this case were attributed to unusually high control values. A mild but significant decrease in serum cholesterol was observed initially in high dose females at treatment day 42 and in the high dose males at day 92. These trends persisted in these groups throughout the study and were more perceptible towards the end of the study. This effect may be related to compound administration.

BUN values for the control males at treatment day 189 were unusually low and may possibly be related to a technical artefact; as a result, the group mean values for all treated males at this interval were significantly higher but, in fact, these values were in the normal range. BUN values both in control and all treated male groups at treatment day 364 were unusually low; this again reflects a possible technical artefact.

Other parameters evaluated exhibited inconsistent significant changes which are considered unrelated to treatment.

Urinalysis. Group mean values of urinalysis parameters evaluated are presented in Table 8; individual values are presented in the Appendix. The results of urinalysis showed no evidence of treatment related effects, except possibly in pH. A significant decrease in urinary pH was observed in the high dose females at treatment day 92. This trend continued in this group until the end of the study. Similar, significant decreases in urinary pH were observed in the high dose males and low and medium dose females at treatment day 364 and in medium dose females at treatment day 547; at all other intervals the urinary pH of these groups was unremarkable. The decrease in urinary pH appears to be compound-related. This may be related to the acidic metabolites of SC-19192 that are excreted in the rat urine¹⁸. Transient significant increases in urinary specific gravity were observed in some treated groups at various times during the study. However, no particular trend or dose-relationship was apparent. Specific gravity changes appear to be random and do not appear to be treatment related.

Table 4B

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Summary of Presence and Direction of All Statistically Significant Changes in
Clinical Laboratory Data (Parameters Measured Serially)

Treatment Group Sex	Days of Treatment											
	42			92			189			364		
	Low M	Med F	High M	Low M	Med F	High M	Low M	Med F	High M	Low M	Med F	High M
PARAMETER												
Hemoglobin	-	-	-	-	-	-	-	-	-	-	-	-
Hematocrit	-	-	-	-	-	-	-	-	-	-	-	-
RBC	-	-	-	-	-	-	-	-	-	-	-	-
WBC	-	-	-	-	-	-	-	-	-	-	-	-
Prothrombin Time	-	-	-	-	-	-	-	-	-	-	-	-
GPT	-	-	-	-	-	-	-	-	-	-	-	-
GOT	-	-	-	-	-	-	-	-	-	-	-	-
Total Cholesterol	-	-	-	-	-	-	-	-	-	-	-	-
BUN	-	-	-	-	-	-	-	-	-	-	-	-
L-Phenylalanine	-	-	-	-	-	-	-	-	-	-	-	-
Bilirubin	-	-	-	-	-	-	-	-	-	-	-	-
AP	-	-	-	-	-	-	-	-	-	-	-	-
Glucose	-	-	-	-	-	-	-	-	-	-	-	-
Urinary pH	-	-	-	-	-	-	-	-	-	-	-	-
Specific Gravity	-	-	-	-	-	-	-	-	-	-	-	-

† or † = Indicates the presence and direction of a statistically significant change.

- = Indicates the absence of a statistically significant change.

Table 5

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988S73

HEMATOLOGY - ERYTHROCYTES

TREATMENT DAY 42
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	HCT %	M A L E S	HGB G/DL	RBC X106/CMM
CONTROL	47 1		14.5 0.2	7.62 0.11
LOW	47 0		14.9 0.2	7.62 0.11
MEDIUM	46 1		14.2 0.2	7.48 0.19
HIGH	47 1		15.1 0.3	7.66 0.12
		F E M A L E S		
CONTROL	47 1		15.6 0.2	7.47 0.10
LOW	47 0		15.6 0.3	7.42 0.17
MEDIUM	46 1		15.8 0.1	7.64 0.09
HIGH	45 + 0		15.7 0.3	7.42 0.20

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT

FOR VALID STATISTICAL ANALYSIS

Table 5 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988S73

HEMATOLOGY - ERYTHROCYTES

TREATMENT DAY 92
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	HCT %	HGB G/DL	RBC X106/CMH
M A L E S			
CONTROL	47 0	15.8 0.2	8.35 0.07
LOW	48 + 0	16.4 0.3	8.36 0.14
MEDIUM	48 + 0	16.6 * 0.2	8.31 0.08
HIGH	47 1	16.1 0.2	8.29 0.14
F E M A L E S			
CONTROL	46 0	16.0 0.2	8.02 0.16
LOW	47 1	16.2 0.2	8.11 0.10
MEDIUM	46 1	15.0 0.2	7.99 0.14
HIGH	46 + 1	15.7 0.1	7.77 0.07

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 10% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT

FOR VALID STATISTICAL ANALYSIS

Table 5 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0908S73

HEMATOLOGY - ERYTHROCYTES

TREATMENT DAY 189
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	HCT %	M A L E S HGB G/DL	RBC X106/CMM
CONTROL	48 1	14.4 0.3	8.09 0.11
LOW	48 0	14.3 0.2	8.17 0.05
MEDIUM	48 + 0	15.0 0.6	8.15 0.12
HIGH	47 1	14.2 0.3	8.01 0.10
F E M A L E S			
CONTROL	47 1	15.3 0.2	7.70 0.12
LOW	45 + 1	15.3 0.2	7.59 0.23
MEDIUM	45 0	15.6 0.2	7.76 0.14
HIGH	44 + 0	14.9 0.1	7.73 0.20

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT

FOR VALID STATISTICAL ANALYSIS

Table 5 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY - ERYTHROCYTES

TREATMENT DAY 364
 ARITHMETIC MEANS WITH STANDARD ERRORS
 (6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	M A L E S		F E M A L E S	
	HCT %	HGB G/DL	HCT %	HGB G/DL
CONTROL	46 + 1	15.9 0.2	44 1	14.7 0.2
LOW	47 1	15.6 0.3	43 0	14.7 0.1
MEDIUM	46 1	15.7 0.2	44 0	14.9 0.1
HIGH	43 * 2	13.8 * 0.6	44 1	14.4 0.4
CONTROL				
LOW				
MEDIUM				
HIGH				

RBC
X106/CMM8.33
0.158.34
0.208.30
0.127.47 *
0.447.52
0.147.50
0.087.78
0.137.38
0.24

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 10% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT

FOR VALID STATISTICAL ANALYSIS

Table 5 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988573

HEMATOLOGY - ERYTHROCYTES

TREATMENT DAY 734
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	HCT %	M A L E S	HGB G/DL	RBC X106/CMH
CONTROL	47 2		15.8 0.7	7.56 0.41
LOW	46 2		16.2 0.5	11.85 4.44
MEDIUM	50 3		17.1 0.7	8.42 0.45
HIGH	48 1		16.2 0.4	7.84 0.17
F E M A L E S				
CONTROL	48 2		16.2 0.5	7.60 0.22
LOW	50 2		17.5 0.6	8.11 0.39
MEDIUM	49 1		16.5 0.4	7.90 0.19
HIGH	45 1		15.8 0.4	7.63 0.15

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT FOR VALID STATISTICAL ANALYSIS

Table 6

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY - LEUCOCYTES

TREATMENT DAY 42
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	WBC X103/CMM	M A L E S						DIFFERENTIAL				
		BANDS %	PMN SEGS %	LYM %	MON %	EOS %	BAS %					
CONTROL	10.2	0	13.3	85.5	0.0	1.2	0.0					
	1.2	0	1.9	1.8	0.0	0.4	0.0					
LOW	11.3	0	9.7	90.0	0.0	0.3	0.0					
	1.6	0	2.1	2.1	0.0	0.2	0.0					
MEDIUM	11.4	0	14.2	85.0	0.0	0.8	0.0					
	1.4	0	4.4	4.6	0.0	0.3	0.0					
HIGH	10.2	0	12.3	86.7	0.0	1.0	0.0					
	1.0	0	0.7	0.8	0.0	0.4	0.0					
F E M A L E S												
CONTROL	11.8	0	12.0	86.8	0.0	0.8	0.0					
	1.9	0	4.0	4.4	0.0	0.3	0.0					
LOW	8.7	0	13.8	85.0	0.2	0.7	0.2					
	0.7	0	4.0	3.7	0.2	0.4	0.2					
MEDIUM	8.6	0	15.7	84.8	0.0	1.2	0.0					
	1.4	0	3.6	3.8	0.0	0.3	0.0					
HIGH	11.9	0	10.8	86.8	0.2	2.2 *	0.0					
	1.2	0	3.3	3.4	0.2	0.3	0.0					

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
FOR VALID STATISTICAL ANALYSIS

Table 6 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT0989S73

HEMATOLOGY - LEUCOCYTES

TREATMENT DAY 92
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	WBC X103/CMH	M A L E S							DIFFERENTIAL		
		BANDS %	PMN SEGS %	LYM %	MON %	EOS %	BAS %				
CONTROL	11.6	0	7.8	91.0	0.0	1.2	0.6				
	1.4	0	1.1	1.0	0.0	0.4	0.0				
LOW	9.6	0	12.3	85.3	0.0	2.3	0.6				
	1.4	0	1.4	1.7	0.0	1.6	0.0				
MEDIUM	10.4	0	14.2	84.5	0.0	1.3	0.6				
	1.3	0	4.0	3.7	0.0	0.7	0.0				
HIGH	12.5	0	12.8	86.2	0.0	1.0	0.0				
	1.0	0	3.5	3.6	0.0	0.3	0.0				
F E M A L E S											
CONTROL	11.5	0	12.2	87.0	0.0	0.8	0.0				
	1.5	0	3.4	3.8	0.0	0.5	0.0				
LOW	9.3	0	13.8	83.3	0.2	2.7	0.6				
	1.1	0	2.5	2.4	0.2	1.0	0.0				
MEDIUM	10.6	0	11.0	88.2	0.0	0.8	0.0				
	1.5	0	1.5	1.9	0.0	0.5	0.0				
HIGH	11.3	0	12.3	86.7	0.2	0.8	0.0				
	0.9	0	1.8	1.7	0.2	0.4	0.0				

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
FOR VALID STATISTICAL ANALYSIS

Table 6 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0989S73

HEMATOLOGY - LEUCOCYTES

TREATMENT DAY 149
 ARITHMETIC MEANS WITH STANDARD ERRORS
 (6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	WBC X10 ³ /CHM	M A L E S						DIFFERENTIAL			
		BANDS %	PMN SEGS %	LYM %	MON %	EOS %	BAS %				
CONTROL	8.1	0	15.3	83.2	0.2	1.3	0.0	0.0	0.0		
	0.4	1.3	1.0	0.2	0.4	0.0					
LOW	10.8	0	14.7	83.2	0.0	2.2	0.0	0.0	0.0		
	1.5	1.5	1.4	0.0	0.8	0.0					
MEDIUM	11.6 *	0	13.0	84.5	0.0	2.5	0.0	0.0	0.0		
	0.9	1.5	2.0	0.0	0.8	0.0					
HIGH	11.2	0	16.7	82.3	0.0	1.0	0.0	0.0	0.0		
	1.3	2.0	2.1	0.0	0.4	0.0					
F E M A L E S											
CONTROL	9.5	0	8.5	91.0	0.0	0.5	0.0	0.0	0.0		
	0.8	1.7	1.5	0.0	0.2	0.0					
LOW	7.6	0	9.2	89.5	0.0	1.3	0.0	0.0	0.0		
	1.0	2.3	2.6	0.0	0.3	0.0					
MEDIUM	7.9	0	10.5	87.7	0.0	1.8 *	0.0	0.0	0.0		
	1.0	1.9	1.9	0.0	0.5	0.0					
HIGH	7.4	0	10.0	88.5	0.0	1.5	0.0	0.0	0.0		
	0.5	1.5	1.7	0.0	0.5	0.0					

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT

FOR VALID STATISTICAL ANALYSIS

Table 6 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#G988S73

HEMATOLOGY - LEUCOCYTES

TREATMENT DAY 364
 ARITHMETIC MEANS WITH STANDARD ERRORS
 (6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	WBC X103/CMM	M A L E S					D I F F E R E N T I A L				BAS %
		BANDS %	PMN SEGS %	LYM %	MON %	EOS %					
CONTROL	9.3	0	12.7	84.8	0.5	1.8	0.0	0.0	0.0	0.0	
	1.0	1.5	1.6	0.3	1.5						
LOW	8.8	0	15.2	82.7	0.2	2.0	0.0	0.0	0.0	0.0	
	0.6	3.2	3.9	0.2	0.7						
MEDIUM	10.3	0	17.2	81.3	0.0	1.5	0.0	0.0	0.0	0.0	
	1.5	5.3	5.7	0.0	0.7						
HIGH	9.9	0	26.0	72.2	0.5	1.2	0.0	0.0	0.0	0.0	
	1.7	7.7	7.5	0.2	0.5						
F E M A L E S											
CONTROL	7.8	0	16.2	82.0	0.3	1.5	0.0	0.0	0.0	0.0	
	0.9	3.4	3.5	0.3	0.4						
LOW	5.7	0	20.0	77.5	0.2	2.3	0.0	0.0	0.0	0.0	
	0.2	2.6	2.6	0.2	0.8						
MEDIUM	6.4	0	17.2	80.7	0.2	1.7	0.0	0.0	0.2	0.2	
	0.8	2.8	2.3	0.2	0.7						
HIGH	5.5 *	0	18.0	81.3	0.0	0.5	0.0	0.0	0.0	0.0	
	0.8	4.2	4.0	0.0	0.3						

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 10% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
 FOR VALID STATISTICAL ANALYSIS

Table 6 (cont.)

SC-19192; 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988573

HEMATOLOGY - LEUCOCYTES

TREATMENT DAY 547
 ARITHMETIC MEANS WITH STANDARD ERRORS
 (6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	WBC X103/CMM	M A L E S					DIFFERENTIAL			
		BANDS %	PMN SEGS %	LYM %	MON %	EOS %	BAS %			
CONTROL	9.0	0	20.8	73.3	3.8	1.7	0.0			
	1.4	0	3.1	3.6	0.7	0.7	0.0			
LOW	8.9	0	19.8	75.2	2.8	2.0	0.0			
	1.1	0	2.1	2.8	0.6	0.6	0.0			
MEDIUM	9.2	0	20.7	73.8	3.0	2.2	0.0			
	1.3	0	2.9	2.7	0.7	0.4	0.0			
HIGH	6.3	0	24.2	70.7	3.3	1.7	0.0			
	0.6	0	2.8	2.7	0.6	0.2	0.0			
F E M A L E S										
CONTROL	9.0	0	18.2	77.7	3.0	1.0	0.0			
	1.2	0	3.7	3.3	0.4	0.5	0.0			
LOW	6.9	0	18.0	78.3	1.7	1.8	0.0			
	0.7	0	2.3	2.1	0.6	0.7	0.0			
MEDIUM	7.5	0	27.2	59.0	2.2	1.7	0.0			
	1.0	0	8.4	8.3	0.5	0.6	0.0			
HIGH	6.2	0	23.2	71.8	2.5	2.2	0.0			
	0.4	0	2.1	2.2	0.7	0.9	0.0			

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT

FOR VALID STATISTICAL ANALYSIS

Table 6 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: FI#6988S73

HEMATOLOGY - LEUCOCYTES

TREATMENT DAY 734
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	WBC X103/CMM	M A L E S							DIFFERENTIAL		
		BANDS %	PMN SEGS %	LYM %	MON %	EOS %	BAS %				
CONTROL	15.1	0	41.0	56.0	1.3	1.3	0.0	0.0	0.0	0.0	
	1.7	0	8.1	8.3	0.4	0.5					
LOW	11.2	0	30.3	66.7	1.2	1.8	0.0	0.0	0.0	0.0	
	2.1	0	5.9	5.7	0.5	0.7					
MEDIUM	9.2 *	0	27.0	73.2	1.0	1.7	0.0	0.0	0.0	0.0	
	0.7	0	2.9	3.4	0.5	0.3					
HIGH	9.0 *	0	28.0	69.5	1.2	1.3	0.0	0.0	0.0	0.0	
	1.4	0	2.3	2.7	0.6	0.5					
F E M A L E S											
CONTROL	15.3	0	36.0	63.3	2.8	0.8	0.0	0.0	0.0	0.0	
	2.1	0	5.9	5.6	0.6	0.3					
LOW	9.3	0	37.7	58.8	1.8	1.7	0.0	0.0	0.0	0.0	
	1.3	0	5.6	5.7	0.4	0.6					
MEDIUM	7.1	0	24.2	72.0	2.2	1.7	0.0	0.0	0.0	0.0	
	0.3	0	4.1	4.1	0.7	0.6					
HIGH	6.2 *	0	31.7	65.2	2.0	1.2	0.0	0.0	0.0	0.0	
	0.8	0	3.5	3.5	0.4	0.3					

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
FOR VALID STATISTICAL ANALYSIS

Table 6a

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#G988S73

HEMATOLOGY - COAGULOGRAM

TREATMENT DAY 42
 ARITHMETIC MEANS WITH STANDARD ERRORS
 (6 ANIMALS/SEX/TREATMENT GROUP)

M A L E S

PRO TIME
SECTREATMENT
GROUP

CONTROL

12.0
0.2

LOW

11.5
0.4

MEDIUM

11.6
0.3

HIGH

12.3
0.3

F E M A L E S

CONTROL

12.1
0.3

LOW

12.1
0.2

MEDIUM

12.4
0.4

HIGH

12.6
0.3

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 10% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
 FOR VALID STATISTICAL ANALYSIS

Table 6a (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988573

HEMATOLOGY - COAGULOGRAM

TREATMENT DAY 92
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

M A L E S

PRO TIME
SECTREATMENT
GROUP

CONTROL

12.6
0.4

LOW

12.3
0.4

MEDIUM

12.4
0.2

HIGH

12.1
0.2

F E M A L E S

CONTROL

12.0
0.4

LOW

12.3
0.7

MEDIUM

11.9
0.4

HIGH

12.5
0.6* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL ($P < 0.05$)* LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
FOR VALID STATISTICAL ANALYSIS

Table 6a (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988573

HEMATOLOGY - COAGULOGRAM

TREATMENT DAY 189
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

M A L E S

PRO TIME
SECTREATMENT
GROUP

CONTROL

11.1
0.3

LOW

11.4
0.2

MEDIUM

11.5
0.3

HIGH

11.6
0.3

F E M A L E S

CONTROL

10.4
0.2

LOW

10.4
0.3

MEDIUM

10.7
0.4

HIGH

10.6
0.4* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL ($P < 0.05$)+ LESS THAN 10% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
FOR VALID STATISTICAL ANALYSIS

Table 6a (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988573

HEMATOLOGY - COAGULOGRAM

TREATMENT DAY 364
 ARITHMETIC MEANS WITH STANDARD ERRORS
 (6 ANIMALS/SEX/TREATMENT GROUP)

M A L E S
 PRO TIME
 SEC

TREATMENT
GROUP

CONTROL

11.5
 0.2

LOW

11.3
 0.5

MEDIUM

11.4
 0.4

HIGH

11.0
 0.3

F E M A L E S

CONTROL

9.8
 0.2

LOW

8.8
 0.3

MEDIUM

9.6
 0.4

HIGH

10.1
 0.4

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
 FOR VALID STATISTICAL ANALYSIS

Table 6a (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0908S73

HEMATOLOGY - COAGULOGRAM

TREATMENT DAY 547
 ARITHMETIC MEANS WITH STANDARD ERRORS
 (6 ANIMALS/SEX/TREATMENT GROUP)

M A L E S

PRO TIME
SECTREATMENT
GROUP

CONTROL

11.2
0.2

LOW

11.2
0.2

MEDIUM

11.5
0.2

HIGH

11.4
0.3

F E M A L E S

CONTROL

10.2
0.1

LOW

10.2
0.3

MEDIUM

10.5
0.3

HIGH

10.6
0.4* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL ($P < 0.05$)

* LESS THAN 10% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
 FOR VALID STATISTICAL ANALYSIS

Table 6a (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT0988S73

HEMATOLOGY - COAGULOGRAM

TREATMENT DAY 734
 ARITHMETIC MEANS WITH STANDARD ERRORS
 (6 ANIMALS/SEX/TREATMENT GROUP)

M A L E S

TREATMENT GROUP	PRO TIME SEC
CONTROL	11.3 0.4
LOW	10.9 0.2
MEDIUM	10.8 0.2
HIGH	11.2 0.3

F E M A L E S

CONTROL	10.3 0.2
LOW	11.3 * 0.4
MEDIUM	10.8 0.3
HIGH	10.6 0.3

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
 FOR VALID STATISTICAL ANALYSIS

Table 7

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988573

CLINICAL CHEMISTRY

TREATMENT DAY 42
 ARITHMETIC MEANS WITH STANDARD ERRORS
 (6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	TTL BILI MG/DL	AP IU/L	M A L E S GPT IU/L	GOT IU/L	TTL CHOL MG/DL
CONTROL	0.09 0.01	270 8	27 4	110 5	92 7
LOW	0.09 0.01	284 15	29 3	85 6	86 5
MEDIUM	0.10 0.01	257 16	39 12	87 4	92 3
HIGH	0.07 0.02	268 15	32 6	92 7	89 4
CONTROL	0.11 0.01	221 15	14 1	115 9	85 3
LOW	0.12 0.01	198 15	12 0	87 2	86 5
MEDIUM	0.11 0.00	198 17	12 1	103 9	76 4
HIGH	0.11 0.01	216 21	14 2	101 7	74 2

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
FOR VALID STATISTICAL ANALYSIS

Table 7 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988573

CLINICAL CHEMISTRY

TREATMENT DAY 42
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	M A L E S			PHENYLAL MG/DL
	GLUCOSE MG/DL	BUN MG/DL		
CONTROL	185 13	23.9 1.0		3.4 + 0.2
LOW	179 13	21.1 * 0.8		3.0 0.2
MEDIUM	182 7	22.0 1.0		3.2 0.2
HIGH	198 4	23.3 0.8		3.4 0.1
F E M A L E S				
CONTROL	189 9	18.1 0.6		3.2 + 0.1
LOW	203 4	17.7 0.9		3.5 + 0.2
MEDIUM	205 10	21.6 3.2		3.2 + 0.1
HIGH	211 11	18.9 1.2		3.0 + 0.2

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT FOR VALID STATISTICAL ANALYSIS

Table 7 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988573

CLINICAL CHEMISTRY						
TREATMENT DAY 92						
ARITHMETIC MEANS WITH STANDARD ERRORS (6 ANIMALS/SEX/TREATMENT GROUP)						
TREATMENT GROUP	TTL BILI MG/DL	M A L E S				
		AP IU/L	GPT IU/L	GOT IU/L	TTL CHOL MG/DL	
CONTROL	0.18 0.01	156 9	43 3	99 3	83 3	
LOW	0.18 0.04	186 10	55 11	102 12	76 5	
MEDIUM	0.13 0.02	151 16	45 3	92 3	74 2	
HIGH	0.16 0.01	173 22	43 4	102 6	70 * 1	
F E M A L E S						
CONTROL	0.22 0.01	169 15	37 2	103 11	95 + 3	
LOW	0.20 0.01	145 15	33 * 1	81 * 3	80 ** 3	
MEDIUM	0.21 0.01	152 21	34 2	94 9	84 3	
HIGH	0.23 0.02	164 19	38 3	92 4	86 7	

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT

FOR VALID STATISTICAL ANALYSIS

Table 7 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988573

CLINICAL CHEMISTRY				
TREATMENT DAY 189				
ARITHMETIC MEANS WITH STANDARD ERRORS				
(6 ANIMALS/SEX/TREATMENT GROUP)				
TREATMENT GROUP	TTL BILI MG/DL	M A L E S		
		AP IU/L	GPT IU/L	GOT IU/L
CONTROL	0.08 0.01	114 6	25 3	126 8
LOW	0.10 0.01	141 14	32 4	126 13
MEDIUM	0.09 0.01	111 12	27 1	126 7
HIGH	0.10 0.01	130 7	39 8	142 13
F E M A L E S				
CONTROL	0.13 0.01	115 11	33 7	116 11
LOW	0.14 0.00	98 10	25 3	70 6
MEDIUM	0.12 0.01	123 18	24 2	92 11
HIGH	0.13 0.02	130 17	39 10	111 18
				TTL CHOL MG/DL
				103 6
				91 9
				89 4
				75 5
				107 6
				101 9
				88 5
				86 5

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT

FOR VALID STATISTICAL ANALYSIS

Table 7 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

CLINICAL CHEMISTRY				
TREATMENT DAY 189				
ARITHMETIC MEANS WITH STANDARD ERRORS (6 ANIMALS/SEX/TREATMENT GROUP)				
TREATMENT GROUP	GLUCOSE MG/DL	M A L E S		PHENYLAL MG/DL
		BUN MG/DL		
CONTROL	173 11	9.0 1.2		3.0 + 0.2
LOW	175 6	18.0 * 1.4		3.3 0.2
MEDIUM	161 5	19.2 * 1.9		3.4 + 0.1
HIGH	163 11	15.9 * 2.1		3.4 0.1
F E M A L E S				
CONTROL	142 6	17.5 0.5		3.5 + 0.1
LOW	147 4	16.1 1.0		3.2 + 0.1
MEDIUM	144 4	17.4 1.1		3.2 + 0.2
HIGH	149 3	17.0 0.4		3.2 0.1

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT

FOR VALIO STATISTICAL ANALYSIS

Table 7 (cont.)

SC-19192; 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PI#0988S73

CLINICAL CHEMISTRY

TREATMENT DAY 364
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	TTL BILI MG/DL	AP IU/L	M A L E S GPT IU/L	GOT IU/L	TTL CHOL MG/DL
CONTROL	0.09 0.01	125 11	38 11	152 + 21	79 8
LOW	0.11 0.01	124 13	42 14	101 ** 9	71 8
MEDIUM	0.11 0.01	139 18	42 6	122 + 7	72 8
HIGH	0.10 0.01	139 10	60 11	131 + 16	56 * 5
F E M A L E S					
CONTROL	0.14 0.01	108 15	38 7	143 + 19	90 + 6
LOW	0.14 0.01	110 18	25 5	89 16	89 11
MEDIUM	0.17 0.02	105 14	30 4	96 12	69 6
HIGH	0.15 0.01	131 23	35 8	132 32	57 * 4

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT

FOR VALID STATISTICAL ANALYSIS

Table 7 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988573

CLINICAL CHEMISTRY

TREATMENT DAY 364
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	GLUCOSE MG/DL	M A L E S		PHENYLAL MG/DL
		GLUCOSE MG/DL	PHENYLAL MG/DL	
CONTROL	123	2.4	3.2	
	8	0.8	0.1	
LOW	115	3.1	3.1 +	
	6	0.6	0.1	
MEDIUM	127	5.0 *	3.1	
	6	0.5	0.1	
HIGH	122	6.0 *	2.8 **	
	10	1.0	0.1	
F E M A L E S				
CONTROL	133	10.4	3.0 +	
	5	1.4	0.1	
LOW	132	11.8	2.7	
	5	3.8	0.1	
MEDIUM	121	9.7	2.7	
	6	2.2	0.1	
HIGH	131	11.3	2.9	
	9	2.1	0.1	

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
FOR VALID STATISTICAL ANALYSIS

Table 7 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988S73

CLINICAL CHEMISTRY

TREATMENT DAY 547
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	TTL BILI MG/DL	M A L E S		F E M A L E S	
		AP IU/L	GPT IU/L		GOT IU/L
CONTROL	5.17 0.01	50 + 3	35 8		186 36
LOW	4.18 0.01	56 5	36 9		146 34
MEDIUM	0.22 + 0.01	52 + 7	65 15		164 18
HIGH	0.21 + 0.01	91 ** 11	96 + 19		233 31
CONTROL	0.22 0.02	54 7	55 9		81 + 9
LOW	0.22 0.01	44 1	42 6		76 + 8
MEDIUM	0.21 + 0.01	44 + 5	41 3		63 + 4
HIGH	0.24 0.01	48 7	68 28		117 ** 17

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
FOR VALID STATISTICAL ANALYSIS

Table 7 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988S73

CLINICAL CHEMISTRY			
TREATMENT DAY 547			
ARITHMETIC MEANS WITH STANDARD ERRORS			
(6 ANIMALS/SEX/TREATMENT GROUP)			
TREATMENT GROUP	M A L E S		PHENYLAL MG/DL
	GLUCOSE MG/DL		
CONTROL	97		3.5
	6		0.2
LOW	108		3.3
	4		0.2
MEDIUM	98		3.3
	7		0.3
HIGH	115		2.8
	10		0.2
F E M A L E S			
CONTROL	104		2.8
	8		0.2
LOW	127 *		2.3 *
	5		0.1
MEDIUM	101		2.7
	7		0.1
HIGH	118		2.5
	9		0.1

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT

FOR VALID STATISTICAL ANALYSIS

Table 7 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988S73

CLINICAL CHEMISTRY

TREATMENT DAY 734
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	TTL BILI MG/DL	AP IU/L	M A L E S GPT IU/L	GOT IU/L	TTL CHOL MG/DL
CONTROL	0.05 0.01	113 26	31 4	100 11	136 19
LOW	0.05 0.01	76 11	43 8	82 9	126 3
MEDIUM	0.08 0.01	124 65	43 7	91 7	139 7
HIGH	0.09 0.02	134 29	63 * 12	130 30	98 * 6
F E M A L E S					
CONTROL	0.03 0.01	38 8	37 12	141 26	142 13
LOW	0.07 * 0.01	35 5	29 5	100 9	108 * 4
MEDIUM	0.12 * 0.01	35 6	36 4	94 * 11	104 * 11
HIGH	0.16 * 0.02	48 4	51 15	74 * 5	58 * 3

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
FOR VALID STATISTICAL ANALYSIS

Table 7 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PI#0989S73

CLINICAL CHEMISTRY

TREATMENT DAY 734
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	GLUCOSE MG/DL	PHENYLAL MG/DL	M A L E S		K MMOL/L	CA MMOL/L
			NA MMOL/L			
CONTROL	91	3.4	151		5.0	2.6 +
	15	0.3	1		0.2	0.0
LOW	115	3.2	146 *		4.8	2.6 +
	8	0.1	1		0.2	0.1
MEDIUM	129 *	2.9	145 *		5.0	2.8 **
	5	0.3	2		0.2	0.0
HIGH	124 *	2.6 *	145 *		4.7	2.7 **
	7	0.1	1		0.3	0.0
F E M A L E S						
CONTROL	111	2.5	137		3.8	2.8 +
	12	0.1	4		0.2	0.1
LOW	103	2.6	144 +		3.5 +	2.9 **
	4	0.1	4		0.1	0.0
MEDIUM	125	2.3	148 *		3.8	2.9 **
	9	0.1	3		0.1	0.0
HIGH	135	2.1 *	146		3.6	2.8 +
	5	0.1	1		0.2	0.0

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
FOR VALID STATISTICAL ANALYSIS

Table 7 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

CLINICAL CHEMISTRY

TREATMENT DAY 734
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	TTL PROT G/DL	PROTEIN ELECTROPHORESIS						ALB/GLOB RATIO
		ALB %	ALPHA1 %	ALPHA2 %	ALPHA3 %	BETA1&2 %	GAMMA %	
M A L E S								
CONTROL	6.8	25.1	25.0	6.3	5.9	23.2	14.3	3.3
	0.3	1.7	0.9	0.2	0.3	1.9	1.8	0.0
LOW	5.9	31.6	19.9 *	6.5	5.0	19.5 *	15.9	0.5
	0.1	3.5	0.7	0.2	0.3	1.3	2.2	0.1
MEDIUM	7.1	33.1 *	20.5 *	5.5 *	4.8	18.9 *	16.4	3.5 *
	0.1	2.8	1.2	0.4	3.3	0.9	1.9	0.1
HIGH	5.6	38.6 *	17.6 *	5.8	5.4	17.3 *	15.6	0.6 *
	0.2	2.3	0.2	3.2	0.5	0.7	1.6	0.0
F E M A L E S								
CONTROL	7.9	41.9	18.5	4.7	4.9	17.8	12.3	3.7
	0.2	1.3	1.1	0.4	0.3	0.8	1.0	0.1
LOW	8.2	40.3	16.4	4.6	6.1	17.5	15.1	3.7
	0.3	1.7	0.7	0.6	1.2	1.1	1.4	0.1
MEDIUM	7.7	45.1	16.3	4.7	5.9	15.7	12.8	0.8
	0.2	3.3	1.4	0.4	1.1	0.5	1.9	0.1
HIGH	7.1 *	50.5 *	12.4 *	3.4	3.6	16.1	14.2	1.0 *
	0.1	1.1	1.2	0.4	0.6	0.8	1.6	0.1

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT FOR VALID STATISTICAL ANALYSIS

Table 8

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

URINALYSIS

TREATMENT DAY 42
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	PH	SP GRAV	GLUCOSE	KETONES	M A L E S		PROTEIN	BILI	OC BLOOD	UROBILI
CONTROL	8.5 0.2	1.019 0.003	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
LOW	8.3 0.1	1.029 * 0.003	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
MEDIUM	8.5 0.2	1.028 0.003	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
HIGH	8.4 0.2	1.029 * 0.002	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
F E M A L E S										
CONTROL	8.6 0.2	1.025 0.002	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
LOW	8.4 0.2	1.027 0.003	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
MEDIUM	8.0 0.4	1.027 0.003	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
HIGH	8.7 0.2	1.029 0.002	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT

FOR VALID STATISTICAL ANALYSIS

Table 8 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

TREATMENT GROUP	URINALYSIS					TREATMENT DAY 42 ARITHMETIC MEANS WITH STANDARD ERRORS (6 ANIMALS/SEX/TREATMENT GROUP)				
	MICROSCOPIC FINDINGS					M A L E S				
	RBC AVE#/HPF	WBC AVE#/HPF	CASTS AVE#/LPF	CRYSTALS	BACTERIA	PHENYLKE PKU				
CONTROL	0	0	0	0	2	0				
	0	0	0	0	1	0				
LOW	0	0	0	1 *	1	0				
	0	0	0	0	0	0				
MEDIUM	0	0	0	1	1	0				
	0	0	0	0	0	0				
HIGH	0	0	0	1	1	0				
	0	0	0	0	0	0				
F E M A L E S										
CONTROL	0	0	0	1	1	0				
	0	0	0	0	0	0				
LOW	0	0	0	1	1	0				
	0	0	0	0	0	0				
MEDIUM	0	0	0	1	1	0				
	0	0	0	0	0	0				
HIGH	0	0	0	1	1	0				
	0	0	0	0	0	0				

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
FOR VALID STATISTICAL ANALYSIS

Table 8 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988573

URINALYSIS

TREATMENT DAY 92
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	PH	SP GRAV	GLUCOSE	M A L E S KETONES	PROTEIN	BILI	OC BLOOD
CONTROL	8.3 0.2	1.028 0.002	0 0	0 0	0 0	0 0	0 0
LOW	7.7 0.4	1.029 0.003	0 0	0 0	0 0	0 0	0 0
MEDIUM	8.1 0.1	1.032 0.002	0 0	0 0	0 0	0 0	0 0
HIGH	7.8 0.3	1.030 0.003	0 0	0 0	0 0	0 0	0 0
F E M A L E S							
CONTROL	8.2 0.1	1.029 0.002	0 0	0 0	0 0	0 0	0 0
LOW	8.1 0.3	1.029 0.004	0 0	0 0	0 0	0 0	0 0
MEDIUM	8.3 0.2	1.033 0.003	0 0	0 0	0 0	0 0	0 0
HIGH	7.2 * 0.4	1.027 0.003	0 0	0 0	0 0	0 0	0 0

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL ($P < 0.05$)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT FOR VALID STATISTICAL ANALYSIS

Table 8 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988573

URINALYSIS

TREATMENT DAY 190
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	PH	SP GRAV	GLUCOSE	KETONES	PROTEIN	BILI	OC BLOOD	UROBILI
M A L E S								
CONTROL	7.5 0.3	1.037 0.007	0 0	0 0	1 0	0 0	0 0	0 0
LOW	7.5 0.2	1.045 0.005	0 0	0 0	1 0	0 0	0 0	0 0
MEDIUM	7.5 0.2	1.058 0.010	0 0	0 0	2 0	0 0	0 0	0 0
HIGH	6.7 0.5	1.068 * 0.008	0 0	0 0	1 0	0 0	0 0	0 0
F E M A L E S								
CONTROL	8.2 0.3	1.028 0.002	0 0	0 0	0 0	0 0	0 0	0 0
LOW	7.7 0.3	1.030 0.002	0 0	0 0	0 0	0 0	0 0	0 0
MEDIUM	7.6 0.5	1.029 0.002	0 0	0 0	0 0	0 0	0 0	0 0
HIGH	7.0 * 0.3	1.028 0.003	0 0	0 0	0 0	0 0	0 0	0 0

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
FOR VALID STATISTICAL ANALYSIS

Table 8 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

URINALYSIS

TREATMENT DAY 190
 ARITHMETIC MEANS WITH STANDARD ERRORS
 (6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	MICROSCOPIC FINDINGS					BACTERIA	PHENYLKE PKU
	RBC AVE#/HPF	WBC AVE#/HPF	CASTS AVE#/LPF	CRYSTALS			
M A L E S							
CONTROL	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
LOW	0	0	0	0	1	1	0
	0	0	0	0	0	0	0
MEDIUM	0	0	0	1	1	1	0
	0	0	0	0	1	1	0
HIGH	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
F E M A L E S							
CONTROL	0	0	0	1	1	1	0
	0	0	0	0	0	0	0
LOW	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
MEDIUM	0	0	0	0	0	1	0
	0	0	0	0	0	0	0
HIGH	0	0	0	0	0	1	0
	0	0	0	0	0	0	0

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

* LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
 FOR VALID STATISTICAL ANALYSIS

Table 8 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988573

URINALYSIS

TREATMENT DAY 364
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	PH	SP GRAV	GLUCOSE	KETONES	M A L E S PROTEIN	BILI	OC BLOOD	UROBILI
CONTROL	6.7 0.2	1.054 0.008	0 0	0 0	2 0	0 0	0 0	0 0
LOW	6.3 0.3	1.039 0.007	0 0	0 0	2 0	0 0	0 0	0 0
MEDIUM	6.3 0.1	1.044 0.007	0 0	0 0	2 0	0 0	1 1	0 0
HIGH	6.0 * 0.0	1.048 0.004	0 0	0 0	1 * 0	0 0	1 0	0 0
F E M A L E S								
CONTROL	6.8 0.2	1.024 0.003	0 0	0 0	1 1	0 0	0 0	0 0
LOW	6.2 * 0.1	1.020 0.003	0 0	0 0	1 1	0 0	0 0	0 0
MEDIUM	6.2 * 0.2	1.027 0.003	0 0	0 0	0 0	0 0	0 0	0 0
HIGH	6.1 * 0.1	1.028 0.003	0 0	0 0	0 0	0 0	0 0	0 0

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

* LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
FOR VALID STATISTICAL ANALYSIS

Table 8 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

URINALYSIS

TREATMENT DAY 364
 ARITHMETIC MEANS WITH STANDARD ERRORS
 (6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	MALES					FEMALES					PHENYLKE PKU
	R3C AVE#/HPF	WBC AVE#/HPF	CASIS AVE#/LPF	CRYSTALS	BACTERIA	R3C AVE#/HPF	WBC AVE#/HPF	CASIS AVE#/LPF	CRYSTALS	BACTERIA	
CONTROL	1	1	0	1	2	0	1	0	0	0	0
	1	1	0	0	0						0
LOW	0	3	0	1	1	0	0	0	0	0	0
	0	3	0	0	0						0
MEDIUM	3	1	0	1	1	0	0	0	0	0	0
	3	1	0	0	0						0
HIGH	7	5	0	1	1	0	4	0	0	1	0
	4	4	0	0	1					1	0
CONTROL	0	1	1	0	1	0	1	0	0	0	0
	0	1	0	0	0						0
LOW	1	0	0	0	1	0	0	0	0	0	0
	1	0	0	0	0						0
MEDIUM	0	0	0	0	1	0	0	0	0	0	0
	0	0	0	0	0						0
HIGH	0	0	0	0	1	0	0	0	0	1	0
	0	0	0	0	1					1	0

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
 FOR VALID STATISTICAL ANALYSIS

Table 8 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

URINALYSIS

TREATMENT DAY 547
 ARITHMETIC MEANS WITH STANDARD ERRORS
 (6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	PH	SP GRAV	PROTEIN	M A L E S BILI	OC BLOOD	UROBILI
CONTROL	6.5 0.2	1.031 0.004	1 0	0 0	0 0	0 0
LOW	6.9 0.4	1.027 0.003	1 0	0 0	0 0	0 0
MEDIUM	6.1 0.1	1.026 0.003	1 0	0 0	0 0	0 0
HIGH	6.5 0.2	1.026 0.005	1 0	0 0	0 0	0 0
F E M A L E S						
CONTROL	7.0 0.3	1.023 0.004	1 0	0 0	0 0	0 0
LOW	7.0 0.3	1.028 0.004	1 0	0 0	0 0	0 0
MEDIUM	6.3 * 0.2	1.041 * 0.004	1 0	0 0	0 0	0 0
HIGH	6.0 * 0.0	1.043 * 0.004	0 0	0 0	0 0	0 0

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
 FOR VALID STATISTICAL ANALYSIS

Table 8 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PI#0988S73

URINALYSIS						
TREATMENT DAY 547						
ARITHMETIC MEANS WITH STANDARD ERRORS						
(6 ANIMALS/SEX/TREATMENT GROUP)						
TREATMENT GROUP	MICROSCOPIC FINDINGS					
	M A L E S					
	RBC AVE#/HPF	WBC AVE#/HPF	CASTS AVE#/LPF	CRYSTALS	BACTERIA	PHENYLKE PKU
CONTROL	0 0	1 0	0 0	1 0	1 0	0 0
LOW	1 1	1 0	0 0	1 0	1 0	0 0
MEDIUM	0 0	1 0	0 0	1 0	1 0	0 0
HIGH	0 0	1 0	0 0	0 0	1 0	0 0
F E M A L E S						
CONTROL	0 0	1 0	0 0	1 0	1 0	0 0
LOW	3 3	1 0	0 0	0 0	1 0	0 0
MEDIUM	0 0	1 0	0 0	1 0	1 0	0 0
HIGH	0 0	0 0	0 0	1 0	1 0	0 0

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

* LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
FOR VALID STATISTICAL ANALYSIS

Table 8 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

URINALYSIS

TREATMENT DAY 734
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	PH	SP GRAV	GLUCOSE	M A L E S GLUCOSE	KETONES	PROTEIN	BILI	OC BLOOD
CONTROL	6.5 0.2	1.021 0.004	1	1	0	3	0	1
LOW	6.5 0.3	1.028 0.002	0	0	0	3	0	0
MEDIUM	6.2 0.2	1.027 0.004	0	0	0	3	0	1
HIGH	6.0 0.0	1.034 * 0.004	0	0	0	1 *	0	0
F E M A L E S								
CONTROL	6.3 0.2	1.028 0.004	0	0	0	2	0	0
LOW	6.2 0.2	1.029 0.004	0	0	0	2	0	0
MEDIUM	6.0 0.3	1.021 0.003	0	0	0	1	0	0
HIGH	5.2 * 0.2	1.028 0.004	0	0	0	1 *	0	0

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
FOR VALID STATISTICAL ANALYSIS

Table 8 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

URINALYSIS

TREATMENT DAY 734
ARITHMETIC MEANS WITH STANDARD ERRORS
(6 ANIMALS/SEX/TREATMENT GROUP)

TREATMENT GROUP	MICROSCOPIC FINDINGS					PHENYLKE PKU
	RBC AVE#/HPF	WBC AVE#/HPF	CASTS AVE#/LPF	CRYSTALS	BACTERIA	
M A L E S						
CONTROL	2	2	0	1	2	0
	1	1	0	0	0	0
LOW	0	3	0	2 *	3	
	0	1	0	1	0	
MEDIUM	2	7 *	0	1	3	
	1	3	0	0	0	
HIGH	0	2	0	1	2	0
	0	1	0	0	0	0
F E M A L E S						
CONTROL	1	7	0	1	3	0
	1	1	0	0	0	0
LOW	0	2 *	0	1	2	
	0	1	0	0	1	
MEDIUM	1	0 *	0	1	2	
	1	0	0	0	0	
HIGH	0	1 *	0	1	2	0
	0	1	0	0	0	0

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
FOR VALID STATISTICAL ANALYSIS

POSTMORTEM OBSERVATIONSOrgan weights.

Group mean organ weights and organ/body weight ratios are presented in Table 9 and 9a; individual values may be found in the Appendix. No biologically meaningful compound-related variations in organ weights were observed in any of the organs. Significant decreases in the following organ weights were observed: heart weight at the medium dose males and high dose males and females; liver weight at the low and high dose females; and thyroid weight at the low and medium dose males. The corresponding organ/body weight ratios in these groups showed inconsistent changes or, in general, were unremarkable. In addition, microscopically, these organs were unremarkable. Hence, the significant absolute organ weight changes described above are considered unrelated to treatment.

Table 9 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988573

AUTOPSY ORGAN WEIGHTS

TREATMENT DAY 805
ARITHMETIC MEANS WITH STANDARD ERRORS

TREATMENT GROUP	VEN PROS MG	M A L E S			OVARIES MG	UTERUS MG
		SEM VES MG	TESTES G			
CONTROL	531	356	3.20		133.6	982
	50	44	0.24		43.8	86
LOW	642	309	2.73		100.3	750
	119	40	0.14		27.4	115
MEDIUM	616	392	2.96		232.7	945
	72	83	0.14		154.9	125
HIGH	604	308	3.19		157.4	882
	69	32	0.15		65.0	74
F E M A L E S						
CONTROL						
LOW						
MEDIUM						
HIGH						

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL ($P < 0.05$)+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
FOR VALID STATISTICAL ANALYSIS

Table 9a
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73
ORGAN/BODY WEIGHT RATIOS

TREATMENT GROUP	BODY WT G	TREATMENT DAY 805 ARITHMETIC MEANS WITH STANDARD ERRORS				
		HEART X10-3	M A L E S KIDNEYS X10-3	LIVER X10-3	ADRENALS X10-3	THYROID X10-3
CONTROL	560	3.58	8.97	30.9	0.194	0.093
	21	0.16	0.66	1.2	0.022	0.016
LOW	538	3.51	8.55	31.0	0.217	0.068
	21	0.23	0.73	1.1	0.065	0.009
MEDIUM	536	3.39	9.10	29.8	0.129	0.063 *
	23	0.20	1.07	1.8	0.018	0.006
HIGH	522	3.06	8.23	30.4	0.129	0.073
	29	0.16	0.65	1.0	0.010	0.007
			F E M A L E S			
CONTROL	466	3.00	5.96	30.6	0.226	0.077
	21	0.11	0.23	1.0	0.021	0.007
LOW	400 *	3.35	6.59	30.9	0.270	0.088
	17	0.19	0.34	1.2	0.040	0.007
MEDIUM	412 *	3.16	6.65	31.5	0.366	0.097
	16	0.18	0.30	0.9	0.102	0.021
HIGH	343 *	3.31	7.72 *	34.9 *	0.394	0.075
	10	0.12	0.24	0.9	0.117	0.005
						PITUITARY X10-3
						0.036
						0.004
						0.063
						0.030
						0.075
						0.034
						0.031
						0.004
						0.161
						0.045
						0.186
						0.041
						0.139
						0.052
						0.267
						0.119

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL (P < 0.05)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT FOR VALID STATISTICAL ANALYSIS

Table 9a (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988573
 ORGAN/BODY WEIGHT RATIOS

TREATMENT GROUP	VEN PROS X10-3	TREATMENT DAY 805 ARITHMETIC MEANS WITH STANDARD ERRORS		OVARIES X10-3	UTERUS X10-3
		SEM VES X10-3	M A L E S TESTES X10-3		
CONTROL	0.92 0.06	0.66 0.10	5.73 0.41		
LOW	1.29 0.26	0.58 0.07	5.21 0.25		
MEDIUM	1.15 0.11	0.75 0.16	5.60 0.30		
HIGH	1.17 0.13	0.59 0.06	6.26 0.33		
F E M A L E S					
CONTROL				0.31 0.11	2.20 0.21
LOW				0.25 0.07	1.85 0.24
MEDIUM				0.52 0.33	2.29 0.34
HIGH				0.47 0.20	2.58 0.20

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL ($P < 0.05$)

+ LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
 FOR VALID STATISTICAL ANALYSIS

Gross and microscopic findings.

Complete postmortem (gross and microscopic) findings for each of the 144 control and 216 treated rats started on the study are presented in the Appendix. Those organs examined microscopically are presented in Table 10; about 24 different organs from each of 134 control and 206 treated rats were examined, totalling about 7,600 tissue sections. All non-neoplastic histopathologic changes are summarized in Table 11. All neoplastic lesions are described separately on page 89 and summarized in Tables 12 and 13. Twenty rats, ten from control groups (nine control males: C21CM, G16CM, G18CM, G26CM, J2CM, J5CM, L10CM, L15CM, L21CM; one control female: H24CF) and ten from treated groups (one low dose male: L11LM; three medium dose males: A14MM, G28MM, J25MM; three high dose males: A3HM, C15HM, G13HM; three high dose females: D4HF, D16HF, F6HF) in which severe autolysis precluded meaningful histologic evaluation of a majority of organs were excluded from the study as indicated in the Appendix.

Careful review of Table 11 reveals that administration of SC-19192 was not associated with an increase in incidence or severity of commonly encountered non-neoplastic lesions nor were lesions of an unusual nature encountered. A large number of lesions of suspected infectious or degenerative (aging process) etiology were observed in both sexes in all treated and control groups, however. These lesions were considered to be of "spontaneous" origin, and will be related briefly.

Spontaneous pulmonary alterations were found in the majority of control and test animals. They included chronic murine pneumonia,

Table 10

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Tissues Examined Microscopically
(Males/Females)

Organ	Control	Low Dose	Medium Dose	High Dose
No. of rats started on study	72/72	36/36	36/36	36/36
Stomach	63/70	35/36	31/36	33/33
Small intestine	55/64	30/35	31/32	31/32
Large intestine	54/63	33/33	30/32	29/30
Lung	62/71	35/36	33/35	33/33
Heart	63/69	34/35	33/36	33/33
Kidney	63/71	35/35	33/36	33/33
Liver	62/70	35/36	33/36	33/33
Spleen	59/70	35/36	33/35	33/33
Pancreas	58/65	35/34	30/34	32/33
Pituitary	52/60	30/33	28/30	30/33
Thyroid	55/67	30/34	33/35	32/31
Adrenal	63/69	34/35	33/35	32/33
Mammary gland	26/50	19/28	21/28	19/27
Testis/ovary	62/66	34/33	33/31	33/33
Seminal vesicle/uterus	59/69	35/34	33/34	30/33
Prostate/vagina	62/58	35/29	33/23	30/31
Urinary bladder	60/68	34/33	32/32	31/33
Lymph node	32/34	8/9	8/6	20/22
Nerve	58/59	19/16	14/18	28/30
Salivary gland	59/67	20/20	15/19	32/31
Brain	56/67	33/35	32/34	31/33
Spinal cord	44/56	28/30	25/25	26/31
Bone with marrow	50/66	15/9	10/10	33/31
Eye	39/46	10/7	10/10	25/26
No. of rats lost due to autolysis	9/1	1/0	3/0	3/3

accompanied in most cases by bronchiectasis of various degrees of severity, chronic interstitial pneumonitis with significant chronic inflammatory changes in alveolar septa, acute or chronic bronchitis, peribronchial lymphoid hyperplasia, edema, emphysema, focal abscessation, or perivascular lymphocytic infiltration. Most of the animals found dead exhibited a certain degree of hyperemia.

A few animals demonstrated pathologic changes of the gastrointestinal tract. Gastric ulcer, gastritis, focal mucosal necrosis, submucosal edema, focal mucosal calcifications, glandular dilatation, pigmentation of mucosal epithelium, and squamous hyperplasia were found occasionally in stomach sections of control and treated animals. No significant changes were seen in the small intestine. In the large intestine, cross sections of nematodes were seen in a few control and treated rats.

A generally low incidence of myocardial alterations included occasional slight nonsuppurative myocarditis, focal fibrosis, mild hypertrophy and congestion of vessels. The lower incidence of myocarditis in medium and high dose groups was considered spontaneous and not related to treatment.

Spontaneous chronic nephritis, expressed by different degrees of glomerulosclerosis, dilatation of renal tubules filled with eosinophilic material and extensive infiltration by chronic inflammatory cells, or interstitial nephritis, where chronic inflammatory changes were contained mostly in interstitial tissue, were found in all groups with slightly higher incidence in control, low and medium dose males. The lower incidence

of inflammatory changes in the high dose group male rats was considered coincidental and not related to treatment because no dose relationship was apparent. Other incidental renal lesions found with comparable frequency in all experimental groups included congestion, mineral deposits in the cortico-medullary junction, focal tubular dilatation, pyelitis, cyst, abscessation, transitional cell hyperplasia, and focal tubular necrosis.

Various inflammatory changes found in liver sections of small numbers of control and test animals included nonsuppurative hepatitis, pericholangitis and perivascularitis. Focal or nodular hyperplasia was seen occasionally in all groups and was consistent with the age and strain of rats. Other spontaneous changes of the liver included various degrees of congestion, fatty change, focal necrosis, focal cytoplasmic degeneration, small bile duct proliferation and occasional extramedullary hematopoiesis, without any significant differences between groups.

Extramedullary hematopoiesis and/or pigment deposition in the spleen occurred in control and test groups of animals with essentially comparable incidence and degree as did lymphoid or reticulum cell hyperplasia. Splenitis or congestion were observed in a very small number of animals.

Incidental changes of the pancreas demonstrated in a few animals of each group included mild forms of pancreatitis, ductal hyperplasia, glandular atrophy, islet cell hyperplasia, and chronic arteritis.

Pituitary sections from small numbers of control and treated animals demonstrated chromophobe hyperplasia, congestion, occasional cyst or hemorrhage.

Focal squamous metaplasia, follicular hyperplasia or follicular atrophy were found sporadically in the thyroid in all groups.

Angiectasis of the adrenal was occasionally observed in male animals while a higher incidence was found in both control and treated female rats. Various other pathologic changes of the adrenal without significant increase in any particular experimental group included focal or nodular cortical hyperplasia, vacuolization of zona fasciculata, focal necrosis, congestion, medullary hyperplasia, focal hemorrhage, and occasional cyst or pigmentation in the cortex.

Non-neoplastic changes of the mammary gland were occasionally encountered and included a cyst, abscess, or galactoceles.

A common change found in the testes of animals from control and treated groups was seminiferous tubular atrophy often accompanied by tubular atrophy of the seminal vesicle and glandular atrophy of the prostate, a complex which is compatible with aging. Other incidental lesions were arteritis, interstitial cell hyperplasia, focal fibrosis, and focal calcifications. Similarly, seminal vesicles occasionally exhibited tubular atrophy, arteritis, or tubular hypertrophy. The most common finding in the prostate was glandular atrophy and prostatitis, with a few animals having

glandular hypertrophy or focal calcifications. Again, these changes were compatible with the age and did not show a preponderance in any experimental group.

Evaluation of the urinary bladder was especially rigorous, being performed with particular attention directed toward detecting any alterations whatever. Spontaneous changes found in small numbers of animals, evenly distributed between control and test groups, included occasional cystitis, submucosal edema, mucosal trabeculation, calculus, epithelial dysplasia and muscular hypertrophy. None of these changes were compound-related.

Incidental inflammatory changes of various degrees of severity observed in the uterus of control and test animals included endometritis, cervicitis and abscessation. Other sporadic findings included endometrial hyperplasia, polyp, cyst, congestion and squamous metaplasia.

Follicular or luteal cysts were observed commonly in the ovaries of animals of all groups and were compatible with the age. Isolated instances of oophoritis, atrophy and congestion were noted.

A few control and treated rats exhibited reticulum cell hyperplasia involving the lymph nodes.

Abnormal findings were unusual in the brain of any of the animals. Sporadic cases of abscessation, meningitis, vasculitis, congestion, focal calcification and focal hemorrhage had no significant distribution between treated or control rats.

Examination of bone containing marrow showed no significant pathologic changes. Occasional hypercellularity or hypocellularity was observed.

In the eye, a few cases of keratitis, dacryoadenitis, retinal degeneration, or synechia were seen evenly distributed between all groups.

No pathologic changes were detected in sections of vagina, nerve, salivary gland, and spinal cord from any of the animals examined.

In conclusion, all non-neoplastic alterations observed were considered to be spontaneous in nature, compatible with the age and strain of rats in the experiment and unrelated to administration of SC-19192.

Table 11

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Histopathologic Summary*
(All non-neoplastic changes)

	MALES							FEMALES									
	INCIDENCE**				%			INCIDENCE**				%					
	C	L	M	H	C	L	M	H	C	L	M	H	C	L	M	H	
STOMACH																	
Ulcer	3/63			1/33	5			3		1/36	1/36	1/33		3		3	3
Submucosal edema	1/63	1/35			2	3											
Focal calcification		2/35	1/31			6	3			1/36					3		
Gastritis	1/63			2/33	2			6	1/70			1/33	1				3
Focal necrosis			1/31	1/33			3	3									
Glandular dilatation									1/70			1/33	1				3
Mucosal pigmentation									3/70	1/36			4	3			
Squamous hyperplasia										1/36		1/33		3			3
LARGE INTESTINE																	
Nematodiasis	2/54	1/33	2/30	2/29	4	3	7	7	4/63	3/33	1/32		6	9		3	
HEART																	
Myocarditis	11/63	8/34	2/33	3/33	17	23	6	9	6/69	1/35	3/36	1/33	9	3	8		3
Fibrosis	2/63	6/34	2/33	1/33	3	18	6	3	2/69		2/36	1/33	3		6		3
Congestion	2/63	2/34	1/33		3	6	3		1/69				1				
Hypertrophy		2/34	3/33	1/33		6	9	3	4/69		1/36		6		3		
LUNG																	
Chronic murine pneumonia	25/62	15/35	14/33	11/33	40	43	42	33	31/71	14/36	17/35	14/33	44	39	49		42
Chronic interstitial pneumonitis	4/62	2/35	2/33	4/33	6	6	6	12			4/35	1/33			11		3
Bronchitis	4/62	5/35	1/33	1/33	6	14	3	3	1/71	2/36			1	6			
Peribronchial lymphoid hyperplasia	5/62	4/35	1/33	4/33	8	11	3	12	5/71	2/36	3/35	5/33	7	6	9		15

* Microscopic findings were entered if found in more than one animal.

** No. of organs affected/No. of organs examined.

C = Control; L = Low; M = Medium; H = High.

Table 11 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

	MALES							FEMALES								
	INCIDENCE				%			INCIDENCE				%				
	C	L	M	H	C	L	M	H	C	L	M	H	C	L	M	H
SPLEEN																
Reticulum cell hyperplasia	1/59	1/35		1/33	2	3		3	2/70	2/36			3	6		
Pigmentation	9/59	8/35	5/33	3/33	15	23	15	9	24/70	13/36	14/35	7/33	34	36	40	21
Congestion	3/59	1/35			5	3			2/70	1/36		2/33	3	3		6
Splenitis	1/59		1/33	1/33	2		3	3								
Extramedullary hematopoiesis	1/59	5/35			2	14			5/70	2/36	2/35	1/33	7	6	6	3
Lymphoid hyperplasia									1/70	1/36			1	3		
PANCREAS																
Pancreatitis	5/58	2/35		1/32	9	6		3	3/65		1/34	1/33	5	3	3	3
Chronic arteritis	6/58	5/35	3/30		10	14	10		1/65	3/34			1		9	
Ductal hyperplasia	1/58		1/30		2		3		1/65				1			
Glandular atrophy	1/58				2				2/65				3			
Islet cell hyperplasia			1/30				3		1/65				1			
PITUITARY																
Chromophobe hyperplasia	2/52	3/30	2/28	4/30	4	10	7	13	8/60	4/33	8/30	3/33	13	12	27	9
Congestion	2/52	1/30	2/28	2/30	4	3	7	7	5/60	1/33	2/30		8	3	7	
Cyst	1/52	2/30	1/28	1/30	2	7	4	3			1/30				3	
Hemorrhage									3/60		2/30	2/33	5		7	6
THYROID																
Follicular hyperplasia	5/55	2/30	2/33	1/32	9	7	6	3	1/67	1/34			1	3		
Squamous metaplasia	4/55	6/30	1/33	5/32	7	20	3	16	5/67	8/34	6/35	2/31	7	23	17	6
Follicular atrophy									2/67				3			
ADRENAL																
Angiectasis	3/63	2/34	1/33	2/32	5	6	3	6	28/69	15/35	16/35	13/33	41	43	46	39
Cortical hyperplasia ^a	7/63	5/34	3/33	2/32	11	15	9	6	10/69	3/35	5/35	6/33	14	9	14	18
Vacuolization of zona fasciculata	4/63	7/34	3/33	3/32	6	21	9	6	9/69	3/35	4/35	1/33	13	9	11	3
Necrosis	2/63	1/34			3	3			5/69	1/35		1/33	7	3		3
Congestion	9/63	6/34	5/33	2/32	14	18	15	6	15/69	3/35	4/35	7/33	22	9	11	21
Medullary hyperplasia	4/63	2/34		1/32	6	6		3		1/35				3		
Hemorrhage			1/33	2/32			3	6	3/69	2/35	2/35	2/33	4	6	6	6

^a = focal and/or nodular

Table 11 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

	MALES										FEMALES									
	INCIDENCE					%					INCIDENCE					%				
	C	L	M	H	C	L	M	H			C	L	M	H	C	L	M	H		
ADRENAL (cont.)																				
Cyst											1/69	1/35			1	3			3	3
Pigmentation																				
MAMMARY GLAND																				
Cyst	2/26				8						3/50				6					
Abscessation		3/19				16					2/50				4				4	
Galactoceles											2/50				4				4	
TESTIS																				
Tubular atrophy	23/62	17/34	19/33	4/33	37	50	58	12												
Arteritis	5/62	6/34	5/33		8	18	15													
Interstitial cell hyperplasia	2/62	1/34			3	3														
Fibrosis	1/62				2															
Calcification	1/62	1/34			2	3														
SEMINAL VESICLE																				
Tubular atrophy	4/59	2/35	9/33	2/30	7	6	27	7												
Tubular hypertrophy	1/59	2/35	1/33		2	6	3													
Arteritis	4/59	4/35			7	11														
PROSTATE																				
Glandular atrophy	15/62	8/35	10/33	2/30	24	23	30	7												
Prostatitis	7/62	8/35	3/33	2/30	11	23	9	7												
Glandular hypertrophy	1/62		2/30		2			7												
Calcification	1/62	1/35	1/33		2	3	3													
URINARY BLADDER																				
Cystitis	3/60		1/32	1/31	5		3	3			2/68				3					
Submucosal edema	4/60	4/34	3/32	2/31	7	12	9	6			2/68	1/33	1/32	2/33	3	3		6		
Trabeculation		2/34	1/32			6	3				1/68		1/32	2/33	1	3		6		
Calculus	1/60	1/34	1/32		2	3	3													
Epithelial dysplasia											1/68				1					
Muscular hypertrophy											3/68		1/32	1/33	4			3		

Table 11 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

	MALES						FEMALES										
	INCIDENCE			H	%			INCIDENCE			H	%					
	C	L	M		C	L	M	C	L	M		C	L	M	H		
UTERUS																	
Endometritis																	
Abscessation																	
Endometrial hyperplasia																	
Cyst																	
Polyp																	
Congestion																	
Cervicitis																	
Squamous metaplasia																	
OVARY																	
Cyst																	
Congestion																	
Atrophy																	
Oophoritis																	
LYMPH NODE																	
Reticulum cell hyperplasia																	
BRAIN																	
Abscessation	2/56	1/33			4	3											
Meningitis	1/56	1/33	1/32		2	3	3										
Vasculitis	1/56				2												
Congestion	1/56				2					1/35							
Calcification	1/56	3/33			2	3				1/35							
Hemorrhage																	
BONE MARROW																	
Hypercellularity	4/50	1/15			8	7											
Hypocellularity																	
EYE																	
Keratitis	5/39	2/10	1/10		13	20	10										
Dacryoadenitis	1/39			1/25	3												
Retinal degeneration		1/10				10											
Synechia		1/10				10											

Table 11 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

	MALES							FEMALES								
	INCIDENCE				%			INCIDENCE				%				
	C	L	M	H	C	L	M	H	C	L	M	H	C	L	M	H
LUNG (cont.)																
Edema	3/62	2/35		2/33	5	6		6	1/71	2/36		1/33	1	6		3
Hyperemia	9/62	6/35	5/33	6/33	14	17	15	18	8/71	6/36	6/35	3/33	11	17	17	9
Abscessation		1/35				11			1/71				1			
Emphysema									2/71		2/35	1/33	3	6		3
Perivascular lymphocytic infiltration									1/71	1/36			1	3		
KIDNEY																
Chronic nephritis	20/63	19/35	10/33	2/33	32	54	30	6	6/71	1/35	2/36		8	3	6	
Interstitial nephritis	20/63	9/35	13/33	3/33	32	26	39	9	10/71	3/35	3/36	2/33	14	9	8	6
Congestion	9/63	6/35	4/33	1/33	14	17	12	3	8/71	4/35	5/36	1/33	11	11	14	3
Mineral deposits	1/63	2/35	2/33	1/33	2	6	6	3	18/71	11/35	10/36	10/33	25	31	28	30
Tubular dilatation	5/63			2/33	8			6	6/71	4/35	3/36		8	11	8	
Pyelitis	2/63	4/35	1/33		3	11	3		2/71				3			
Cyst	1/63		2/33		2		6		1/71		1/36		1		3	
Abscessation		1/35				3			1/71				1			
Transitional cell hyperplasia																
Tubular necrosis									4/71			1/33	6	3		3
									3/71	1/35	1/36		4	3		
LIVER																
Hepatitis	1/62	3/35	1/33	4/33	2	9	3	12	6/70	2/36	3/36	2/33	9	6	8	6
Congestion	26/62	9/35	10/33	8/33	42	26	30	24	26/70	13/36	13/36	5/33	37	36	36	15
Fatty change	5/62	1/35	2/33		8	3	6		4/70	3/36			6	8		
Necrosis	5/62				8				4/70	2/36		1/33	6	6		3
Cytoplasmic degeneration	6/62	5/35	4/33	5/33	10	14	12	15	4/70	1/36	1/36	3/33	6	3	3	9
Bile duct proliferation	4/62	1/35	1/33		6	3	3		2/70	2/36		1/33	3	6		3
Hyperplasias	5/62	4/35	2/33	3/33	8	11	6	9	11/70	6/36	2/36	2/33	16	17	6	6
Pericholangitis	6/62	4/35	1/33	4/33	10	11	3	12	1/70	1/36	1/36	6/33	1	3	3	18
Perivascularitis		2/35				6					1/36				3	
Extramedullary hematopoiesis																
		2/35		1/33		6		3	2/70		1/36		3			3

a - focal and/or nodular.

Tumor incidence.

A detailed investigation of tumorigenic potential was conducted. All gross lesions found in any tissues were diagnosed. Brain and bladder received special attention, with seven coronal sections of brain representing all major neuroanatomic areas, and sections from four different levels of urinary bladder being examined from each control and treated animal.

The incidence of various types of histologically-proven tumors is presented in Table 13. This table records the histologic types of primary tumors per organ. In cases where multiple primary neoplasms of the mammary gland were observed, the following procedure was employed in entering such tumors in the table: multiple, histologically identical tumors in the same animal are listed as a single entry; when both benign and malignant neoplasms of similar histologic type (e.g., adenoma and adenocarcinoma) are encountered, only the malignant neoplasm is entered; if two or more different histological types were found in the same animal, each type is recorded.

Table 12 presents the identification of animals bearing histologically-proven neoplasms and indicates the day of initial gross detection of a tumor. All primary tumors found in any animal from this study are listed, with the sole exception of multiple primary neoplasms of mammary glands. If two histologically identical tumors were initially detected at different times in the same animal, then both were entered. Similarly,

all tumors of different histological types (e.g., adenoma and myxoma), or of varying prognostic implications (e.g., fibroadenoma and adenocarcinoma), detected either on the same or different days of treatment in the same animal, were listed separately. In cases of multiple histologically identical tumors found on the same day, only one was entered for each animal in the table.

All neoplasms were categorized according to primary site; secondary (metastatic) growths are identified in the pathology report on individual animals in the Appendix. Malignant neoplasms of lymphoid or reticuloendothelial tissues are categorized as such; the presence of neoplastic infiltrate in various organs is expected and is recorded in the Appendix, but it is not further utilized in tumor data analysis.

One tissue mass reported at necropsy in low dose female rat No. MLF (Path. No. 95844) was not located during subsequent tissue examination and processing; since a microscopic diagnosis was not available, the nature of the mass (non-neoplastic or neoplastic) was not determined.

KEY FOR TABLE 12

FD = Found Dead

KE = Killed in extremis

KD = Killed by design

B = Benign

M = Malignant

Table 12

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Identification of Animals Bearing Histologically-Proven Tumors

Rat No.	Treatment Group	Sex	Initial Detection (Days)	Anatomic Location; primary tumor	Date of the Animal (Days on Study)			Microscopic Diagnosis	B or M
					FD	KE	KD		
A4CM	Control	M	718	Urinary bladder	718			Transitional cell carcinoma	M
A6CM	Control	M	747	Liver	747			Cholangioma	B
A7CM	Control	M	557	Pituitary	557			Adenocarcinoma	M
A15CM	Control	M	805	Testis			805	Interstitial cell tumor	B
C17CM	Control	M	490	Mammary gland	542			Squamous cell carcinoma	M
C25CM	Control	M	805	Adrenal			805	Adenoma	B
			805	Site unknown				Carcinoma	M
C26CM	Control	M	805	Adrenal			805	Pheochromocytoma	B
E7CM	Control	M	630	Brain	630			Astrocytoma	M
E16CM	Control	M	805	Pancreas			805	Islet cell adenoma	B
			805	Adrenal				Pheochromocytoma	B
			805	Brain				Astrocytoma	M
			735	Subcutaneous mass				Fibroma	B
E22CM	Control	M	708	Pituitary	708			Chromophobe adenoma	B
			708	Reticuloendothelial tissues				Reticulum cell sarcoma	M
E30CM	Control	M	805	Adrenal			805	Pheochromocytoma	B
G14CM	Control	M	609	Reticuloendothelial tissues	609			Reticulum cell sarcoma	M
G20CM	Control	M	769	Adrenal	769			Pheochromocytoma	B
G27CM	Control	M	801	Pituitary	801			Chromophobe adenoma	B
			801	Adrenal				Pheochromocytoma	B
J3CM	Control	M	682	Testis	682			Hemangioma	B
			682	Lymphoid tissues				Lymphosarcoma	M
J4CM	Control	M	684	Pituitary	684			Chromophobe adenoma	B
			420	Mammary gland				Fibroadenoma	B

Table 12 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Rat No.	Treatment Group	Sex	Initial Detection (Days)	Anatomic Location;		Fate of the Animal (Days on Study)			Microscopic Diagnosis	B or M
				primary tumor		FD	KE	KD		
J15CM	Control	M	784	Pancreas		784			Islet cell adenoma	B
J23CM	Control	M	754	Adrenal		754			Adenoma	B
J29CM	Control	M	656	Pituitary		656			Adenocarcinoma	M
L1CM	Control	M	805	Liver				805	Angioma	B
L7CM	Control	M	625	Pituitary		625			Chromophobe adenoma	B
L9CM	Control	M	805	Pituitary				805	Chromophobe adenoma	B
L23CM	Control	M	805	Thyroid				805	Adenocarcinoma	M
L25CM	Control	M	805	Pituitary				805	Chromophobe adenoma	B
			805	Parathyroid					Adenoma	B
L29CM	Control	M	805	Pancreas				805	Islet cell adenoma	B
			805	Pituitary					Chromophobe adenoma	B
L30CM	Control	M	732	Pancreas		732			Islet cell adenoma	B
A5LM	Low	M	805	Pituitary				805	Chromophobe adenoma	B
			805	Adrenal					Pheochromocytoma	B
A13LM	Low	M	805	Adrenal				805	Malignant pheochromocytoma	M
			560	Mammary gland					Fibroadenoma	B
			784	Mammary gland					Hemangioendothelioma	B
			805	Subcutaneous mass					Liposarcoma	M
A17LM	Low	M	689	Pituitary		689			Adenocarcinoma	M
A20LM	Low	M	785	Thyroid			785		Adenoma	B
A26LM	Low	M	805	Adrenal				805	Pheochromocytoma	B
			805	Testis					Interstitial cell tumor	B
C12LM	Low	M	736	Adrenal			736		Pheochromocytoma	B
C22LM	Low	M	805	Stomach				805	Papilloma	B
C27LM	Low	M	805	Pituitary				805	Chromophobe adenoma	B
			805	Thyroid					Adenocarcinoma	M
C28LM	Low	M	805	Pituitary				805	Chromophobe adenoma	B
E18LM	Low	M	777	Pituitary			777		Chromophobe adenoma	B

Table 12 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Rat No.	Treatment Group	Sex	Initial Detection (Days)	Anatomic Location; primary tumor	Fate of the Animal (Days on Study)			Microscopic Diagnosis	B or M
					FD	KE	KD		
E29LM	Low	M	714	Pituitary	714			Chromophobe adenoma	B
G2LM	Low	M	689	Adrenal	689			Adenoma	B
J8LM	Low	M	805	Mediastinum			805	Liposarcoma	M
J9LM	Low	M	805	Adrenal			805	Pheochromocytoma	B
L28LM	Low	M	805	Pituitary			805	Chromophobe adenoma	B
			805	Brain				Oligodendroglioma	M
A8MM	Medium	M	805	Reticuloendothelial tissue			805	Reticulum cell sarcoma	M
			805	Adrenal				Pheochromocytoma	B
A16MM	Medium	M	670	Pituitary	670			Chromophobe adenoma	B
A18MM	Medium	M	741	Adrenal	741			Adenoma	B
			728	Subcutaneous mass				Fibroma	B
A25MM	Medium	M	805	Testis			805	Interstitial cell tumor	B
			805	Mesentery				Lipoma	B
C1MM	Medium	M	805	Adrenal			805	Pheochromocytoma	B
			763	Mammary gland				Adenocarcinoma	M
			805	Urinary bladder				Transitional cell carcinoma	M
C18MM	Medium	M	805	Kidney			805	Adenoma	B
			805	Pituitary				Chromophobe adenoma	B
E17MM	Medium	M	805	Pituitary			805	Chromophobe adenoma	B
			805	Adrenal				Adenoma	B
G19MM	Medium	M	707	Liver	707			Hepatocellular adenoma	B
			707	Pituitary				Chromophobe adenoma	B
G21MM	Medium	M	805	Pituitary			805	Chromophobe adenoma	B
G22MM	Medium	M	805	Omentum			805	Lipoma	B
J19MM	Medium	M	754	Large intestine	754			Leiomyoma	B
			754	Pancreas				Islet cell adenoma	B
			754	Adrenal				Pheochromocytoma	B
			754	Reticuloendothelial tissue				Reticulum cell sarcoma	M

Table 12 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Rat No.	Treatment Group	Sex	Initial Detection (Days)	Anatomic Location; primary tumor	Fate of the Animal (Days on Study)			Microscopic Diagnosis	B or M
					FD	KE	KD		
L8HM	Medium	M	805	Adrenal			805	Pheochromocytoma	B
L14HM	Medium	M	792	Pituitary	792			Chromophobe adenoma	B
A1HM	High	M	805	Pancreas			805	Adenoma	B
A9HM	High	M	805	Adrenal			805	Pheochromocytoma	B
A29HM	High	M	805	Lung			805	Adenoma	
			805	Adrenal				Pheochromocytoma	B
			805	Stomach				Papilloma	
C2HM	High	M	805	Adrenal			805	Pheochromocytoma	B
			693	Mammary gland				Fibroma	B
C16HM	High	M	648	Pituitary	648			Chromophobe adenoma	B
C24HM	High	M	805	Adrenal			805	Pheochromocytoma	B
E12HM	High	M	775	Reticuloendothelial tissue	775			Reticulum cell sarcoma	M
E14HM	High	M	805	Adrenal			805	Pheochromocytoma	B
E23HM	High	M	733	Pituitary	733			Chromophobe adenoma	B
			672	Mammary gland				Myxoma	B
			733	Site unknown				Undifferentiated carcinoma	M
G24HM	High	M	640	Omentum	640			Lipoma	B
G30HM	High	M	805	Pancreas			805	Islet cell adenoma	B
			805	Adrenal				Pheochromocytoma	B
L5HM	High	M	672	Subcutaneous mass	720			Fibrosarcoma	M
L22HM	High	M	805	Pituitary			805	Chromophobe adenoma	B
L27HM	High	M	805	Pituitary			805	Chromophobe adenoma	B
			805	Testis				Interstitial cell tumor	B

Table 12 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Rat No.	Treatment Group	Sex	Initial Detection (Days)	Anatomic Location; primary tumor	Fate of the Animal (Days on Study)			Microscopic Diagnosis	B or M
					FD	KE	KD		
B2CF	Control	F	759 469	Adrenal Mammary gland		759		Adenoma Adenoma	B B
B6CF	Control	F	805 686 805	Pituitary Mammary gland Omentum			805	Chromophobe adenoma Fibroadenoma Lipoma	B B B
B10CF	Control	F	692 672	Adrenal Mammary gland	692			Adenoma Fibroadenoma	B B
B17CF	Control	F	434 644	Mammary gland Mammary gland	644			Adenocarcinoma Cystadenoma	M B
B18CF	Control	F	651	Mesentery		765		Fibrolipoma	B
B22CF	Control	F	504 399	Pituitary Mammary gland	504			Adenocarcinoma Fibroadenoma	M B
B26CF	Control	F	790 700 756 790	Pituitary Mammary gland Mammary gland Reticuloendothelial tissue	790			Chromophobe adenoma Cystadenoma Cystadenoma Reticulum cell sarcoma	B B B M
B30CF	Control	F	635 476 635	Pituitary Mammary gland Mammary gland	635			Chromophobe adenoma Fibroadenoma Fibroadenoma	B B B
D6CF	Control	F	805	Mammary gland			805	Fibroadenoma	B
D13CF	Control	F	596 596	Liver Mediastinum	596			Cholangioma Lipoma	B B
D17CF	Control	F	469 682	Mammary gland Omentum	682			Fibroadenoma Liposarcoma	B M
D19CF	Control	F	805 805 805	Mammary gland Mammary gland Mammary gland			805	Fibroadenoma Cystadenoma Adenocarcinoma	B B M
D20CF	Control	F	700	Pituitary	700			Chromophobe adenoma	B
D21CF	Control	F	577	Uterus	577			Hemangioma	B
D22CF	Control	F	469	Mammary gland	802			Fibroadenoma	B

Table 12 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Rat No.	Treatment Group	Sex	Initial		Anatomic Location; primary tumor	Fate of the Animal (Days on Study)			Microscopic Diagnosis	B or M
			Detection (Days)			FD	KE	KD		
D29CF	Control	F	784		Pituitary	784			Chromophobe adenoma	B
			784		Parathyroid				Adenoma	B
			392		Mammary gland				Fibroadenoma	B
F13CF	Control	F	805		Pituitary			805	Chromophobe adenoma	B
F15CF	Control	F	756		Mammary gland			805	Fibroadenoma	B
F16CF	Control	F	805		Pancreas			805	Islet cell adenoma	B
			805		Pituitary				Chromophobe adenoma	B
			469		Mammary gland				Adenoma	B
			567		Uterus				Fibrosarcoma	M
F17CF	Control	F	805		Adrenal			805	Pheochromocytoma	B
			805		Ovary				Tubular adenoma	B
F27CF	Control	F	719		Mammary gland		719		Fibroadenoma	B
			385		Mammary gland				Adenocarcinoma	M
F28CF	Control	F	539		Reticuloendothelial tissue	539			Reticulum cell sarcoma	M
F30CF	Control	F	805		Pituitary			805	Chromophobe adenoma	B
			469		Mammary gland				Fibroadenoma	B
			805		Ovary				Tubular adenoma	B
			805		Uterus				Fibroma	B
H1CF	Control	F	612		Pituitary	612			Adenoma	B
			581		Mammary gland				Cystadenoma	B
H6CF	Control	F	427		Mammary gland	579			Cystadenoma	B
H11CF	Control	F	525		Mammary gland			805	Fibroadenoma	B
			805		Pituitary				Chromophobe adenoma	B
H12CF	Control	F	668		Pituitary	668			Chromophobe adenoma	B
H13CF	Control	F	427		Mammary gland	685			Fibroadenoma	B
			668		Mammary gland				Fibroadenoma	B
H19CF	Control	F	805		Pituitary			805	Chromophobe adenoma	B
			567		Mammary gland				Fibroadenoma	B
H21CF	Control	F	805		Parathyroid			805	Adenoma	B
			805		Adrenal				Pheochromocytoma	B
			581		Mammary gland				Cystadenoma	B
			693		Mammary gland				Cystadenoma	B

Table 12 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Rat No.	Treatment Group	Sex	Initial Detection (Days)	Anatomic Location; primary tumor	Fate of the Animal (Days on Study)			Microscopic Diagnosis	B or M
					FD	KE	KD		
H25CF	Control	F	693	Adrenal	693			Adenoma	B
			693	Ovary				Hemangioma	B
H30CF	Control	F	805	Pituitary			805	Chromophobe adenoma	B
			665	Mammary gland				Fibroadenoma	B
K1CF	Control	F	588	Mammary gland	697			Cystadenoma	B
			697	Ovary				Tubular adenoma	B
K4CF	Control	F	702	Ovary	702			Hemangioendothelioma	B
K7CF	Control	F	462	Mammary gland	695			Cystadenoma	B
			672	Mammary gland				Cystadenoma	B
K10CF	Control	F	785	Pituitary	785			Chromophobe adenoma	B
K13CF	Control	F	532	Mammary gland			805	Fibroadenoma	B
K20CF	Control	F	371	Mammary gland	581			Fibroadenoma	B
			581	Mammary gland				Fibroadenoma	B
K23CF	Control	F	560	Mammary gland	684			Adenocarcinoma	M
K25CF	Control	F	805	Pituitary			805	Chromophobe adenoma	B
K26CF	Control	F	766	Pituitary	766			Chromophobe adenoma	B
			651	Mammary gland				Fibroadenoma	B
K28CF	Control	F	406	Mammary gland	553			Fibroadenoma	B
			490	Mammary gland				Angiofibroma	B
K29CF	Control	F	805	Pituitary			805	Chromophobe adenoma	B
M4CF	Control	F	728	Mammary gland			805	Cystadenoma	B
M6CF	Control	F	801	Pituitary	801			Chromophobe adenoma	B
			728	Mammary gland				Fibroadenoma	B
			801	Uterus				Fibrosarcoma	M
M7CF	Control	F	720	Pancreas	720			Islet cell adenoma	B
			720	Pituitary				Chromophobe adenoma	B
M10CF	Control	F	476	Mammary gland			805	Cystadenoma	B

Table 12 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Rat No.	Treatment Group	Sex	Initial Detection (Days)	Anatomic Location; primary tumor	Fate of the Animal (Days on Study)			Microscopic Diagnosis	B or M
					FD	KE	KD		
M12CF	Control	F	329 575	Mammary gland Mammary gland	575			Fibroadenoma Fibroadenoma	B B
M15CF	Control	F	623 700	Mammary gland Mammary gland			805	Adenocarcinoma Adenocarcinoma	M M
M16CF	Control	F	455	Mammary gland	617			Adenoma	B
M22CF	Control	F	805 560 588	Pituitary Mammary gland Mammary gland			805	Chromophobe adenoma Adenocarcinoma Adenocarcinoma	B M M
M25CF	Control	F	668	Pituitary	668			Chromophobe adenoma	B
M27CF	Control	F	716 420	Pituitary Mammary gland	716			Chromophobe adenoma Fibroadenoma	B B
B8LF	Low	F	588	Mammary gland	692			Fibroadenoma	B
B15LF	Low	F	385	Mammary gland	386			Adenoma	B
B21LF	Low	F	764 693 721	Pituitary Mammary gland Mammary gland	764			Chromophobe adenoma Cystadenoma Cystadenocarcinoma	B B M
B24LF	Low	F	728	Mammary gland	798			Fibroadenoma	B
B27LF	Low	F	672 805	Mammary gland Ovary			805	Fibroadenoma Fibroma	B B
D10LF	Low	F	238	Subcutaneous mass		271		Angiofibroma	B
D11LF	Low	F	805	Paraovarian mass			805	Lipoma	B
D14LF	Low	F	664	Pituitary	664			Chromophobe adenoma	B
D30LF	Low	F	805 805 805 658	Pituitary Thyroid Adrenal Mammary gland			805	Chromophobe adenoma Adenoma Pheochromocytoma Fibroadenoma	B B B B
F1LF	Low	F	800	Reticuloendothelial tissue	800			Reticulum cell sarcoma	M
F3LF	Low	F	800 728 672	Pituitary Pituitary Mammary gland			728	Chromophobe adenoma Chromophobe adenoma Fibroadenoma	B B B

Table 12 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Rat No.	Treatment Group	Sex	Initial Detection (Days)	Anatomic Location; primary tumor	Date of the Animal (Days on Study)			Microscopic Diagnosis	B or M
					FD	KE	KD		
F8LF	Low	F	672	Mammary gland			805	Fibroadenoma	B
F12LF	Low	F	805	Pituitary			805	Chromophobe adenoma	B
			805	Parathyroid				Adenoma	B
F20LF	Low	F	805	Pituitary			805	Chromophobe adenoma	B
H3LF	Low	F	716	Pituitary	716			Chromophobe adenoma	B
			716	Thyroid				Adenoma	B
			693	Mammary gland				Cystadenoma	B
			716	Uterus				Leiomyoma	B
H4LF	Low	F	483	Mammary gland	698			Adenocarcinoma	M
			693	Mammary gland				Adenocarcinoma	M
H14LF	Low	F	665	Mammary gland		750		Cystadenoma	B
H20LF	Low	F	357	Mammary gland	728			Fibroadenoma	B
			728	Reticuloendothelial tissue				Reticulum cell sarcoma	M
H22LF	Low	F	641	Reticuloendothelial tissue	641			Reticulum cell sarcoma	M
			641	Pituitary				Chromophobe adenoma	B
H27LF	Low	F	482	Mediastinum	482			Liposarcoma	M
K3LF	Low	F	455	Mammary gland	640			Fibroadenoma	B
			525	Mammary gland				Adenocarcinoma	M
K6LF	Low	F	762	Pituitary	762			Adenocarcinoma	M
			490	Mammary gland				Fibroadenoma	B
			512	Mammary gland				Adenoma	B
K8LF	Low	F	805	Pituitary			805	Chromophobe adenoma	B
K19LF	Low	F	693	Pituitary	693			Chromophobe adenoma	B
K22LF	Low	F	732	Pituitary		732		Chromophobe adenoma	B
K27LF	Low	F	805	Pituitary			805	Chromophobe adenoma	B
			805	Uterus				Fibrosarcoma	M
M9LF	Low	F	805	Pituitary			805	Chromophobe adenoma	B
			805	Mammary gland				Fibroadenoma	B

Table 12 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Rat No.	Treatment Group	Sex	Initial Detection (Days)	Anatomic Location; primary tumor	Fate of the Animal (Days on Study)			Microscopic Diagnosis	B or M
					FD	KE	KD		
M11LF	Low	F	754	Pituitary	754			Chromophobe adenoma	B
M17LF	Low	F	805	Pituitary			805	Chromophobe adenoma	B
			532	Mammary gland				Fibroadenoma	B
			553	Mammary gland				Adenocarcinoma	M
M23LF	Low	F	805	Pituitary			805	Chromophobe adenoma	B
			644	Mammary gland				Fibroadenoma	B
			644	Mammary gland				Adenocarcinoma	M
B4MF	Medium	F	805	Pituitary			805	Chromophobe adenoma	B
B7MF	Medium	F	805	Small intestine			805	Angioma	B
			616	Mammary gland				Fibroadenoma	B
			805	Mammary gland				Adenocarcinoma	M
			805	Uterus				Adenocarcinoma	M
B19LF	Medium	F	738	Uterus			738	Lipoma	B
B23MF	Medium	F	805	Pituitary			805	Chromophobe adenoma	B
B28MF	Medium	F	805	Pituitary			805	Chromophobe adenoma	B
			783	Mammary gland				Adenoma	B
D23MF	Medium	F	766	Reticuloendothelial tissue	766			Reticulum cell sarcoma	M
D24MF	Medium	F	693	Mammary gland			805	Adenocarcinoma	M
D25MF	Medium	F	595	Mammary gland	623			Fibroadenoma	B
F7MF	Medium	F	651	Mammary gland	763			Fibroadenoma	B
F9MF	Medium	F	744	Pituitary	744			Chromophobe adenoma	B
			672	Mammary gland				Cystadenoma	B
F21MF	Medium	F	389	Mammary gland	653			Benign mixed tumor	B
			532	Mammary gland				Cystadenoma	B
F24MF	Medium	F	747	Pituitary			747	Chromophobe adenoma	B
H2MF	Medium	F	748	Pituitary	748			Chromophobe adenoma	B
			748	Adrenal				Pheochromocytoma	B
			686	Mammary gland				Cystadenoma	B

Table 12 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Rat No.	Treatment Group	Sex	Initial Detection (Days)	Anatomic Location; primary tumor	Fate of the Animal (Days on Study)			Microscopic Diagnosis	B or M
					FD	KE	KD		
H8MF	Medium	F	706	Pituitary		706		Chromophobe adenoma	B
H17MF	Medium	F	706	Mammary gland				Cystadenoma	B
H26MF	Medium	F	378	Mammary gland	635			Fibroadenoma	B
H28MF	Medium	F	657	Uterus	657			Fibroma	B
H29MF	Medium	F	805	Thyroid			805	Adenoma	B
			581	Mammary gland				Fibroadenoma	B
			632	Reticuloendothelial tissue	662			Reticulum cell sarcoma	M
K9MF	Medium	F	805	Liver			805	Hepatocellular adenoma	B
			805	Pituitary				Chromophobe adenoma	B
			805	Thyroid				Adenocarcinoma	M
			805	Reticuloendothelial tissue				Reticulum cell sarcoma	M
K15MF	Medium	F	588	Mammary gland	768			Fibroadenoma	B
			651	Mammary gland				Fibroadenoma	B
K16MF	Medium	F	512	Mammary gland	619			Fibroadenoma	B
			619	Uterus				Fibroma	B
M8MF	Medium	F	757	Thyroid	757			Undifferentiated carcinoma	M
M21MF	Medium	F	623	Thyroid	623			Adenoma	B
			455	Mammary gland				Carcinosarcoma	M
M28MF	Medium	F	644	Mammary gland			805	Fibroadenoma	B
			805	Mammary gland				Fibroadenoma	B
B3HF	High	F	92	Mammary gland	669			Adenocarcinoma	M
			669	Mammary gland				Adenocarcinoma	M
B12HF	High	F	805	Pituitary			805	Chromophobe adenoma	B
			532	Mammary gland				Adenocarcinoma	M
B20HF	High	F	805	Pancreas			805	Islet cell adenoma	B
B29HF	High	F	779	Pituitary	779			Chromophobe adenoma	B
			721	Mammary gland				Cystadenoma	B
D2HF	High	F	669	Brain	669			Astrocytoma	M

Table 12 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Rat No.	Treatment Group	Sex	Initial Detection (Days)	Anatomic Location; primary tumor	Fate of the Animal (Days on Study)			Microscopic Diagnosis	B or M
					FD	KE	KD		
D28HF	H1gh	F	805	Pituitary			805	Chromophobe adenoma	B
F14HF	H1gh	F	709	Pituitary	709			Chromophobe adenoma	B
F29HF	H1gh	F	434	Mammary gland				Fibroadenoma	B
			483	Mammary gland	774			Adenocarcinoma	M
H9HF	H1gh	F	805	Pituitary			805	Adenoma	B
			805	Brain				Oligodendroglioma	M
H15HF	H1gh	F	805	Pituitary			805	Chromophobe adenoma	B
			805	Thyroid				Adenoma	B
			805	Mammary gland				Fibroadenoma	B
			805	Lymph node				Benign lymphoma	B
H23HF	H1gh	F	805	Pituitary			805	Chromophobe adenoma	B
K5HF	H1gh	F	728	Mammary gland			805	Fibroadenoma	B
K11HF	H1gh	F	805	Pituitary			805	Chromophobe adenoma	B
			455	Mammary gland				Fibroadenoma	B
			512	Mammary gland				Cystadenoma	B
			512	Mammary gland				Adenocarcinoma	M
K17HF	H1gh	F	678	Pituitary	678			Adenocarcinoma	M
			588	Mammary gland				Adenocarcinoma	M
K18HF	H1gh	F	588	Mammary gland	652			Adenoma	B
K21HF	H1gh	F	779	Pituitary		779		Adenocarcinoma	M
M2HF	H1gh	F	805	Pituitary			805	Chromophobe adenoma	B
M3HF	H1gh	F	560	Mammary gland	741			Fibroadenoma	B
M5HF	H1gh	F	805	Stomach			805	Adenocarcinoma	M
			644	Mammary gland				Fibroadenoma	B
M14HF	H1gh	F	805	Pituitary			805	Chromophobe adenoma	B
M18HF	H1gh	F	715	Reticuloendothelial tissue	715			Reticulum cell sarcoma	M
			715	Uterus				Fibrosarcoma	M

Table 13

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Frequency of types of histologically-proven tumors

Tumor Type	MALES				FEMALES			
	Control	Low Dose	Medium Dose	High Dose	Control	Low Dose	Medium Dose	High Dose
Stomach	(63) ^a	(35)	(31)	(33)	(70)	(36)	(36)	(33)
Papilloma	0	1	1	1	0	0	0	0
Adenocarcinoma	0	0	0	0	0	0	0	1
Small Intestine	(55)	(30)	(31)	(31)	(64)	(35)	(32)	(32)
Angioma	0	0	0	0	0	0	1	0
Large Intestine	(54)	(33)	(30)	(29)	(63)	(33)	(32)	(30)
Leiomyoma	0	0	1	0	0	0	0	0
Lung	(62)	(35)	(33)	(33)	(71)	(36)	(35)	(33)
Adenoma	0	0	0	1	0	0	0	0
Kidney	(63)	(35)	(33)	(33)	(71)	(35)	(36)	(33)
Adenoma	0	0	1	0	0	0	0	0
Liver	(62)	(35)	(33)	(33)	(70)	(36)	(36)	(33)
Cholangioma	1	0	0	0	1	0	0	0
Angioma	1	0	0	0	0	0	0	0
Hepatocellular Adenoma	0	0	1	0	0	0	1	0
Pancreas	(58)	(35)	(30)	(32)	(65)	(34)	(34)	(33)
Islet Cell Adenoma	4	0	1	1	2	0	0	1
Adenoma	0	0	0	1	0	0	0	0
Pituitary	(52)	(30)	(28)	(30)	(60)	(33)	(30)	(33)
Adenocarcinoma	2	1	0	0	1	1	0	2
Chromophobe Adenoma	7	6	6	4	21	17	8	9
Adenoma	0	0	0	0	1	0	0	1

a - Numbers in parentheses indicate total number of organs examined microscopically.

Table 13 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Tumor Type	MALES				FEMALES			
	Control	Low Dose	Medium Dose	High Dose	Control	Low Dose	Medium Dose	High Dose
Thyroid	(55) ^a	(30)	(33)	(32)	(67)	(34)	(35)	(31)
Adenocarcinoma	1	1	0	0	0	0	1	0
Adenoma	0	1	0	0	0	2	2	1
Adenoma, Parathyroid	1	0	0	0	2	1	0	0
Undifferentiated Carcinoma	0	0	0	0	0	0	1	0
Adrenal	(63)	(34)	(33)	(32)	(69)	(35)	(35)	(33)
Adenoma	2	1	2	0	3	0	0	0
Pheochromocytoma	5	4	4	6	2	1	1	0
Malignant Pheochromocytoma	0	1	0	0	0	0	0	0
Mammary Gland	(26)	(19)	(21)	(19)	(50)	(28)	(28)	(27)
Adenoma*	1	1	0	0	32	12	12	6
Adenocarcinoma	0	0	1	0	6	5	2	5
Carcinosarcoma	0	0	0	0	0	0	1	0
Squamous Cell Carcinoma	1	0	0	0	0	0	0	0
Myxoma	0	0	0	1	0	0	0	0
Hemangioendothelioma	0	1	0	0	0	0	0	0
Benign Mixed Tumor	0	0	0	0	0	0	1	0
Fibroma**	0	0	0	1	1	0	0	0
Testis	(62)	(34)	(33)	(33)				
Interstitial Cell Tumor	1	1	1	1				
Hemangioma	1	0	0	0				
Ovary					(66)	(33)	(31)	(33)
Tubular Adenoma					3	0	0	0
Hemangioma					1	0	0	0
Hemangioendothelioma					1	0	0	0
Fibroma					0	1	0	0

* Includes: adenoma, fibroadenoma, cystadenoma.

** Includes: fibroma, angiofibroma.

^a - Numbers in parentheses indicate total number of organs examined microscopically.

Table 13 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Tumor Type	MALES				FEMALES			
	Control	Low Dose	Medium Dose	High Dose	Control	Low Dose	Medium Dose	High Dose
Uterus					(69) ^a	(34)	(34)	(33)
Hemangioma					1	0	0	0
Fibrosarcoma					2	1	0	1
Fibroma					1	0	2	0
Leiomyoma					0	1	0	0
Adenocarcinoma					0	0	1	0
Lipoma					0	0	1	0
					0	0	1	0
Urinary Bladder								
Transitional Cell Carcinoma	(60)	(34)	(32)	(31)	(68)	(33)	(32)	(33)
	1	0	1	0	0	0	0	0
Lymph Node								
Benign Lymphoma	(32)	(8)	(8)	(20)	(34)	(9)	(6)	(22)
	0	0	0	0	0	0	0	1
Salivary Gland								
Undifferentiated Carcinoma	(59)	(20)	(15)	(32)	(67)	(20)	(19)	(31)
	0	0	0	0	0	0	1	0
Brain								
Astrocytoma	(56)	(33)	(32)	(31)	(67)	(35)	(34)	(33)
Oligodendroglioma	2	0	0	0	0	0	0	1
	0	1	0	0	0	0	0	1
Reticuloendothelial Tissues								
Reticulum Cell Sarcoma	2	0	2	1	2	3	3	1
Lymphoid Tissues								
Lymphosarcoma	1	0	0	0	0	0	0	0
Mediastinum								
Liposarcoma	0	1	0	0	0	1	0	0
Lipoma	0	0	0	0	1	0	0	0
Mesentery								
Lipoma	0	0	1	0	0	0	0	0
Fibrolipoma	0	0	0	0	1	0	0	0

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a - Numbers in parentheses indicate total number of organs examined microscopically.

Table 13 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Tumor Type	MALES				FEMALES			
	Control	Low Dose	Medium Dose	High Dose	Control	Low Dose	Medium Dose	High Dose
Omentum								
Lipoma	0	0	1	1	1	0	0	0
Liposarcoma	0	0	0	0	1	0	0	0
Subcutaneous Mass								
Fibroma	1	0	1	0	0	0	0	0
Liposarcoma	0	1	0	0	0	0	0	0
Fibrosarcoma	0	0	0	1	0	0	0	0
Angiofibroma	0	0	0	0	0	1	0	0
Paraovarian Mass								
Lipoma					0	1	0	0
Primary Site Unknown								
Carcinoma	1	0	0	1	0	0	0	0

The statistical analyses of tumor incidence data are presented in Tables 14 - 20. The definition of terminology employed in these tables is described on page 108. It includes all rats, whether dead, killed in extremis, or killed by design, which had histologically-proven tumors. Tumor types presented in this table are any tumor, only benign tumor, and any malignant tumor as well as any mammary tumor, malignant mammary tumor, benign mammary tumor, and any pituitary tumor; the latter four categories were included since they represent the types of tumors most frequently found in this study.

In no instance in either sex at any of the treated levels was the adjusted tumor incidence (refer to page 108 for definition) of any of the tumor types analyzed significantly higher than that of the respective controls. The adjusted tumor incidences for only benign tumor, any mammary tumor, and benign mammary tumor in the high dose group of female rats were significantly lower than that of the control females. This lower occurrence of the above-mentioned tumor types was considered coincidental and not treatment related. There were no statistically significant differences between adjusted tumor incidence data for the control and treated males.

In conclusion, neither the nature nor the incidence of tumors in treated male or female groups differed notably from the respective concurrent control group. No unusual tumor types were encountered, and tumor incidence rates in all groups were well within established ranges for rats of this strain and age.^{19,20,21} Thus, SC-19192 at the doses employed caused neither an increase in tumor incidence, nor the occurrence of unusual tumor types in the CRcd rat of either sex.

Definitions of Terminology Employed for Tables 14-20

COLUMN NO.

- (1) Treatment group.
- (2) Number of animals, started ----- number of animals in each treatment group at the beginning of the study.
- (3) Number of animals, microscopically evaluated.
- (4) Animal with tumor ----- number of animals with tumors during the period of study.
- (5) Effective group ----- average number of animals at risk of tumor during the period of study.
- (6) Survival probability ----- probability of animal surviving during the period of study.
- (7) Tumor index, unadjusted ----- the probability of contracting tumor based on number of animals started.
- (8) Tumor index, adjusted ----- the probability of contracting tumor based on effective number of animals (effective group).
- (9) Chi-square with 1 degree of freedom.
- (10) Excess over control ----- the difference of control and treated adjusted tumor indices.
- (11) Lower limit of 95% confidence interval for the difference of the two tumor indices.
- (12) Upper limit of 95% confidence interval for the difference of the two tumor indices.

Table 14

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Tumor Incidence - Statistical Analysis

Any Tumor - Benign and Malignant

Treatment Group (1)	Number of animal sta. mic. (2) (3)	Animal with tumors (4)	Effective group (5)	Survival probab. (6)	Tumor-index unadj. (7)	Chi-square adj. (8)	Excess over control (10)	95% confidence limits (11) (12)
MALES								
Control	72	63	26	37.12	0.23	36.11	70.03	
Low Dose	36	35	15	22.41	0.40	41.67	66.93	0.0014
							-3.11	-27.53 21.32
Medium Dose	36	33	13	24.67	0.50	36.11	52.70	1.2406
							-17.33	-41.94 7.27
High Dose	36	33	14	23.74	0.47	38.89	58.96	0.3730
							-11.07	-35.74 13.60
FEMALES								
Control	72	71	53	62.09	0.21	73.61	85.36	
Low Dose	36	36	30	34.06	0.26	83.33	88.09	0.0039
							2.73	-11.26 16.72
Medium Dose	36	36	24	32.19	0.38	66.67	74.57	1.0064
							-10.79	-28.22 6.64
High Dose	36	33	21	31.66	0.53	58.33	66.34	3.4896
							-19.02	-37.68 -0.36

* Differs significantly from control ($p < 0.05$).

Table 15

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Tumor Incidence - Statistical Analysis

(Benign Tumor Only)

Treatment Group (1)	Number of animal sta. mic. (2) (3)	Animal with tumors (4)	Effective group (5)	Survival probab. (6)	Tumor-index unadj. (7)	Chi-square (9)	Excess over control (10)	95% confidence limits (11) (12)
MALES								
Control	72	63	15	37.03	0.36	20.83	40.50	
Low Dose	36	35	10	22.44	0.45	27.78	44.57	4.07 -21.87 30.01
Medium Dose	36	33	10	24.64	0.53	27.78	40.58	0.08 -24.94 25.10
High Dose	36	33	11	23.68	0.56	30.56	46.45	5.94 -19.62 31.50
FEMALES								
Control	72	71	41	64.47	0.38	56.94	63.60	
Low Dose	36	36	19	34.09	0.60	52.78	55.73	-7.87 -28.26 12.53
Medium Dose	36	36	17	32.39	0.52	47.22	52.49	-11.11 -31.93 9.72
High Dose	36	33	11	31.51	0.74	30.56	34.91	5.9100* -49.06 -8.32

* Differs significantly from control ($p < 0.05$).

Table 16

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Tumor Incidence - Statistical Analysis

(Malignant Tumor only)

Treatment Group (1)	Number of animal sta. mic. (2) (3)	Animal with tumors (4)	Effective group (5)	Survival probab. (6)	Tumor-index unadj. (7)	Chi-square (9)	Excess over control (10)	95% confidence limits (11) (12)
MALES								
Control	72 63	11	44.89	0.36	15.28 24.50			
Low Dose	36 35	5	22.75	0.57	13.89 21.98	0.0051	-2.53	-23.69 18.64
Medium Dose	36 33	3	25.00	0.61	8.33 12.00	0.8840	-12.50	-30.41 5.40
High Dose	36 33	3	24.00	0.54	8.33 12.50	0.7492	-12.00	-30.26 6.25
FEMALES								
Control	72 71	12	62.70	0.69	16.67 19.14			
Low Dose	36 36	11	34.27	0.70	30.56 32.10	1.4023	12.96	-5.46 31.37
Medium Dose	36 36	7	29.83	0.77	19.44 23.46	0.0425	4.32	-13.73 22.38
High Dose	36 33	10	32.60	0.67	27.78 30.68	1.0241	11.54	-7.05 30.13

* Differs significantly from control ($p < 0.05$).

Table 17

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Tumor Incidence - Statistical Analysis

(Any Mammary Tumor)

Treatment Group (1)	Number of animal sta. mic. (2) (3)	Animal with tumors (4)	Effective group (5)	Survival probab. (6)	Tumor-index unadj. (7)	Chi-square (9)	Excess over control (10)	95% confidence limits (11) (12)
MALES								
Control	72	63	2	63.00	0.45	2.78	3.17	
Low Dose	36	35	1	31.00	0.59	2.78	3.23	0.3731 0.05 -7.53 7.63
Medium Dose	36	33	1	27.00	0.64	2.78	3.70	0.2627 0.53 -7.81 8.87
High Dose	36	33	2	26.50	0.59	5.56	7.55	0.1251 4.37 -6.58 15.32
FEMALES								
Control	72	71	38	67.11	0.42	52.78	56.62	
Low Dose	36	36	17	34.30	0.59	47.22	49.56	0.2159 -7.06 -27.57 13.45
Medium Dose	36	36	15	32.64	0.58	41.67	45.96	0.6210 -10.67 -31.48 10.14
High Dose	36	33	11	32.95	0.67	30.56	33.38	3.8920* -23.24 -43.24 -3.24

* Differs significantly from control ($p < 0.05$).

Table 18

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Tumor Incidence - Statistical Analysis

(Benign Mammary Tumor Only)

Treatment Group (1)	Number of animal sta. mic. (2) (3)	Animal with tumors (4)	Effective group (5)	Survival probab. (6)	Tumor-index unadj. (7)	Chi-square (9)	Excess over control (10)	95% confidence limits (11) (12)
MALES								
Control	72	63	1	64.00	0.46	1.39	1.56	
Low Dose	36	35	1	31.00	0.59	2.78	3.23	-5.26 8.59
Medium Dose	36	33	0	36.00	0.64	0.00	0.00	-4.60 1.48
High Dose	36	33	2	26.50	0.59	5.56	7.55	-4.52 16.49
FEMALES								
Control	72	71	34	66.98	0.46	47.22	50.76	
Low Dose	36	36	15	34.33	0.66	41.67	43.70	-27.52 13.40
Medium Dose	36	36	13	32.69	0.61	36.11	39.77	-31.60 9.63
High Dose	36	33	8	32.72	0.73	22.22	24.45	-45.29 -7.33

* Differs significantly from control ($p < 0.05$).

Table 19

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Tumor Incidence - Statistical Analysis

(Malignant Mammary Tumor Only)

Treatment Group (1)	Number of animal sta. mic. (2) (3)	Animal with tumors (4)	Effective group (5)	Survival probab. (6)	Tumor-index unadj. (7)	Chi-square (9)	Excess over control (10)	95% confidence limits (11) (12)
MALES								
Control	72	63	1	63.00	0.46	1.39	1.59	
Low Dose	36	35	0	36.00	0.60	0.00	0.00	-1.59 -4.67 1.50
Medium Dose	36	33	1	27.00	0.64	2.78	3.70	2.12 -5.65 9.88
High Dose	36	33	0	36.00	0.63	0.00	0.00	-1.59 -4.67 1.50
FEMALES								
Control	72	71	6	65.60	0.77	8.33	9.15	
Low Dose	36	36	6	32.00	0.82	16.67	18.75	9.60 -5.61 24.82
Medium Dose	36	36	2	32.50	0.86	5.56	6.15	-2.99 -13.81 7.82
High Dose	36	33	5	32.40	0.76	13.89	15.43	6.29 -7.98 20.55

* Differs significantly from control ($p < 0.05$).

Table 20

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Tumor Incidence - Statistical Analysis

(Any Pituitary Tumor)

Treatment Group (1)	Number of animal sta. mfc. (2) (3)	Animal with tumors (4)	Effective group (5)	Survival probab. (6)	Tumor-index unadj. (7)	Chi-square (8)	Excess over control (10)	95% confidence limits (11) (12)
MALES								
Control	72	63	9	44.42	0.39	12.50	20.26	
Low Dose	36	35	7	22.57	0.51	19.44	31.02	0.4523
							10.75	-11.69 33.20
Medium Dose	36	33	6	24.50	0.56	16.67	24.49	0.0104
							4.23	-16.50 24.96
High Dose	36	33	4	24.00	0.57	11.11	16.67	0.0015
							-3.60	-22.62 15.43
FEMALES								
Control	72	71	23	59.98	0.62	31.94	38.34	
Low Dose	36	36	18	34.00	0.64	50.00	52.94	1.3333
							14.60	-6.21 35.40
Medium Dose	36	36	8	32.00	0.77	22.22	25.00	1.1194
							-13.34	-32.75 6.06
High Dose	36	33	12	31.20	0.74	33.33	38.46	0.0211
							4.23	-17.78 26.24

* Differs significantly from control ($p < 0.05$).

SUMMARY AND CONCLUSIONS

A 115 week oral tumorigenicity study of SC-19192 was conducted employing continuous dietary administration to four week old Charles River CD strain male and female rats. The compound was administered at mean daily dosage levels of 0, 0.75, 1.5 and 3.0 g/kg of body weight. Routine physical, ophthalmoscopic and clinical laboratory examinations were performed periodically. All animals were necropsied and representative tissues from control and treated animals were processed for microscopic examination.

There was no evidence that the administration of SC-19192 at any level produced any effect on behavior or physical examination findings in the rat. The incidence of common signs, including spontaneous disease, signs of aging, etc., were comparable between control and treated animals. Likewise, the results of periodic ophthalmoscopic examinations revealed no indication of a compound-related effect. During the course of the study, two transient unidentified infectious diseases became apparent in the colony, and affected both the control and treated rats equally. No compound-induced decrease in survival rate was observed in any of the groups throughout the treatment period.

Body weight was not affected notably during the early part of the study, when the growth rate was rapid and the dietary concentration of SC-19192 was relatively low. Later in the study, significant reductions in body weight were consistently present in both male and female groups at the high dose level, and were periodically present at lower doses. Food intake

was not consistently affected except mid-study in the high dose male group. The dietary concentration of SC-19192 reached a high of 3.9% and 7.9% at the medium and high dose levels, respectively, during the latter part of the study. During this time the various diets were not isocaloric, a fact that may have influenced body weight and food intake. Group mean values (g/kg/day) for compound ingestion over the entire 115 week treatment period were within roughly 10% of the proposed doses of 0.75, 1.5 and 3.0 g/kg/day of SC-19192.

There were no biologically meaningful, statistically significant compound-related changes in the hematology, clinical chemistry and urinalysis parameters evaluated except possibly serum cholesterol and urinary pH. A mild but significant decrease in serum cholesterol was observed initially in high dose females at treatment day 42 and in the high dose males at day 92. This trend persisted in these animals throughout the study. In general, the serum cholesterol at the low and medium dose levels remained within normal limits. A significant decrease in urinary pH was observed one or more times in all treated female groups, and was clearly treatment-related at the high dose level. A tendency for a dose relationship was apparent. This effect may be related to the acidic metabolites of SC-19192 that are excreted in the rat urine.

No biologically meaningful compound-related variations in organ weights were observed.

Histopathologic examination was performed on available tissues from all animals in the study; also, all usual and unusual gross lesions and tissue masses were examined microscopically. Microscopic evaluation of seven coronal sections, representing the major neuroanatomic areas, was performed on each brain. Urinary bladder, likewise, received rigorous examination; after gross examination of the fixed hemisected bladder, four intermittent transverse bladder sections were examined microscopically.

Histopathological examination revealed no evidence of any treatment-related non-neoplastic changes in any organ or tissue. All non-neoplastic alterations observed were considered to be spontaneous in nature, being compatible with the age and strain of rat in the experiment, and were considered unrelated to oral administration of SC-19192.

Tumor data were statistically analyzed by sex employing an actuarial (Life-table) technique which adjusts for differing survival rates between groups. Using this method, tumor incidence (adjusted) was based on the number of animals actually at risk in each group and sex. In no instance in either sex at any of the treated levels was the adjusted tumor incidence of any of the types of tumors analyzed (any tumor, only benign tumor, any malignant tumor, any mammary tumor, benign mammary tumor, malignant mammary tumor, and any pituitary tumor) significantly higher than that of the respective controls.

It is concluded that continuous dietary administration of SC-19192 to four week old rats of both sexes for 115 weeks at dose levels of 3.0 g/kg/day or less, causes no biologically meaningful alterations in survival rate, rate of body weight gain, physical exam and hematology findings, and postmortem gross or microscopic changes. No significant increase in incidence of tumors of any type was observed. A consistent significant decrease in the absolute body weight was observed at the high dose level in both sexes. Food intake was consistently affected in high dose males only. SC-19192 produced a significant decrease in urinary pH in the high dose female group, which was attributed to the acidic metabolites of SC-19192 in the urine; also a mild but significant decrease in serum cholesterol was observed at the high dose level only. Biologically meaningful alterations were not consistently observed at lower dose levels (1.5 g/kg/day or less), however.

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Pathology-Toxicology
Project No. 988S73

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APPENDIX

Tables of Individual Values

Appendix Table 1

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Individual Ophthalmoscopic Findings

Treatment Group	Rat Number	Sex	Treatment Week	Observations
Control	A10CM	M	52	Cornea - superficial haziness (bilat.).
			98	Cornea - unchanged (bilateral).
			101	Animal died.
	A11CM	M	52	Cornea - superficial haziness (L. eye).
			98	Cornea - superficial haziness (bilat.). Lens Cortex - prominent Y suture (bilateral).
			107	Animal died.
	A15CM	M	98	Cornea - superficial haziness and scar (bilateral). Lens - posterior subcapsular opacity (R. eye).
	A27CM	M	98	Cornea - superficial haziness (bilat.).
	B2CF	F	98	Cornea - superficial haziness (L. eye).
	B6CF	F	98	Lens - posterior cortical discrete opacity (L. eye). Chromodacryorrhea (R. eye).
	B9CF	F	98	Cornea - stromal opacity (R. eye). Corneal scar (L. eye).
			99	Animal died.
	B11CF	F	31	Cornea - superficial haziness (R. eye).

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Individual Ophthalmoscopic Findings

Treatment Group	Rat Number	Sex	Treatment Week	Observations
Control	B17CF	F	31	Cornea - superficial focal translucent opacities (R. eye).
			52	Cornea - unchanged (R. eye).
			76	Cornea - unchanged (R. eye). Appearance of exophthalmia, increased aqueous humor, enlarged anterior chamber (L. eye).
			77	Eye - severe exophthalmia, marked anterior segment inflammation and infection; entire orbit severely hyperemic; corneal stroma infiltrated with foreign material (staphyloma?) (L. eye).
			92	Animal died.
	B26CF	F	98	Lens - focal, tiny, posterior cortical droplets (L. eye).
	B30CF	F	31	Cornea - superficial haziness (bilateral).
			52	Cornea - unchanged (bilateral).
			90	Animal died.
	C17CM	M	76	Severe anterior segment inflammation process (R. eye).
			77	Animal died.
	C19CM	M	52	Lens - posterior subcapsular focal opacification (R. eye).
			96	Animal died.
	D6CF	F	27	Lens - discrete posterior subcapsular translucent opacities (L. eye).
			52	Lens - only one opacity noticed (L. eye).
			98	Lens - three posterior opacities noted--not translucent.
	D12CF	F	52	Retina - pale; vasoconstriction evident. Retinal atrophy (L. eye).
			98	Retina - unchanged (L. eye).

Appendix Table 1 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Individual Ophthalmoscopic Findings

Treatment Group	Rat Number	Sex	Treatment Week	Observations
Control	D18CF	F	27	Cornea - superficial haziness (R. eye).
			52	Cornea - unchanged (R. eye).
			98	Cornea - superficial haziness (bilat.) Retina - hemorrhagic area in right aspect of optic disc (L. eye).
	D20CF	F	52	Cornea - superficial haziness (bilat.).
			98	Cornea - unchanged (bilateral).
			100	Animal died.
	E2CM	M	52	Lens - droplet opacity posterior sub-capsule (R. eye).
			98	Lens - lesion no longer present (R. eye).
	D13CM	M	98	Cornea - plaque (translucent) elevations (L. eye).
	E25CM	M	31	Lens - translucent cortical opacity; medially located (L. eye).
			52	Lens - unchanged (L. eye).
			98	Lens - unchanged (L. eye).
	F5CF	F	98	Lens cortex - prominent Y sutures (bilateral).
			101	Animal died.
	F13CF	F	52	Lens - anterior capsule lesion extending through anterior chamber to endothelium of cornea (R. eye).
			98	Lens - unchanged (R. eye). Cornea - superficial haziness (R. eye).
	F16CF	F	98	Lens - nuclear and cortical opacification (cataract) (R. eye).
	F26CF	F	52	Palpebral hyperemia, chromodacryorrhea (R. eye).
			98	Unchanged (R. eye).

Appendix Table 1 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Individual Ophthalmoscopic Findings

Treatment Group	Rat Number	Sex	Treatment Week	Observations
Control	G16CM	M	52	Cornea - linear imperfections (L. eye).
			96	Animal died.
	G29CM	M	98	Lens - posterior cortical discrete focal opacity (R. eye).
	H11CF	F	97	Lens cortex - evident Y-sutures (bilat.).
	H13CF	F	97	Lens cortex - evident Y-sutures (bilat.).
			98	Animal died.
	H16CF	F	97	Lens cortex - evident Y-sutures (bilat.).
	H25CF	F	97	Lens - posterior cortical cloudiness (bilateral). Posterior cortical pin-point opacity (L. eye).
			99	Animal died.
	H30CF	F	97	Lens - posterior cortical discrete focal opacity (L. eye).
	J3CM	M	52	Cornea - corneal scar (R. eye).
			78	Animal died.
	J4CM	M	97	Cornea - corneal scar and haziness (L. eye).
	J15CM	M	52	Lens - anterior capsular opacification 12 o'clock (L. eye). Retina - superior periphery appears pale. (L. eye).
			97	Lens - unchanged (L. eye). Retina - peripheral area has pale appearance; vascularization abnormal (L. eye).
	J21CM	M	97	Lens - focal cortical opacities (R. eye).
			111	Animal died.

Appendix Table 1 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Individual Ophthalmoscopic Findings

Treatment Group	Rat Number	Sex	Treatment Week	Observations
Control	J24CM	M	97	Cornea - deep stromal scar (L. eye).
	K13CF	F	52	Cornea - superficial haziness (L. eye). Palpebral edema.
			97	Cornea - unchanged (L. eye).
	K26CF	F	52	Cornea - evidence of chromodacryorrhea and superficial haziness (L. eye). Palpebral hyperemia.
			97	Cornea - lesion no longer present (L. eye).
	K28CF	F	52	Cornea - focal opacification (R. eye).
			79	Animal died.
	L7CM	M	52	Lens - posterior subcapsular focal opacity (R. eye). Cornea - superficial haziness (L. eye).
			89	Animal died.
	L9CM	M	52	Eye - chromodacryorrhea (L. eye).
			97	Eye - unchanged (L. eye). Lens cortex - evident Y-sutures (bilat.).
	L26CM	M	97	Cornea - superficial haziness (L. eye).
	L29CM	M	97	Lens - cortical discrete focal opacity (L. eye).
	M4CF	F	97	Lens - posterior cortical focal opacity (R. eye).
Low Dose	M10CF	F	97	Retina - very pale fundi (bilateral).
	M13CF	F	97	Lens - peripheral cortical streak (L. eye).
	A26LM	M	52	Retina - appears pale, vasculature constricted; retinal dystrophy. Microvasculature prominent in several areas (R. eye).
			98	Retina - unchanged (R. eye). Lens cortex - prominent Y-sutures (R. eye). Lens - anterior cortical and nuclear opacities (R. eye).

Appendix Table 1 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Individual Ophthalmoscopic Findings

Treatment Group	Rat Number	Sex	Treatment Week	Observations
Low Dose	B24LF	F	98	Cornea - stromal opacity, vascularization, extending to medial aspect of cornea from center (L. eye).
	B25LF	F	98	Lens cortex - prominent Y-sutures (bilat.).
	B27LF	F	98	Lens cortex - faintly prominent Y-sutures (bilateral).
	C12LM	M	98	Lens cortex - prominent Y-sutures (bilat.). Retina - "wooly" appearing fundus (bilat.).
			105	Killed in extremis.
	C27LM	M	52	Cornea - superficial haziness (L. eye).
			98	Cornea - unchanged (L. eye).
	C28LM	M	98	Lens - posterior cortical opacity (R. eye).
	D11LF	F	52	Cornea - superficial haziness (bilateral).
			98	Cornea - lesion no longer present (bilat.).
	E15LM	M	52	Lens - posterior subcapsular opalescent opacities (bilateral).
			98	Lens - unchanged (bilateral).
	E18LM	M	98	Lens - posterior cortical focal opacity (L. eye).
	E19LM	M	98	Cornea - superficial haziness (bilateral).
	F1LF	F	98	Eye - prominent hyaloid remnant (L. eye).
	F20LF	F	52	Cornea - haziness of corneal surface (R. eye). Eye - chromodacryorrhea (R. eye).
			98	Cornea - still evident but some regression apparent (R. eye). Eye - still evident but some regression apparent (R. eye).

Appendix Table 1 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Individual Ophthalmoscopic Findings

Treatment Group	Rat Number	Sex	Treatment Week	Observations
Low Dose	G5LM	M	98	Lens - posterior cortical cloudiness and streak opacities (L. eye). Lens - posterior cortical streak opacity (R. eye). Lens cortex - prominent Y-suture (bilat.).
			104	Animal died.
	H27LF	F	52	Eye - palpebral inflammation, some chromodacryorrhea (R. eye).
			79	Animal died.
	J13LM	M	98	Cornea - corneal scar and surrounding haziness (R. eye).
	J16LM	M	98	Cornea - superficial streak (R. eye).
	K6LF	F	98	Lens - pin-point posterior cortical opacity (R. eye).
	K8LF	F	98	Lens - posterior cortical pin-point opacity (R. eye).
	L2LM	M	52	Cornea - superficial haziness (L. eye).
			69	Animal died.
	L28LM	M	52	Cornea - corneal irregularities (transparent elevations) (bilateral).
			98	Cornea - unchanged (bilateral).
	M23LF	F	98	Lens - posterior cortical discrete "bubble" opacity (L. eye). Cornea - central corneal "pitting" (L. eye). Lens - discrete pin-point posterior cortical opacity (R. eye).
Medium Dose	A18MM	M	98	Cornea - corneal scar (L. eye).
			106	Animal died.
	A22MM	M	98	Lens - posterior cortical translucent opacification (R. eye).

Appendix Table 1 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Individual Ophthalmoscopic Findings

Treatment Group	Rat Number	Sex	Treatment Week	Observations
Medium Dose	B4MF	F	52	Lens - posterior subcapsular focal opacity (L. eye).
			98	Lens - unchanged (L. eye).
	B5MF	F	52	Lens - posterior subcapsular feather opacities (L. eye).
			98	Lens - unchanged (L. eye).
	B7MF	F	98	Lens cortex - prominent Y-suture (bilat.).
	C18MM	M	98	Lens - discrete, focal, medial cortex opacity (L. eye).
	D1MF	F	52	Cornea - superficial linear opacity (R. eye).
			88	Animal died.
	D9MF	F	52	Lens - peripheral cortex vascular demarcation (R. eye).
			98	Lens - unchanged (R. eye).
	D24MF	F	52	Cornea - superficial corneal haziness (bilateral).
			98	Cornea - lesion no longer present (bilateral).
	E24MM	M	98	Lens - posterior subcapsular focal opacity (L. eye).
	E27MM	M	57	Cornea - corneal ulceration with complete cornea vascularization; purulent exudate from center of corneal lesion (bilateral).
			59	Animal died.
	F2MF	F	98	Lens cortex - Y-sutures evident (bilateral).
	F9MF	F	52	Cornea - clear "plaque-like" <u>elevation</u> of corneal epithelial surface (L. eye).
			98	Cornea - corneal surface now appears normal (L. eye).
			106	Animal died.

Appendix Table 1 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Individual Ophthalmoscopic Findings

Treatment Group	Rat Number	Sex	Treatment Week	Observations
Medium Dose	F24MF	F	98	Lens cortex - prominent Y-suture (bilat.)
	G11MM	M	52	Cornea - generalized superficial corneal haziness (bilateral).
			56	Animal died.
	G19MM	M	52	Cornea - superficial corneal haziness (L. eye).
			98	Cornea - unchanged (L. eye).
			101	Animal died.
	G21MM	M	52	Cornea - superficial haziness (R. eye).
			98	Cornea - superficial haziness (bilateral).
	G28MM	M	52	Cornea - superficial corneal haziness (bilateral).
			98	Cornea - unchanged (bilateral).
	H8MF	F	98	Lens cortex - prominent Y-sutures (bilat.).
			102	Animal killed in extremis.
	H28MF	F	52	Cornea - superficial haziness (bilateral).
			98	Cornea - unchanged (bilateral).
	J14MM	M	98	Lens - posterior focal cortical opacities (L. eye).
	L6MM	M	98	Iris - anterior synechiae; corneal vascularization (L. eye). Corneal haziness (R. eye).
			99	Animal died.
	L8MM	M	52	Lens - posterior subcapsular focal opacity (bilateral).
			98	Lens - unchanged (bilateral).
	L14MM	M	98	Lens cortex - prominent Y-sutures (bilat.).

Appendix Table 1 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Individual Ophthalmoscopic Findings

Treatment Group	Rat Number	Sex	Treatment Week	Observations
Medium Dose	M29MF	F	52	Lens - iritis; hyperemia of iris. Posterior synechiae; anterior sub-capsular cortical opacification (R. eye).
			98	Lens - posterior subluxation of lens 12:00 to 3:00, no dilation, complete opacification posterior to iris, hyperemia of iris, enlarged anterior chamber (R. eye).
High Dose	A29HM	M	98	Lens cortex - prominent Y-suture (bilat.).
	B13HF	F	31	Cornea - focal superficial corneal haziness (bilateral).
			52	Cornea - unchanged (bilateral).
			98	Cornea - unchanged (R. eye). Cornea - clear (L. eye).
				Lens - posterior cortical opacity (R. eye). Posterior cortical opacity (R. eye). Posterior cortical focal opacity (L. eye).
	C2HM	M	52	Cornea - superficial haziness (bilat.).
			98	Cornea - unchanged (bilateral).
	C13HM	M	31	Cornea - superficial haziness (bilateral).
			50	Animal died.
	C14HM	M	98	Lens - posterior cortical opacity (R. eye).
			102	Animal died.
	C15HM	M	31	Cornea - superficial haziness; evidence of anterior inflammation. Palpebrae - slight inflammation and hyperemia (L. eye).
			52	Cornea - lesion unchanged, evidence of stromal opacification (L. eye). Superficial haziness (R. eye).
			98	Cornea - stromal opacity, pale fundus, and chromodacryorrhea (L. eye). Stromal opacity (R. eye).

Appendix Table 1 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Individual Ophthalmoscopic Findings

Treatment Group	Rat Number	Sex	Treatment Week	Observations
High Dose	D16HF	F	52	Cornea - superficial haziness (bilat.).
			72	Animal died.
	E14HM	M	98	Cornea - superficial haziness (bilat.).
	E23HM	M	98	Lens - anterior capsular streak opacity (bilateral).
			104	Animal died.
	E28HM	M	31	Palpebrae - mild inflammation; slight hyperemia (bilateral).
			52	Palpebrae - lesion unchanged (bilateral).
			90	Animal died.
	F6HF	F	52	Cornea - punctate lesions of cornea (R. eye).
			98	Cornea - corneal lesions of cornea (R. eye). Lens - cortical focal opacity and streak (L. eye). Posterior lens cortex - contains scattered droplet opacities; anterior capsular streaks, medial aspect. Possible posterior synechiae (R. eye).
	F14HF	F	98	Lens cortex - prominent Y-suture (bilat.).
	F23HF	F	98	Lens - peripheral and posterior cortical translucent opacification (R. eye).
	G17HM	M	52	Cornea - iris filament adherent to endothelial surface of cornea (L. eye).
			98	Cornea - lesion unchanged (L. eye).
	H7HF	F	98	Lens - posterior cortical streak and cloudiness (R. eye).
	J6HM	M	98	Lens - posterior focal subcapsular opacity (R. eye).

Appendix Table 1 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY IN THE RAT

Individual Ophthalmoscopic Findings

Treatment Group	Rat Number	Sex	Treatment Week	Observations
High Dose	J18HM	M	98	Lens - posterior cortical and medial cortical focal opacities (L. eye).
			103	Animal died.
	K21HF	F	52	Lens - anterior capsular opacification (R. eye).
			98	Lens - lesion unchanged (R. eye).
	K24HF	F	98	Lens cortex - prominent Y-suture (bilateral). Lens - posterior lens cortex opacity, also subcapsular cortical streak (R. eye).
	L5HM	M	98	Lens - peripheral cortical streak; posterior cortical focal opacity (L. eye). Posterior cortical focal opacity (R. eye).
			103	Animal died.
	L19HM	M	52	Lens - posterior subcapsular focal opacity (L. eye).
			94	Animal died.
	L22HM	M	52	Cornea - corneal haziness (bilateral).
			98	Cornea - lesion unchanged (bilateral).
	L24HM	M	52	Lens - focal posterior subcapsular opacity (R. eye).
			98	Lens - opacity enlarged slightly, small adjacent opacity now evident (R. eye).
	M2HF	F	98	Lens - anterior capsular streaks (R. eye).
	M5HF	F	98	Lens cortex - prominent Y-suture (bilat.).
	M18HF	F	52	Lens - posterior subcapsular opacification (R. eye).
			98	Lens - anterior capsular streaking; posterior synechiae with incomplete dilation; increase in posterior cortical cloudiness and diffusion of opacity (R. eye).

Appendix Table 2
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988S73

HEMATOLOGY-ERYTHROCYTES

TREATMENT DAY 42
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	HCT %	HGB G/DL	RBC X106/CMH
CONTROL			
A02CM	45	14.1	7.62
A04CM	49	14.9	7.99
A06CM	46	14.0	7.51
A07CM	48	14.9	7.60
A10CM	46	14.7	7.83
A11CM	45	14.5	7.19
LOW			
A05LM	48	15.5	8.00
A13LM	46	14.9	7.63
A17LM	48	15.4	7.90
A20LM	46	14.7	7.33
A23LM	47	14.5	7.48
A26LM	47	14.1	7.38
MEDIUM			
A08MM	46	13.8	6.91
A14MM	45	14.7	7.52
A16MM	43	13.6	7.07
A18MM	47	13.6	7.76
A22MM	47	14.9	8.17
A25MM	46	14.5	7.47
HIGH			
A01HM	46	14.9	7.83
A03HM	48	16.2	7.68
A09HM	49	15.6	7.77
A24HM	48	15.2	8.04
A28HM	45	14.1	7.20
A29HM	47	14.7	7.43

Appendix Table 2 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988573

HEMATOLOGY-LEUCOCYTES

TREATMENT DAY 42
 INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	WBC X103/CMM	DIFFERENTIAL					EOS %	BAS %
		BANDS %	PMN SEGS %	LYM %	MON %			
CONTROL								
A02CM	9.5	0	9	90	0	1	0	
A04CM	11.8	0	12	85	0	3	0	
A06CM	10.8	0	21	79	0	0	0	
A07CM	14.7	0	9	90	0	1	0	
A10CM	7.3	0	12	87	0	1	0	
A11CM	7.1	0	17	82	0	1	0	
LOW								
A05LM	10.5	0	3	97	0	0	0	
A13LM	5.8	0	18	82	0	0	0	
A17LM	8.4	0	7	92	0	1	0	
A20LM	16.3	0	11	89	0	0	0	
A23LM	14.4	0	12	87	0	1	0	
A26LM	12.4	0	7	93	0	0	0	
MEDIUM								
A08MM	10.7	0	35	64	0	1	0	
A14MM	13.9	0	6	94	0	0	0	
A16MM	13.1	0	10	89	0	1	0	
A18MM	15.8	0	6	94	0	0	0	
A22MM	7.0	0	16	82	0	2	0	
A25MM	8.0	0	12	87	0	1	0	
HIGH								
A01HM	12.4	0	13	86	0	1	0	
A03HM	8.7	0	11	89	0	0	0	
A09HM	9.6	0	13	85	0	2	0	
A24HM	12.4	0	15	85	0	0	0	
A28HM	6.2	0	10	89	0	1	0	
A29HM	12.1	0	12	86	0	2	0	

Appendix Table 2 (cont.)
 SC-191921 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0908573

HEMATOLOGY-ERYTHROCYTES

TREATMENT DAY 42
 INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	HCT %	HGB G/DL	RBC X106/CMM
CONTROL			
B01CF	45	15.2	7.53
B02CF	46	15.2	7.22
B06CF	48	15.8	7.88
B09CF	46	15.6	7.49
B10CF	48	15.8	7.23
B11CF	48	16.2	7.49
LOW			
B08LF	46	14.9	7.11
B15LF	47	16.1	7.49
B21LF	46	15.1	6.81
B24LF	46	15.6	7.58
B25LF	46	15.4	7.52
B27LF	48	16.6	8.00
MEDIUM			
B04MF	46	16.0	7.84
B05MF	46	15.7	7.77
B07MF	48	16.2	7.52
B19MF	44	15.4	7.40
B23MF	49	15.7	7.87
B28MF	44	15.8	7.43
HIGH			
B03HF	46	15.1	7.52
B12HF	44	15.3	7.18
B13HF	45	15.6	6.84
B14HF	44	15.4	7.12
B20HF	LOST	15.6	7.62
B29HF	47	17.0	8.24

Appendix Table 2 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-LEUCOCYTES

TREATMENT GROUP AND ANIMAL NO	WBC X103/CMH	TREATMENT DAY 42 INDIVIDUAL VALUES FOR FEMALES						
		DIFFERENTIAL					EOS %	BAS %
		BANDS %	PMN SEGS %	LYM %	MON %			
CONTROL								
B01CF	8.1	2	28	69	0	1	0	
B02CF	9.4	0	14	84	0	2	0	
B06CF	19.7	0	6	94	0	0	0	
B09CF	14.8	0	5	94	0	1	0	
B10CF	8.6	0	17	82	0	1	0	
B11CF	10.4	0	2	98	0	0	0	
LOW								
B09LF	6.0	0	32	68	0	0	0	
B15LF	10.5	0	8	90	0	2	0	
B21LF	9.2	0	12	88	0	0	0	
B24LF	9.8	0	9	90	0	0	1	
B25LF	7.8	1	17	82	0	0	0	
B27LF	8.7	0	5	92	1	2	0	
MEDIUM								
B04MF	9.0	0	10	88	0	2	0	
B05MF	6.7	0	19	90	0	1	0	
B07MF	5.0	0	30	68	0	2	0	
B19MF	13.7	0	17	83	0	0	0	
B23MF	5.8	0	4	95	0	1	0	
B28MF	11.4	0	14	85	0	1	0	
HIGH								
B03HF	10.4	0	4	94	0	2	0	
B12HF	12.5	0	26	71	0	3	0	
B13HF	13.7	0	8	90	0	2	0	
B14HF	9.6	0	7	90	0	3	0	
B20HF	8.6	0	7	91	0	2	0	
B29HF	16.7	0	13	85	1	1	0	

Appendix Table 2 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PI#0988S73

HEMATOLOGY-COAGULOGRAM

TREATMENT DAY 42
 INDIVIDUAL VALUES FOR FEMALES

TREATMENT
 GROUP AND
 ANIMAL NO

PRO TIME
 SEC

CONTROL

B01CF	11.9
B02CF	11.9
B06CF	11.9
B09CF	13.5
B10CF	11.2
B11CF	12.4

LOW

B08LF	11.5
B15LF	11.9
B21LF	12.7
B24LF	11.8
B25LF	12.7
B27LF	12.2

MEDIUM

B04MF	12.2
B05MF	12.4
B07MF	11.7
B19MF	11.6
B23MF	14.2
B28MF	12.4

HIGH

B03HF	12.4
B12HF	11.4
B13HF	12.7
B14HF	13.3
B20HF	13.4
B29HF	12.2

Appendix Table 2 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-ERYTHROCYTES

TREATMENT DAY 91
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	HCT %	HGB G/DL	RBC X106/CMM
CONTROL			
A02CM	46	14.9	8.10
A04CM	48	16.2	8.65
A06CM	46	15.8	8.32
A07CM	48	16.6	8.27
A10CM	47	15.8	8.34
A11CM	47	15.8	8.41
LOW			
A05LM	49	16.7	8.63
A13LM	47	15.6	8.29
A17LM	47	17.3	8.55
A20LM	LOST	15.6	7.71
A23LM	48	16.7	8.41
A26LM	49	16.4	8.55
MEDIUM			
A08MM	48	16.2	7.99
A14MM	48	16.6	8.38
A16MM	47	17.0	8.53
A18MM	LOST	17.0	8.42
A22MM	48	17.1	8.36
A25MM	47	16.0	8.21
HIGH			
A01HM	45	15.8	8.05
A03HM	47	15.6	8.67
A09HM	49	16.6	8.36
A24HM	48	16.7	8.52
A28HM	45	15.5	7.75
A29HM	48	16.7	8.42

Appendix Table 2 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PI#0988S73

HEMATOLOGY-LEUCOCYTES

TREATMENT DAY 91
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	WBC X103/CMH	DIFFERENTIAL					EOS %	BAS %
		BANDS %	PMN SEGS %	LYM %	MON %			
CONTROL								
A02CM	9.7	0	8	90	0	2	0	
A04CM	11.4	0	13	87	0	0	0	
A06CM	16.8	0	7	91	0	2	0	
A07CM	14.4	0	6	94	0	0	0	
A10CM	10.4	0	7	92	0	1	0	
A11CM	6.9	0	6	92	0	2	0	
LOW								
A05LM	12.8	0	17	81	0	2	0	
A13LM	13.2	0	12	88	0	0	0	
A17LM	9.1	0	7	90	0	3	0	
A20LM	7.9	0	14	85	0	1	0	
A23LM	10.4	0	13	80	0	7	0	
A26LM	4.3	0	11	88	0	1	0	
MEDIUM								
A08MM	7.8	0	12	86	0	2	0	
A14MM	16.6	0	7	93	0	0	0	
A16MM	8.1	0	12	86	0	2	0	
A18MM	9.8	0	15	85	0	0	0	
A22MM	11.1	0	6	90	0	4	0	
A25MM	8.9	0	33	67	0	0	0	
HIGH								
A01HM	11.9	0	5	94	0	1	0	
A03HM	10.9	0	28	70	0	2	0	
A09HM	11.0	0	9	90	0	1	0	
A24HM	13.7	0	6	93	0	1	0	
A28HM	16.8	0	13	86	0	1	0	
A29HM	10.9	0	16	84	0	0	0	

Appendix Table 2 (cont.)

SC-191921 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-COAGULOGRAM

TREATMENT DAY 91
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	PRO TIME SEC
CONTROL	
A02CM	14.5
A04CM	12.3
A06CM	12.0
A07CM	11.3
A10CM	12.7
A11CM	12.7
LOW	
A05LM	12.1
A13LM	13.3
A17LM	12.3
A20LM	11.7
A23LM	13.3
A26LM	10.9
MEDIUM	
A084M	12.8
A144M	12.0
A164M	13.1
A184M	12.1
A224M	12.5
A254M	12.0
HIGH	
A01HM	12.7
A03HM	12.0
A09HM	11.9
A24HM	12.3
A28HM	11.5
A29HM	12.1

Appendix Table 2 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PI#0988S73

HEMATOLOGY-ERYTHROCYTES

TREATMENT DAY 92
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	HCT %	HGB G/DL	RBC X106/CMM
CONTROL			
B01CF	47	15.8	8.79
B02CF	46	15.6	8.04
B06CF	45	16.4	7.91
B09CF	48	15.8	7.91
B10CF	46	16.6	7.88
B11CF	46	15.8	7.62
LOW			
B08LF	46	16.2	8.44
B15LF	48	16.8	8.29
B21LF	44	15.8	7.95
B24LF	48	16.2	7.97
B25LF	45	15.6	7.75
B27LF	48	16.9	8.23
MEDIUM			
B04MF	45	15.6	7.97
B05MF	46	16.2	8.46
B07MF	46	16.0	8.05
B19MF	44	16.0	7.52
B23MF	49	16.6	8.24
B28MF	45	15.5	7.68
HIGH			
B03HF	46	15.3	7.62
B12HF	LOST	15.8	7.63
B13HF	LOST	15.6	7.76
B14HF	44	15.5	7.75
B20HF	46	15.8	7.73
B29HF	48	16.2	8.11

Appendix Table 2 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-LEUCOCYTES

TREATMENT DAY 92
 INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	WBC X103/CHM	DIFFERENTIAL					EOS %	BAS %
		BANDS %	PMN SEGS %	LYM %	MON %			
CONTROL								
301CF	9.1	0	9	90	0	1	0	
802CF	11.1	0	12	87	0	1	0	
806CF	7.8	0	10	90	0	0	0	
309CF	18.4	0	28	69	0	3	0	
910CF	12.7	0	10	90	0	0	0	
811CF	9.8	0	4	96	0	0	0	
LOW								
808LF	5.2	0	15	83	0	2	0	
815LF	8.1	0	22	74	0	4	0	
921LF	13.0	0	18	81	0	1	0	
924LF	10.4	0	15	84	0	1	0	
825LF	8.6	0	6	92	1	1	0	
927LF	10.5	0	7	86	0	7	0	
MEDIUM								
804MF	17.6	0	8	92	0	0	0	
805MF	9.6	0	16	81	0	3	0	
807MF	8.0	0	14	86	0	0	0	
819MF	7.6	0	11	88	0	1	0	
823MF	11.7	0	6	94	0	0	0	
828MF	9.3	0	11	88	0	1	0	
HIGH								
803HF	13.2	0	11	86	1	2	0	
912HF	11.4	0	9	91	0	0	0	
813HF	12.5	0	10	89	0	1	0	
814HF	13.7	0	11	87	0	2	0	
820HF	8.3	0	12	88	0	0	0	
829HF	9.7	0	21	79	0	0	0	

Appendix Table 2 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-COAGULOGRAM

TREATMENT DAY 92
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	PRO TIME SEC
CONTROL	
B01CF	13.2
B02CF	12.3
B06CF	10.6
B09CF	11.4
B10CF	11.8
B11CF	12.8
LOW	
B08LF	14.5
B15LF	11.2
B21LF	12.2
B24LF	10.5
B25LF	14.4
B27LF	11.1
MEDIUM	
B04MF	12.4
B05MF	12.1
B07MF	13.3
B19MF	12.3
B23MF	10.9
B28MF	10.4
HIGH	
B03HF	11.7
B12HF	14.5
B13HF	11.3
B14HF	11.9
B20HF	11.5
B29HF	14.0

Appendix Table 2 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-ERYTHROCYTES

TREATMENT DAY 189
 INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	HCT %	HGB G/DL	RBC X106/CMM
CONTROL			
A02CM	46	13.4	7.87
A04CM	49	15.1	8.38
A06CM	45	13.8	7.90
A07CM	48	14.1	7.85
A10CM	47	14.3	8.07
A11CM	50	15.6	8.48
LOW			
A05LM	48	14.3	8.25
A13LM	47	13.8	7.99
A17LM	47	14.0	8.36
A20LM	48	14.5	8.11
A23LM	48	14.9	8.15
A26LM	47	14.3	8.17
MEDIUM			
A08MM	48	15.3	7.96
A14MM	LOST	14.1	8.41
A16MM	49	14.5	7.73
A18MM	47	13.6	8.49
A22MM	47	17.9	8.21
A25MM	47	14.9	8.11
HIGH			
A01HM	44	14.0	8.27
A03HM	47	13.4	7.79
A09HM	48	15.1	8.31
A24HM	47	15.1	7.87
A28HM	47	13.8	7.79
A29HM	46	14.1	8.03

Appendix Table 2 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-LEUCOCYTES

TREATMENT DAY 189
 INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	WBC X103/CMM	DIFFERENTIAL					EOS %	BAS %
		BANDS %	PMN SEGS %	LYM %	MON %			
CONTROL								
A02CM	8.2	0	13	83	1	3	0	
A04CH	7.9	0	12	86	0	2	0	
A06CM	7.6	0	21	79	0	0	0	
A07CM	7.0	0	14	85	0	1	0	
A10CM	9.6	0	17	82	0	1	0	
A11CM	8.2	0	15	84	0	1	0	
LOW								
A05LM	6.9	0	16	83	0	1	0	
A13LM	9.5	0	13	81	0	6	0	
A17LM	8.2	0	10	88	0	2	0	
A20LM	11.1	0	13	85	0	2	0	
A23LM	12.1	0	15	84	0	1	0	
A26LM	17.1	0	21	78	0	1	0	
MEDIUM								
A08MM	10.9	0	11	88	0	1	0	
A14MM	13.2	0	12	86	0	2	0	
A16MM	9.6	0	8	89	0	3	0	
A18MM	14.8	0	12	87	0	1	0	
A22MM	11.7	0	16	80	0	2	0	
A25MM	9.2	0	17	77	0	6	0	
HIGH								
A01HM	7.5	0	19	80	0	1	0	
A03HM	15.2	0	21	78	0	1	0	
A09HM	13.2	0	8	91	0	1	0	
A24HM	13.2	0	14	86	0	0	0	
A28HM	8.7	0	20	80	0	0	0	
A29HM	9.2	0	18	79	0	3	0	

Appendix Table 2 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-COAGULOGRAM

TREATMENT DAY 189
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	PRO TIME SEC
CONTROL	
A02CM	11.2
A04CM	11.6
A06CM	10.7
A07CM	10.5
A10CM	10.3
A11CM	12.3
LOW	
A05LM	11.9
A13LM	11.3
A17LM	11.0
A20LM	11.8
A23LM	10.8
A26LM	11.6
MEDIUM	
A08HM	10.8
A14HM	10.3
A16HM	11.4
A18HM	11.8
A22HM	12.3
A25HM	12.2
HIGH	
A01HM	11.7
A03HM	11.5
A09HM	10.6
A24HM	11.7
A28HM	12.8
A29HM	11.3

Appendix Table 2 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0908573

HEMATOLOGY-ERYTHROCYTES

TREATMENT DAY 189
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	HCT %	HGB G/DL	RBC X106/CMM
CONTROL			
801CF	48	15.6	8.05
802CF	47	16.0	7.83
806CF	44	15.1	7.40
809CF	48	14.5	8.03
810CF	47	15.5	7.48
811CF	45	15.3	7.42
LOW			
808LF	44	15.3	7.35
815LF	43	14.7	6.65
821LF	45	15.3	7.71
824LF	45	15.6	7.63
825LF	45	15.3	7.80
827LF	47	15.8	8.39
MEDIUM			
804MF	45	16.0	7.64
805MF	46	16.2	8.16
807MF	45	15.8	7.24
819MF	45	14.9	7.58
823MF	47	15.6	8.08
828MF	44	14.9	7.84
HIGH			
803HF	44	15.3	7.04
812HF	44	15.1	7.97
813HF	45	14.9	7.72
814HF	43	14.3	7.35
820HF	45	15.1	7.92
829HF	44	14.9	8.41

Appendix Table 2 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-LEUCOCYTES

TREATMENT DAY 189
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	WBC X103/CMM	DIFFERENTIAL					EOS %	BAS %
		BANDS %	PMN SEGS %	LYM %	MON %			
CONTROL								
B01CF	7.5	0	11	89	0	0	0	
B02CF	9.7	0	4	95	0	1	0	
B06CF	11.9	0	14	86	0	0	0	
B09CF	11.6	0	7	92	0	1	0	
B10CF	8.1	0	11	89	0	0	0	
B11CF	8.5	0	4	95	0	1	0	
LOW								
B08LF	5.7	0	9	90	0	1	0	
B15LF	5.0	0	2	97	0	1	0	
B21LF	7.2	0	6	93	0	1	0	
B24LF	7.6	0	8	91	0	1	0	
B25LF	12.2	0	19	78	0	3	0	
B27LF	8.2	0	11	88	0	1	0	
MEDIUM								
B04MF	8.1	0	7	92	0	1	0	
B05MF	8.2	0	8	90	0	2	0	
B07MF	5.3	0	13	87	0	0	0	
B19MF	5.0	0	13	85	0	2	0	
B23MF	11.5	0	5	92	0	3	0	
B28MF	9.5	0	17	80	0	3	0	
HIGH								
B03HF	7.3	0	8	90	0	2	0	
B12HF	9.5	0	11	86	0	3	0	
B13HF	7.3	0	5	95	0	0	0	
B14HF	5.9	0	8	90	0	0	0	
B20HF	6.7	0	15	83	0	2	0	
B29HF	7.7	0	13	87	0	2	0	

Appendix Table 2 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-COAGULOGRAM

TREATMENT DAY 189
 INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	PRO TIME SEC
CONTROL	
801CF	10.7
802CF	11.0
806CF	10.4
809CF	10.8
810CF	9.3
811CF	10.4
LOW	
808LF	10.7
815LF	9.8
821LF	9.7
824LF	10.4
825LF	10.3
827LF	11.5
MEDIUM	
804MF	12.0
805MF	11.5
807MF	10.7
819MF	9.5
823MF	11.2
828MF	9.5
HIGH	
803HF	12.1
812HF	10.3
813HF	10.9
814HF	9.1
820HF	10.6
829HF	10.5

Appendix Table 2 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PI00988S73

HEMATOLOGY-ERYTHROCYTES

TREATMENT DAY 364
 INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	HCT %	HGB G/DL	RBC X106/CHM
CONTROL			
A02CH	49	16.3	8.04
A04CH	LOST	16.5	9.02
A06CH	47	15.6	8.19
A07CH	44	16.3	8.15
A10CH	49	15.6	8.38
A11CH	43	15.0	8.20
LOW			
A05LM	48	16.5	8.95
A13LM	45	15.2	8.70
A17LM	48	15.9	8.65
A20LM	48	16.1	7.83
A23LM	47	15.6	7.75
A26LM	44	14.6	8.15
MEDIUM			
A08MM	47	16.1	8.53
A14MM	45	15.4	7.79
A16MM	46	15.4	8.38
A18MM	49	16.3	8.41
A22MM	45	15.2	8.11
A25MM	46	15.6	8.58
HIGH			
A01HM	48	14.1	7.60
A03HM	46	15.6	8.46
A09HM	36	11.5	6.54
A24HM	45	14.8	8.45
A28HM	43	13.5	7.96
A29HM	37	13.2	5.84

Appendix Table 2 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-LEUCOCYTES

TREATMENT DAY 364
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	WBC X103/CMH	DIFFERENTIAL					EOS %	BAS %
		BANDS %	PMN SEGS %	LYM %	MON %			
CONTROL								
A02CM	12.2	0	13	84	2	1	0	
A04CM	9.6	0	12	88	0	0	0	
A06CM	6.5	0	11	86	0	3	0	
A07CM	11.9	0	7	90	0	3	0	
A10CM	7.4	0	18	79	1	2	0	
A11CM	8.4	1	15	82	0	2	0	
LOW								
A05LM	9.8	0	12	88	0	0	0	
A13LM	7.3	0	11	88	0	1	0	
A17LM	7.7	0	15	82	1	2	0	
A20LM	11.4	0	11	86	0	3	0	
A23LM	9.0	0	11	88	0	1	0	
A26LM	7.8	0	31	64	0	5	0	
MEDIUM								
A08MM	11.9	0	16	84	0	0	0	
A14MM	15.7	0	13	86	0	1	0	
A16MM	9.1	0	6	91	0	3	0	
A18MM	8.8	0	13	87	0	0	0	
A22MM	11.7	0	43	53	0	4	0	
A25MM	4.9	0	12	87	0	1	0	
HIGH								
A01HM	8.8	0	10	87	0	3	0	
A03HM	8.1	0	21	78	0	1	0	
A09HM	18.2	0	61	38	1	0	0	
A24HM	9.8	0	11	87	0	2	0	
A28HM	8.3	1	32	66	1	0	0	
A29HM	6.5	0	21	77	1	1	0	

Appendix Table 2 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-COAGULOGRAM

TREATMENT DAY 364
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	PRO TIME SEC
CONTROL	
A02CM	12.1
A04CM	11.6
A06CM	11.5
A07CM	11.3
A10CM	11.0
A11CM	11.3
LOW	
A05LM	11.8
A13LM	11.7
A17LM	12.2
A20LM	12.8
A23LM	10.1
A26LM	9.4
MEDIUM	
A08MM	11.7
A14MM	11.6
A16MM	12.0
A18MM	12.5
A22MM	11.3
A25MM	9.6
HIGH	
A01HM	11.9
A03HM	11.2
A09HM	11.5
A24HM	10.1
A28HM	10.3
A29HM	11.1

Appendix Table 2 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-ERYTHROCYTES

TREATMENT DAY 364
 INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	HCT %	HGB G/DL	RBC X106/CMM
CONTROL			
B01CF	46	15.2	8.03
B02CF	40	13.7	7.14
B06CF	44	14.8	7.48
B09CF	44	15.2	7.81
B10CF	43	14.6	7.31
B11CF	44	14.8	7.36
LOW			
B08LF	44	14.8	7.67
B15LF	44	14.6	7.27
B21LF	44	14.6	7.35
B24LF	43	14.8	7.63
B25LF	43	14.6	7.39
B27LF	42	15.0	7.72
MEDIUM			
B04MF	45	15.0	8.00
B05MF	45	15.0	8.11
B07MF	45	15.0	7.87
B19MF	42	14.6	7.22
B23MF	44	15.2	7.84
B28MF	44	14.8	7.63
HIGH			
B03HF	52	16.3	8.04
B12HF	45	14.1	7.70
B13HF	44	14.6	7.63
B14HF	41	13.9	6.36
B20HF	41	13.7	7.04
B29HF	40	13.7	7.51

Appendix Table 2 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988573

HEMATOLOGY-LEUCOCYTES

TREATMENT DAY 364
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	WBC X103/CMH	DIFFERENTIAL					EOS %	BAS %
		BANDS %	PMN SEGS %	LYM %	MON %			
CONTROL								
B01CF	6.8	0	12	87	0	1	0	
B02CF	7.5	0	11	85	2	2	0	
12.1	12.1	0	18	82	0	0	0	
B09CF	8.1	0	14	85	0	1	0	
B10CF	6.3	0	32	65	0	3	0	
B11CF	6.0	0	10	88	0	2	0	
LOW								
B08LF	5.6	0	21	78	0	1	0	
B15LF	6.1	0	13	85	0	2	0	
B21LF	6.0	0	23	75	0	2	0	
B24LF	4.8	0	14	84	0	2	0	
B25LF	6.2	0	30	68	1	1	0	
B27LF	5.7	0	19	75	0	6	0	
MEDIUM								
B04MF	5.7	0	21	77	0	2	0	
B05MF	7.5	0	16	84	0	0	0	
B07MF	5.0	1	22	75	1	1	0	
B19MF	5.5	0	22	77	0	1	0	
B23MF	5.2	0	4	90	0	5	1	
B28MF	9.8	0	18	81	0	1	0	
HIGH								
B03HF	9.3	0	38	62	0	0	0	
B12HF	4.8	0	19	81	0	0	0	
B13HF	5.5	0	12	88	0	0	0	
B14HF	4.8	1	12	87	0	0	0	
B20HF	4.2	0	12	86	0	2	0	
B29HF	4.7	0	15	84	0	1	0	

Appendix Table 2 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-COAGULOGRAM

TREATMENT DAY 364
 INDIVIDUAL VALUES FOR FEMALES

PRO TIME
 SEC

TREATMENT
 GROUP AND
 ANIMAL NO

CONTROL

B01CF	10.6
B02CF	9.8
B06CF	10.1
B09CF	9.1
B10CF	9.2
B11CF	9.8

LOW

B08LF	9.9
B15LF	8.4
B21LF	9.1
B24LF	9.1
B25LF	8.1
B27LF	8.2

MEDIUM

B04MF	10.8
B05MF	9.8
B07MF	10.5
B19MF	8.8
B23MF	9.7
B28MF	7.9

HIGH

B03HF	12.0
B12HF	10.2
B13HF	9.7
B14HF	9.9
B20HF	10.3
B29HF	8.8

Appendix Table 2 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-ERYTHROCYTES

TREATMENT DAY 546
 INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	HCT %	HGB G/DL	RBC X106/CMM
CONTROL			
A02CM	49	16.1	8.85
A04CM	47	15.5	8.51
A06CM	43	16.1	8.23
A07CM	48	16.1	8.29
A10CM	47	16.1	8.12
A11CM	51	17.6	8.95
LOW			
A05LM	49	15.4	8.67
A13LM	47	16.5	8.49
A17LM	46	15.8	8.04
A20LM	44	15.2	7.53
A23LM	46	16.1	9.12
A26LM	46	15.9	8.19
MEDIUM			
A08MM	47	16.9	8.48
A14MM	47	13.0	6.13
A16MM	48	16.7	8.32
A18MM	50	17.2	8.81
A22MM	44	15.6	7.88
A25MM	51	16.1	9.32
HIGH			
A01HM	42	13.5	7.65
A03HM	48	17.8	7.59
A09HM	48	16.3	8.48
A24HM	47	17.0	8.85
A28HM	45	15.0	7.68
A29HM	46	15.9	8.03

Appendix Table 2 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-LEUCOCYTES

TREATMENT DAY 546
 INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	WBC X103/CMH	DIFFERENTIAL					EOS %	BAS %
		BANDS %	PMN SEGS %	LYM %	MON %			
CONTROL								
A02CM	7.7	0	24	71	3	2	0	
A04CM	15.5	0	11	84	2	3	0	
A06CM	9.4	0	27	70	2	1	0	
A07CM	6.5	1	22	73	4	0	0	
A10CM	6.6	0	12	82	6	0	0	
A11CM	8.5	1	29	60	6	4	0	
LOW								
A05LM	8.7	0	16	81	2	1	0	
A13LM	6.5	0	22	76	1	1	0	
A17LM	7.8	0	16	82	2	0	0	
A20LM	11.4	1	14	78	4	3	0	
A23LM	12.9	0	24	69	3	4	0	
A26LM	6.1	0	27	65	5	3	0	
MEDIUM								
A08MM	9.1	1	8	86	4	1	0	
A14MM	15.2	0	28	66	3	3	0	
A16MM	6.9	0	23	71	5	1	0	
A18MM	8.5	0	25	72	1	2	0	
A22MM	6.5	0	23	73	1	3	0	
A25MM	9.1	1	17	75	4	3	0	
HIGH								
A01HM	6.5	0	24	72	3	1	0	
A03HM	9.4	0	29	68	1	2	0	
A09HM	7.9	0	30	64	4	2	0	
A24HM	5.9	0	18	75	5	2	0	
A28HM	5.0	1	30	64	3	2	0	
A29HM	6.2	0	14	81	4	1	0	

Appendix Table 2 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-COAGULOGRAM

TREATMENT DAY 546
INDIVIDUAL VALUES FOR MALESPRO TIME
SECTREATMENT
GROUP AND
ANIMAL NO

CONTROL

A02CM	10.5
A04CM	11.9
A06CM	11.2
A07CM	11.0
A10CM	10.6
A11CM	11.8

LOW

A05LM	11.7
A13LM	11.3
A17LM	11.2
A20LM	11.3
A23LM	10.0
A26LM	11.6

MEDIUM

A08MM	11.6
A14MM	10.4
A16MM	11.6
A18MM	12.1
A22MM	11.8
A25MM	11.8

HIGH

A01HM	11.5
A03HM	12.6
A09HM	10.2
A24HM	10.9
A28HM	11.5
A29HM	11.6

Appendix Table 2 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-ERYTHROCYTES

TREATMENT DAY 547
 INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	HCT %	HGB G/DL	RBC X106/CMH
CONTROL			
801CF	42	14.5	7.67
802CF	45	14.1	7.20
906CF	43	15.0	7.20
809CF	52	16.5	8.00
810CF	43	16.5	7.35
311CF	44	15.0	7.23
LOW			
808LF	47	15.5	7.46
821LF	44	15.4	7.93
824LF	45	15.4	7.05
825LF	45	15.4	8.07
827LF	44	15.5	8.30
011LF	49	16.5	7.23
MEDIUM			
804MF	46	15.4	7.38
805MF	46	15.0	8.05
807MF	43	14.4	7.46
819MF	48	16.3	7.15
823MF	44	15.2	7.76
828MF	42	14.0	7.71
HIGH			
803HF	47	15.7	7.76
812HF	41	14.0	7.00
813HF	43	15.0	7.49
814HF	41	14.0	7.22
820HF	44	14.1	7.49
829HF	45	15.4	8.60

Appendix Table 2 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-LEUCOCYTES

TREATMENT DAY 547
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	WBC X103/CHM	DIFFERENTIAL					EOS %	BAS %	
		BANDS %	PMN SEGS %	LYM %	MON %				
CONTROL									
B01CF	6.0	0	10	86	4	0	0		
B02CF	7.4	0	10	85	3	2	0		
B06CF	13.0	0	32	67	1	0	0		
B09CF	10.3	0	12	83	3	1	0		
B10CF	5.5	0	24	72	4	0	0		
B11CF	6.0	0	21	73	3	3	0		
LOW									
B08LF	5.2	1	21	76	1	1	0		
B21LF	5.0	0	18	77	2	3	0		
B24LF	8.2	0	22	76	0	0	0		
B25LF	9.5	0	22	73	0	5	0		
B27LF	6.8	0	18	80	1	1	0		
D11LF	6.5	0	7	88	4	1	0		
MEDIUM									
B04MF	5.0	0	6	88	3	3	0		
B05MF	6.0	0	34	60	4	2	0		
B07MF	6.6	0	21	77	2	0	0		
B19MF	11.5	0	65	32	0	3	0		
B23MF	7.1	0	21	77	2	0	0		
B28MF	9.1	0	16	80	2	2	0		
HIGH									
B03HF	5.5	0	26	69	2	3	0		
B12HF	5.4	0	28	64	2	6	0		
B13HF	8.1	1	16	80	3	0	0		
B14HF	5.8	0	26	70	3	1	0		
B20HF	5.5	1	17	74	5	3	0		
B29HF	6.7	0	26	74	0	0	0		

Appendix Table 2 (cont.)

SC-19192; 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-COAGULOGRAM

TREATMENT DAY 547
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	PRO TIME SEC
CONTROL	
B01CF	10.2
B02CF	10.4
B06CF	10.4
B09CF	10.6
B10CF	9.8
B11CF	9.8
LOW	
B08LF	11.8
B21LF	9.5
B24LF	9.8
B25LF	10.0
B27LF	9.8
D11LF	10.6
MEDIUM	
B04MF	11.3
B05MF	10.9
B07MF	10.6
B19MF	9.6
B23MF	11.0
B28MF	9.9
HIGH	
B03HF	11.7
B12HF	9.9
B13HF	12.0
B14HF	10.0
B20HF	9.3
B29HF	10.8

Appendix Table 2 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-ERYTHROCYTES

TREATMENT DAY 734
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	HCT %	HGB G/DL	RBC X106/CMM
CONTROL			
A02CM	52	17.4	8.52
A06CM	41	14.1	6.73
A12CM	51	17.2	8.13
A15CM	48	16.8	8.36
A27CM	49	16.3	7.62
E02CM	38	13.0	6.00
LOW			
A05LM	47	16.0	7.28
A13LM	49	17.0	8.30
A20LM	39	14.1	6.58
A26LM	43	16.0	7.19
E15LM	49	16.7	34.00
E18LM	50	17.2	7.73
MEDIUM			
A08MM	49	16.5	8.45
A18MM	43	15.7	7.23
A22MM	45	16.0	7.32
A25MM	55	18.5	9.22
E10MM	60	20.0	8.20
E17MM	47	16.1	10.12
HIGH			
A01HM	48	16.1	8.00
A09HM	49	16.7	7.95
A29HM	44	14.6	7.42
E12HM	47	16.3	7.33
E14HM	50	17.0	7.87
E21HM	49	16.7	8.48

Appendix Table 2 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

HEMATOLOGY-LEUCOCYTES

TREATMENT DAY 734
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	WBC X103/CMH	DIFFERENTIAL					EOS %	BAS %
		BANDS %	PMN SEGS %	LYM %	MON %			
CONTROL								
A02CM	15.6	0	27	72	1	0	0	
A06CM	20.1	1	58	39	0	2	0	
A12CM	9.4	0	39	59	1	1	0	
A15CM	12.2	0	28	68	2	2	0	
A27CM	14.3	0	22	74	1	3	0	
E02CM	19.3	1	72	24	3	0	0	
LOW								
A05LM	12.5	0	31	67	2	0	0	
A13LM	9.1	0	22	73	0	5	0	
A20LM	11.4	0	58	40	1	1	0	
A26LM	20.7	0	31	66	1	2	0	
E15LM	7.3	0	18	77	3	2	0	
E19LM	6.0	0	22	77	0	1	0	
MEDIUM								
A08MM	10.3	0	30	66	2	2	0	
A18MM	10.5	0	24	76	0	0	0	
A22MM	11.1	0	39	56	3	2	0	
A25MM	7.2	0	18	79	1	2	0	
E10MM	8.0	1	25	72	0	2	0	
E17MM	8.0	0	26	72	0	2	0	
HIGH								
A01HM	15.2	0	36	61	3	0	0	
A09HM	7.6	0	30	66	3	1	0	
A29HM	6.0	0	30	68	0	2	0	
E12HM	7.0	0	19	81	0	0	0	
E14HM	10.6	0	27	70	0	3	0	
E21HM	7.8	0	26	71	1	2	0	

Appendix Table 2 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988S73

HEMATOLOGY-COAGULOGRAM

TREATMENT DAY 734
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	PRO TIME SEC
CONTROL	
A02CM	11.1
A06CM	10.8
A12CM	13.1
A15CM	10.8
A27CM	10.7
E02CM	11.2
LOW	
A05LM	11.8
A13LM	10.1
A20LM	10.7
A26LM	10.9
E15LM	11.2
E18LM	10.8
MEDIUM	
A08MM	11.2
A18MM	10.6
A22MM	11.2
A25MM	10.1
E10MM	11.0
E17MM	10.8
HIGH	
A01HM	11.4
A09HM	12.0
A29HM	11.6
E12HM	10.9
E14HM	11.6
E21HM	10.0

Appendix Table 2 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988S73

HEMATOLOGY-ERYTHROCYTES

TREATMENT DAY 735
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	HCT %	HGB G/DL	RBC X106/CHM
CONTROL			
B01CF	53	17.2	8.11
B02CF	51	17.0	7.99
B06CF	43	14.5	6.92
B11CF	49	16.8	7.76
B16CF	50	17.0	7.91
B18CF	42	14.5	6.94
LOW			
B21LF	46	16.5	7.42
B24LF	46	16.5	7.35
B25LF	50	17.2	8.13
B27LF	48	17.0	7.59
D11LF	61	20.7	9.93
D26LF	49	17.2	8.24
MEDIUM			
B04MF	54	18.0	8.62
B05MF	45	16.5	7.35
B07MF	49	16.1	7.91
B19MF	49	16.5	8.00
B23MF	44	15.2	7.48
B28MF	50	17.0	8.07
HIGH			
B12HF	47	16.5	7.67
B13HF	43	15.2	7.62
B14HF	45	16.3	7.40
B20HF	41	14.5	7.30
B29HF	44	15.6	7.48
D03HF	49	16.8	8.30

Appendix Table 2 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988573

HEMATOLOGY-LEUCOCYTES

TREATMENT DAY 735
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	WBC X103/CHM	DIFFERENTIAL					EOS %	BAS %
		BANDS %	PMN SEGS %	LYM %	MON %			
CONTROL								
801CF	8.8	0	34	60	5	1	0	
802CF	9.9	0	29	67	2	2	0	
806CF	13.2	0	42	57	1	0	0	
811CF	5.4	0	24	71	4	1	0	
816CF	5.3	0	25	72	2	1	0	
818CF	19.0	0	62	35	3	0	0	
LOW								
821LF	6.0	0	39	57	3	1	0	
824LF	7.3	0	33	63	2	2	0	
825LF	7.7	0	45	49	2	4	0	
827LF	14.7	0	60	38	2	0	0	
011LF	13.3	0	23	76	0	1	0	
026LF	9.6	0	26	70	2	2	0	
MEDIUM								
904MF	6.8	0	16	83	1	0	0	
805MF	7.5	0	26	71	2	1	0	
807MF	6.1	0	43	54	1	2	0	
819MF	7.1	0	20	71	5	4	0	
823MF	7.9	0	23	73	3	1	0	
928MF	7.5	0	17	80	1	2	0	
HIGH								
812HF	4.4	0	37	59	2	2	0	
813HF	7.8	0	29	66	4	1	0	
814HF	4.0	0	42	56	1	1	0	
820HF	5.4	0	28	68	2	2	0	
829HF	7.1	0	36	62	1	1	0	
003HF	8.8	0	18	80	2	0	0	

Appendix Table 2 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73
 HEMATOLOGY-COAGULOGRAH
 TREATMENT DAY 735
 INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	PRO TIME SEC
CONTROL	
801CF	10.0
802CF	11.0
806CF	10.1
811CF	10.0
816CF	9.9
818CF	10.6
LOW	
821LF	11.2
824LF	9.7
825LF	12.1
827LF	11.5
011LF	11.9
026LF	11.7
MEDIUM	
804MF	10.8
805MF	12.0
807MF	10.1
819MF	10.6
823MF	11.4
828MF	10.0
HIGH	
812HF	11.1
913HF	11.7
814HF	10.0
820HF	10.1
829HF	10.4
003HF	10.6

Appendix Table 3

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0980S73

CLINICAL CHEMISTRY

TREATMENT DAY 42
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	TYL BILI MG/DL	AP IU/L	GPT IU/L	GOT IU/L	TYL CHOL MG/DL
CONTROL					
A02CM	0.09	272	22	94	74
A04CM	0.09	247	29	125	99
A06CM	0.09	249	42	117	84
A07CM	0.08	274	18	111	123
A10CM	0.11	279	30	116	82
A11CM	0.07	297	21	97	90
LOW					
A05LM	0.08	281	29	96	89
A13LM	0.08	219	41	87	72
A17LM	0.11	312	22	96	97
A20LM	0.07	291	29	88	74
A23LM	0.10	281	23	82	103
A26LM	0.09	322	28	59	83
MEDIUM					
A08MM	0.10	296	24	89	92
A14MM	0.11	204	39	100	103
A16MM	0.15	218	99	86	83
A18MM	0.07	287	22	91	92
A22MM	0.10	250	27	87	92
A25MM	0.08	289	22	67	90
HIGH					
A01HM	0.11	284	18	85	74
A03HM	0.00	237	24	108	90
A09HM	0.09	270	59	121	100
A24HM	0.08	309	31	80	91
A28HM	0.10	215	25	75	82
A29HM	0.05	295	37	82	99

Appendix Table 3 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988S73

CLINICAL CHEMISTRY

TREATMENT DAY 42
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	GLUCOSE MG/DL	BUN MG/DL	PHENYLAL MG/DL
CONTROL			
A02CM	226	25.1	QNS
A04CM	197	22.3	3.1
A06CM	177	26.6	3.8
A07CM	158	25.6	4.0
A10CM	206	19.9	2.7
A11CM	144	24.2	3.4
LOW			
A05LM	169	22.0	2.9
A13LM	198	20.7	2.6
A17LM	176	22.3	2.8
A20LM	193	22.6	3.9
A23LM	124	17.5	3.3
A26LM	213	21.4	2.5
MEDIUM			
A08MM	160	25.8	3.9
A14MM	185	21.8	3.4
A16MM	162	19.9	3.0
A18MM	202	21.5	2.6
A22MM	201	19.4	3.1
A25MM	180	23.4	3.5
HIGH			
A01HM	199	27.1	3.8
A03HM	198	22.9	3.0
A09HM	211	22.7	3.8
A24HM	195	21.6	3.3
A28HM	202	21.6	3.3
A29HM	181	23.8	3.4

QNS = Quantity not sufficient for analysis.

Appendix Table 3 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0980S73

CLINICAL CHEMISTRY

TREATMENT DAY 42
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	TTL BILI MG/DL	AP IU/L	GPT IU/L	GOT IU/L	TTL CHOL MG/DL
CONTROL					
B01CF	0.13	267	15	117	QNS
B02CF	0.12	154	9	111	92
B06CF	0.08	236	18	147	96
B09CF	0.11	228	15	130	75
B10CF	0.10	217	14	83	87
B11CF	0.14	224	15	100	77
LOW					
B08LF	0.10	220	11	84	86
B15LF	0.13	150	11	94	98
B21LF	0.12	175	11	82	69
B24LF	0.12	227	11	86	78
B25LF	0.11	174	12	91	83
B27LF	0.14	242	13	84	104
MEDIUM					
B04MF	0.11	209	17	93	73
B05MF	0.12	248	QNS	141	QNS
B07MF	0.11	215	10	103	82
B19MF	0.12	216	10	116	58
B23MF	0.10	134	11	85	82
B28MF	0.12	165	13	80	85
HIGH					
B03HF	0.13	226	13	136	64
B12HF	0.09	151	16	96	79
B13HF	0.11	279	22	94	74
B14HF	0.08	238	11	89	78
B20HF	0.12	246	9	91	73
B29HF	0.12	154	10	99	QNS

QNS = Quantity not sufficient for analysis.

Appendix Table 3 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

CLINICAL CHEMISTRY				
TREATMENT GROUP AND ANIMAL NO	TREATMENT DAY 42			
	INDIVIDUAL VALUES FOR FEMALES			
	GLUCOSE MG/DL	BUN MG/DL	PHENYLAL MG/DL	
CONTROL				
901CF	201	17.6	QNS	
802CF	227	17.5	QNS	
836CF	172	16.2	3.1	
809CF	162	19.9	3.5	
910CF	189	19.9	QNS	
811CF	185	17.5	3.0	
LOW				
808LF	208	20.1	4.1	
815LF	211	16.8	3.9	
821LF	206	20.1	3.1	
824LF	197	17.3	QNS	
825LF	206	17.7	3.2	
827LF	187	14.4	3.3	
MEDIUM				
804MF	177	20.0	3.5	
805MF	188	22.0	QNS	
807MF	199	17.4	2.9	
819MF	244	13.2	3.0	
823MF	215	36.0	QNS	
828MF	206	21.1	3.6	
HIGH				
803HF	193	17.3	3.0	
812HF	174	23.1	3.2	
813HF	214	19.1	2.3	
814HF	201	21.8	4.0	
820HF	228	15.4	2.5	
829HF	253	16.8	QNS	

QNS = Quantity not sufficient for analysis.

Appendix Table 3 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PI#0988S73

CLINICAL CHEMISTRY

TREATMENT DAY 91
 INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	TTL BILI MG/DL	AP IU/L	GPT IU/L	GOT IU/L	TTL CHOL MG/DL
CONTROL					
A02CM	0.14	166	52	111	90
A04CM	0.17	177	31	92	82
A06CM	0.16	153	51	101	77
A07CM	0.18	164	41	100	96
A10CM	0.19	162	41	94	76
A11CM	0.23	112	43	97	77
LOW					
A05LM	0.14	209	41	82	70
A13LM	0.15	153	42	95	62
A17LM	0.14	162	39	116	81
A20LM	0.33	178	108	155	66
A23LM	0.11	201	48	81	97
A26LM	0.14	212	52	81	78
MEDIUM					
A08MM	0.16	169	46	90	71
A14MM	0.17	86	47	92	75
A16MM	0.16	192	42	81	69
A18MM	0.16	180	50	103	73
A22MM	0.07	158	49	93	72
A25MM	0.04	122	33	94	83
HIGH					
A01HM	0.22	138	35	107	69
A03HM	0.18	165	34	86	67
A09HM	0.17	176	49	110	72
A24HM	0.15	255	55	113	75
A28HM	0.15	100	50	83	70
A29HM	0.11	202	33	114	68

Appendix Table 3 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

CLINICAL CHEMISTRY

TREATMENT DAY 91
 INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	GLUCOSE MG/DL	BUN MG/DL	PHENYLAL MG/DL
CONTROL			
A02CM	176	18.0	2.3
A04CM	193	17.1	2.3
A06CM	174	24.4	3.2
A07CM	177	19.2	3.0
A10CM	195	17.5	2.4
A11CM	148	21.5	2.5
LOW			
A05LM	191	18.6	2.4
A13LM	177	18.3	2.2
A17LM	177	17.5	3.0
A20LM	142	14.5	3.7
A23LM	180	18.7	2.4
A26LM	167	21.5	1.6
MEDIUM			
A08MM	155	20.5	3.0
A14MM	170	19.5	3.3
A16MM	170	20.2	3.9
A18MM	161	23.4	2.5
A22MM	171	18.3	3.3
A25MM	164	19.0	2.3
HIGH			
A01HM	145	21.5	3.2
A03HM	210	20.0	2.4
A09HM	166	19.8	2.5
A24HM	160	17.7	2.7
A28HM	186	21.8	2.2
A29HM	187	23.8	2.3

Appendix Table 3 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988S73

CLINICAL CHEMISTRY

TREATMENT DAY 92
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	TTL BILI MG/DL	AP IU/L	GPT IU/L	GOT IU/L	TTL CHOL MG/DL
CONTROL					
B01CF	0.25	196	42	148	105
B02CF	0.25	97	40	77	97
B06CF	0.18	175	40	122	95
B09CF	0.24	189	36	94	QNS
B10CF	0.22	174	32	92	QNS
B11CF	0.17	181	34	85	83
LOW					
B08LF	0.19	168	31	86	76
B15LF	0.20	82	28	92	QNS
B21LF	0.22	128	28	77	67
B24LF	0.17	179	33	77	83
B25LF	0.19	142	31	77	92
B27LF	0.22	168	31	74	82
MEDIUM					
B04MF	0.24	168	41	122	94
B05MF	0.22	209	42	102	80
B07MF	0.24	198	33	115	83
B19MF	0.20	70	33	75	72
B23MF	0.18	148	28	82	86
B28MF	0.20	121	28	69	88
HIGH					
B03HF	0.26	183	38	102	72
B12HF	0.21	83	47	95	106
B13HF	0.18	219	41	95	105
B14HF	0.25	180	32	82	87
B20HF	0.29	156	45	75	78
B29HF	0.20	162	25	101	68

QNS = Quantity not sufficient for analysis.

Appendix Table 3 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

CLINICAL CHEMISTRY			
TREATMENT GROUP AND ANIMAL NO	TREATMENT DAY 92		
	INDIVIDUAL VALUES FOR FEMALES		
	GLUCOSE MG/DL	BUN MG/DL	PHENYLAL MG/DL
CONTROL			
901CF	134	17.0	2.3
802CF	156	17.6	2.2
806CF	158	17.8	2.2
809CF	157	19.6	2.3
810CF	179	20.0	2.1
811CF	175	20.6	2.0
LOW			
808LF	190	21.5	2.1
815LF	165	16.7	2.2
821LF	177	15.4	2.2
824LF	171	17.8	2.2
825LF	145	18.7	1.8
827LF	145	14.0	1.8
MEDIUM			
804MF	185	21.1	2.0
805MF	143	16.3	2.2
807MF	155	20.7	1.8
819MF	173	17.5	1.8
823MF	142	15.9	1.8
828MF	145	16.1	1.8
HIGH			
903HF	151	18.6	2.1
912HF	173	20.5	2.0
813HF	167	20.4	2.2
814HF	155	18.8	2.2
920HF	177	17.6	2.7
829HF	171	14.6	1.7

Appendix Table 3 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988573

CLINICAL CHEMISTRY

TREATMENT DAY 189
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	TTL 9ILI MG/DL	AP IU/L	GPT IU/L	GOT IU/L	TTL CHOL MG/DL
CONTROL					
A02CM	0.10	130	34	142	120
A04CM	0.07	127	21	117	110
A06CM	0.04	107	24	108	92
A07CM	0.10	101	16	103	115
A10CM	0.06	92	19	144	90
A11CM	0.10	125	36	144	90
LOW					
A05LM	0.07	191	31	149	72
A13LM	0.09	91	21	85	80
A17LM	0.10	117	28	151	100
A20LM	0.11	139	52	164	73
A23LM	0.08	147	31	114	130
A26LM	0.14	158	27	94	89
MEDIUM					
A08MM	0.07	79	21	124	77
A14MM	0.06	67	29	145	106
A16MM	0.12	132	27	95	82
A18MM	0.09	134	28	121	84
A22MM	0.10	120	26	136	92
A25MM	0.13	135	29	136	93
HIGH					
A01HM	0.11	125	34	112	56
A03HM	0.09	111	45	158	77
A09HM	0.10	129	31	142	90
A24HM	0.11	161	23	125	85
A28HM	0.12	127	74	198	65
A29HM	0.06	129	24	117	78

Appendix Table 3 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAY; PT#0988573

CLINICAL CHEMISTRY

TREATMENT DAY 189
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	GLUCOSE MG/DL	BUN MG/DL	PHENYLAL MG/DL
CONTROL			
A02CH	142	9.2	QNS
A04CH	187	9.4	QNS
A06CH	182	13.2	QNS
A07CH	182	10.3	3.2
A10CH	208	6.7	3.5
A11CH	137	5.0	2.3
LOW			
A05LM	192	11.4	3.3
A13LM	156	19.2	3.5
A17LM	189	19.1	3.1
A20LM	178	18.2	4.1
A23LM	169	18.3	3.2
A26LM	166	21.7	2.7
MEDIUM			
A08MM	157	10.0	QNS
A14MM	148	16.5	3.3
A16MM	168	18.6	3.2
A18MM	169	20.7	3.5
A22MM	176	22.7	3.7
A25MM	150	20.7	3.1
HIGH			
A01HM	111	12.0	2.7
A03HM	182	11.3	3.4
A09HM	169	10.3	3.4
A24HM	180	21.6	3.7
A28HM	159	18.9	3.6
A29HM	179	21.2	3.5

QNS = Quantity not sufficient for analysis.

Appendix Table 3 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT0988S73

CLINICAL CHEMISTRY

TREATMENT DAY 189
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	TTL BILI MG/DL	AP IU/L	GPT IU/L	GOT IU/L	TTL CHOL MG/DL
CONTROL					
B01CF	0.12	127	16	126	QNS
B02CF	0.13	62	28	105	95
B06CF	0.14	128	66	167	131
B09CF	0.09	124	35	109	QNS
B10CF	0.15	121	28	93	114
B11CF	0.14	128	26	96	89
LOW					
B08LF	0.15	122	26	86	87
B15LF	0.14	56	41	84	142
B21LF	0.13	98	24	75	QNS
B24LF	0.13	113	20	64	81
B25LF	0.15	86	21	58	101
B27LF	0.13	110	17	53	95
MEDIUM					
B04MF	0.14	167	36	116	87
B05MF	0.15	141	24	123	72
B07MF	0.13	168	20	107	84
B19MF	0.11	56	20	72	82
B23MF	0.08	93	22	76	101
B28MF	0.11	112	22	56	101
HIGH					
B03HF	0.13	119	24	115	85
B12HF	0.18	54	85	183	109
B13HF	0.17	175	49	135	76
B14HF	0.06	128	25	75	89
B20HF	0.13	139	22	88	80
B29HF	0.14	163	27	68	76

QNS = Quantity not sufficient for analysis.

Appendix Table 3 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0908S73

CLINICAL CHEMISTRY

TREATMENT DAY 189
 INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	GLUCOSE MG/DL	BUN MG/DL	PHENYLAL MG/DL
CONTROL			
801CF	134	17.2	QNS
802CF	149	17.7	3.7
806CF	126	17.1	3.3
809CF	131	17.5	QNS
810CF	161	19.8	3.5
811CF	150	16.0	3.4
LOW			
808LF	163	20.4	3.3
815LF	143	16.9	3.2
821LF	143	15.5	QNS
824LF	140	15.6	3.4
825LF	135	13.3	3.1
827LF	158	14.7	2.9
MEDIUM			
804MF	146	19.0	3.5
805MF	159	17.7	3.8
807MF	131	20.9	2.7
819MF	137	15.2	QNS
823MF	145	13.7	3.4
828MF	143	18.0	2.8
HIGH			
803HF	149	17.8	3.4
812HF	161	17.6	3.2
813HF	135	18.2	3.2
814HF	151	16.3	3.2
820HF	151	15.8	3.3
829HF	149	16.1	2.8

QNS = Quantity not sufficient for analysis.

Appendix Table 3 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT0988S73

CLINICAL CHEMISTRY

TREATMENT DAY 364
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	YTL BILI MG/DL	AP IU/L	GPT IU/L	GOT IU/L	YTL CHOL MG/DL
CONTROL					
A02CM	0.08	138	86	248	112
A04CM	0.09	118	17	QNS	71
A06CM	0.09	97	56	140	85
A07CM	0.13	111	16	127	89
A10CM	0.10	112	20	142	58
A11CM	0.07	171	32	101	59
LOW					
A05LM	0.17	82	33	QNS	50
A13LM	0.11	95	29	101	58
A17LM	0.09	113	112	135	86
A20LM	0.10	160	31	QNS	61
A23LM	0.11	141	35	99	103
A26LM	0.08	150	12	69	65
MEDIUM					
A08MM	0.12	146	63	146	59
A14MM	0.12	79	24	QNS	109
A16MM	0.10	161	56	106	71
A18MM	0.08	159	27	120	72
A22MM	0.13	93	43	104	61
A25MM	0.14	193	40	133	59
HIGH					
A01HM	0.08	101	57	190	64
A03HM	0.13	144	53	162	58
A09HM	0.07	127	40	107	71
A24HM	0.11	155	54	97	55
A28HM	0.10	173	112	QNS	39
A29HM	0.10	134	44	97	48

QNS = Quantity not sufficient for analysis.

Appendix Table 3 (cont.)

SC-19192; 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT0908573

CLINICAL CHEMISTRY

TREATMENT DAY 364
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	GLUCOSE MG/DL	BUN MG/DL	PHENYLAL MG/DL
CONTROL			
A02CM	137	2.4	3.6
A04CM	117	0.0	3.5
A06CM	102	4.9	3.2
A07CM	157	0.8	3.3
A10CM	119	2.1	3.0
A11CM	107	4.1	2.8
LOW			
A05LM	87	2.3	3.3
A13LM	119	2.0	QNS
A17LM	111	2.4	3.4
A20LM	117	2.0	QNS
A23LM	126	5.1	2.9
A26LM	128	4.7	2.7
MEDIUM			
A08HM	153	5.8	2.9
A14HM	121	4.0	3.6
A16HM	129	2.8	2.6
A18HM	134	5.7	3.3
A22HM	107	6.3	3.1
A25HM	120	5.2	3.0
HIGH			
A01HM	86	5.3	3.1
A03HM	107	2.4	2.7
A09HM	111	6.6	2.4
A24HM	143	4.7	2.9
A28HM	137	8.1	QNS
A29HM	150	8.9	3.0

QNS = Quantity not sufficient for analysis.

Appendix Table 3 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PI#0988573

CLINICAL CHEMISTRY

TREATMENT DAY 364
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	TTL BILI MG/DL	AP IU/L	GPT IU/L	GOT IU/L	TTL CHOL MG/DL
CONTROL					
B01CF	0.15	135	37	214	93
B02CF	0.13	44	62	148	89
B06CF	0.16	123	28	114	83
B09CF	0.14	141	53	160	69
B10CF	0.12	83	18	77	114
B11CF	0.14	119	29	QNS	QNS
LOW					
B08LF	0.15	123	34	93	67
B15LF	0.15	29	12	67	130
B21LF	0.14	105	12	83	65
B24LF	0.11	156	25	69	85
B25LF	0.14	107	42	86	114
B27LF	0.15	141	24	133	74
MEDIUM					
B04MF	0.18	131	46	137	48
B05MF	0.23	123	27	105	67
B07MF	0.14	149	26	122	66
B19MF	0.14	54	17	77	88
B23MF	0.13	88	30	71	84
B28MF	0.18	85	32	66	63
HIGH					
B03MF	0.11	135	38	276	75
B12MF	0.16	51	49	123	48
B13MF	0.18	151	66	154	50
B14MF	0.13	111	24	79	64
B20MF	0.18	132	19	78	55
B29MF	0.15	203	15	79	47

QNS = Quantity not sufficient for analysis.

Appendix Table 3 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAY; PT#0988S73

TREATMENT GROUP AND ANIMAL NO	CLINICAL CHEMISTRY		
	GLUCOSE MG/DL	BUN MG/DL	PHENYLAL MG/DL

TREATMENT DAY 364
 INDIVIDUAL VALUES FOR FEMALES

CONTROL			
B01CF	121	4.2	3.5
B02CF	139	10.9	2.8
B06CF	117	9.8	2.9
B09CF	126	13.0	2.9
B10CF	143	13.1	2.9
B11CF	150	11.7	QNS
LOW			
B08LF	134	9.3	2.7
B15LF	122	30.0	2.7
B21LF	155	9.6	2.7
B24LF	130	11.5	2.3
B25LF	132	5.3	2.5
B27LF	120	5.0	3.2
MEDIUM			
B04MF	104	14.3	2.7
B05MF	117	10.2	2.7
B07MF	144	17.8	2.9
B19MF	113	5.9	2.9
B23MF	124	3.9	2.3
B28MF	124	6.0	2.7
HIGH			
B03HF	103	7.2	3.6
B12HF	125	18.0	2.7
B13HF	107	16.6	2.7
B14HF	144	12.4	2.8
B20HF	151	6.5	2.9
B29HF	158	7.3	2.9

QNS = Quantity not sufficient for analysis.

Appendix Table 3 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988S73

CLINICAL CHEMISTRY

TREATMENT DAY 546
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	TTL BILI MG/DL	AP IU/L	GPT IU/L	GOT IU/L
CONTROL				
A02CM	0.16	QNS	69	285
A04CM	0.18	QNS	30	290
A06CM	0.17	38	31	190
A07CM	0.22	QNS	11	71
A10CM	0.15	57	28	141
A11CM	0.16	54	40	140
LOW				
A05LM	0.17	44	30	290
A13LM	0.17	38	26	101
A17LM	0.16	56	27	109
A20LM	0.22	59	29	99
A23LM	0.19	66	81	200
A26LM	0.15	70	24	77
MEDIUM				
A08MM	0.21	57	43	215
A14MM	0.23	33	10	141
A16MM	0.21	38	89	210
A18MM	0.20	QNS	47	112
A22MM	0.26	53	105	130
A25MM	0.24	80	95	175
HIGH				
A01HM	0.21	112	101	295
A03HM	0.24	88	114	295
A09HM	0.17	61	42	205
A24HM	0.21	66	53	95
A28HM	0.21	QNS	95	235
A29HM	0.19	130	170	280

QNS = Quantity not sufficient for analysis.

Appendix Table 3 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0986S73

CLINICAL CHEMISTRY
 TREATMENT DAY 546
 INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	GLUCOSE MG/DL	PHENYLAL MG/DL
CONTROL		
A02CM	105	3.8
A04CM	101	3.7
A06CM	73	4.1
A07CM	111	3.4
A10CM	108	3.1
A11CM	84	3.0
LOW		
A05LM	116	4.0
A13LM	115	3.1
A17LM	112	3.5
A20LM	94	3.1
A23LM	112	3.3
A26LM	96	2.7
MEDIUM		
A08MM	94	3.5
A14MM	90	4.9
A16MM	74	2.6
A18MM	124	3.2
A22MM	106	3.0
A25MM	102	2.7
HIGH		
A01HM	89	3.2
A03HM	139	3.3
A09HM	86	3.5
A24HM	108	2.6
A28HM	130	2.4
A29HM	135	2.1

Appendix Table 3 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0986S73

CLINICAL CHEMISTRY

TREATMENT DAY 547
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	TYL BILI MG/DL	AP IU/L	GPT IU/L	GOT IU/L
CONTROL				
B01CF	0.22	52	42	QNS
B02CF	0.24	35	53	QNS
B06CF	0.20	52	71	122
B09CF	0.18	85	75	QNS
B10CF	0.28	47	19	52
B11CF	0.18	50	67	70
LOW				
B08LF	0.20	43	34	QNS
B21LF	0.23	46	53	QNS
B24LF	0.21	43	38	57
B25LF	0.24	41	30	57
B27LF	0.25	47	32	QNS
D11LF	0.21	41	65	114
MEDIUM				
B04MF	QNS	QNS	43	QNS
B05MF	0.21	54	40	QNS
B07MF	0.21	52	32	QNS
B19MF	0.23	53	50	QNS
B23MF	0.19	29	42	77
B28MF	0.21	30	36	48
HIGH				
B03HF	0.28	43	75	QNS
B12HF	0.21	22	33	QNS
B13HF	0.23	70	205	184
B14HF	0.21	46	31	49
B20HF	0.25	60	30	QNS
B29HF	0.28	49	32	QNS

QNS = Quantity not sufficient for analysis.

Appendix Table 3 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PI#0988573

CLINICAL CHEMISTRY

TREATMENT DAY 547
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	GLUCOSE MG/DL	PHENYLAL MG/DL
CONTROL		
B01CF	110	2.4
B02CF	95	2.5
B06CF	88	2.8
B09CF	106	2.7
B10CF	85	4.0
B11CF	138	2.5
LOW		
B08LF	128	2.6
B21LF	150	2.2
B24LF	118	2.2
B25LF	113	2.2
B27LF	126	2.4
B11LF	125	2.5
MEDIUM		
B04MF	90	2.7
B05MF	98	2.6
B07MF	104	3.1
B19MF	78	2.9
B23MF	114	2.1
B28MF	124	2.8
HIGH		
B03HF	82	2.9
B12HF	129	2.4
B13HF	106	2.1
B14HF	149	2.6
B20HF	114	2.6
B29HF	126	2.4

Appendix Table 3 (cont.)

SC-19192; 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

CLINICAL CHEMISTRY

TREATMENT DAY 734
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	TTL BILI MG/DL	AP IU/L	GPT IU/L	GOT IU/L	TTL CHOL MG/DL
CONTROL					
A02CM	0.03	203	45	96	99
A06CM	0.07	170	23	144	215
A12CM	0.06	52	28	86	135
A15CM	0.09	50	18	98	135
A27CM	0.03	74	30	66	146
E02CM	0.04	130	44	138	84
LOW					
A05LM	0.05	57	49	86	139
A13LM	0.09	54	43	73	121
A20LM	0.01	108	20	89	120
A26LM	0.01	56	19	49	122
E15LM	0.06	72	54	76	133
E18LM	0.07	109	72	118	120
MEDIUM					
A08MM	0.13	67	48	105	124
A18MM	0.09	447	60	108	169
A22MM	0.05	57	25	81	147
A25MM	0.07	42	25	64	141
E10MM	0.04	79	68	92	131
E17MM	0.08	52	33	93	121
HIGH					
A01HM	0.08	242	58	275	84
A09HM	0.05	91	38	76	84
A29HM	0.05	201	119	140	94
E12HM	0.10	124	56	98	127
E14HM	0.15	73	52	90	98
E21HM	0.09	71	52	99	99

Appendix Table 3 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

CLINICAL CHEMISTRY						
TREATMENT DAY 734						
INDIVIDUAL VALUES FOR MALES						
TREATMENT GROUP AND ANIMAL NO	GLUCOSE MG/DL	PHENYLAL MG/DL	NA MMOL/L	K MMOL/L	CA MMOL/L	
CONTROL						
A02CM	136	3.0	152	4.6	QNS	
A06CM	37	3.0	153	5.6	2.6	
A12CM	76	3.5	149	4.8	2.7	
A15CM	103	4.0	147	5.6	2.5	
A27CM	121	4.4	153	4.5	2.6	
E02CM	75	2.4	153	4.7	2.4	
LOW						
A05LM	126	2.9	148	4.5	2.4	
A13LM	128	2.9	149	5.1	QNS	
A20LM	103	3.5	147	5.6	QNS	
A26LM	81	3.7	143	5.2	2.8	
E15LM	126	3.1	144	4.3	QNS	
E19LM	126	3.0	144	4.4	QNS	
MEDIUM						
A08MM	114	2.7	147	5.4	QNS	
A18MM	146	2.3	152	5.0	2.9	
A22MM	119	4.3	140	5.9	2.8	
A25MM	126	2.9	142	4.7	QNS	
E10MM	130	2.8	147	4.8	QNS	
E17MM	137	2.5	143	4.3	QNS	
HIGH						
A01HM	111	2.2	145	4.9	QNS	
A09HM	97	2.9	146	5.6	2.7	
A29HM	136	2.4	146	3.8	2.6	
E12HM	129	2.7	146	4.2	2.8	
E14HM	148	2.9	144	4.7	2.7	
E21HM	122	2.7	141	4.8	2.6	

QNS = Quantity not sufficient for analysis.

Appendix Table 3 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988S73

CLINICAL CHEMISTRY

TREATMENT DAY 734
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	TTL PROT G/DL	-----PROTEIN ELECTROPHORESIS-----					ALB/GLOB RATIO
		ALB %	ALPHA1 %	ALPHA2 %	ALPHA3 %	BETA1&2 %	GAMMA %
CONTROL							
A02CM	7.3	23.6	23.2	6.5	5.8	25.3	15.3
A06CM	7.0	18.1	24.5	6.7	6.8	24.6	20.2
A12CM	7.1	25.8	24.6	5.9	5.9	30.0	7.1
A15CM	7.0	30.1	23.7	6.2	6.3	17.7	15.6
A27CM	7.2	24.5	29.2	6.8	4.5	14.7	15.5
E02CM	5.5	28.7	24.7	6.0	6.1	23.0	12.0
LOW							
A05LM	7.2	33.9	17.3	6.8	6.3	20.9	14.2
A13LM	6.5	32.7	20.5	6.5	5.0	18.1	15.9
A20LM	6.7	17.5	22.4	7.2	5.5	21.6	25.3
A26LM	7.1	26.2	20.2	5.9	6.7	24.0	17.1
E15LM	6.9	39.3	18.2	6.4	6.8	16.3	13.6
E18LM	7.0	40.1	20.3	6.4	5.8	15.8	9.5
MEDIUM							
A08MM	5.9	33.1	19.4	6.4	5.5	18.0	18.0
A19MM	6.7	21.1	23.0	5.8	3.9	22.9	22.4
A22MM	7.4	30.8	22.0	5.8	5.5	18.5	16.8
A25MM	7.1	39.6	23.7	5.6	4.3	17.3	8.4
E10MM	7.4	34.3	18.7	5.9	4.6	19.5	16.0
E17MM	7.3	39.7	16.1	3.8	5.3	17.3	16.9
HIGH							
A01HM	5.7	41.0	16.8	5.4	5.4	19.6	11.9
A09HM	7.2	29.1	17.9	5.8	5.7	19.1	22.5
A29HM	6.5	40.1	17.3	5.3	4.1	16.5	16.6
E12HM	5.8	41.4	17.7	6.3	4.8	16.9	12.9
E14HM	6.8	41.8	17.7	6.5	4.6	15.9	13.9
E21HM	6.8	38.3	18.2	5.3	7.9	15.6	15.7

Appendix Table 3 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0908S73

CLINICAL CHEMISTRY						
TREATMENT DAY 735						
INDIVIDUAL VALUES FOR FEMALES						
TREATMENT GROUP AND ANIMAL NO	TTL BILI MG/DL	AP IU/L	GPT IU/L	GOT IU/L	TTL CHOL MG/DL	
CONTROL						
B01CF	0.02	27	32	118	162	
B02CF	0.06	25	96	260	186	
B06CF	0.03	24	19	105	164	
B11CF	0.06	39	28	90	111	
B16CF	0.00	35	25	103	113	
B18CF	0.04	75	19	170	115	
LOW						
B21LF	0.06	15	38	135	97	
B24LF	0.06	31	20	103	93	
B25LF	0.12	33	13	111	111	
B27LF	0.03	33	19	77	109	
D11LF	0.08	43	37	91	115	
D26LF	0.10	53	46	85	121	
MEDIUM						
B04MF	0.15	55	43	107	83	
B05MF	0.09	52	33	109	65	
B07MF	0.16	26	39	115	103	
B19MF	0.09	22	23	107	138	
B23MF	0.10	24	46	74	123	
B28MF	0.15	29	29	50	113	
HIGH						
B12HF	0.15	39	22	68	71	
B13HF	0.23	60	114	80	59	
B14HF	0.13	46	42	79	57	
B20HF	0.19	61	28	64	46	
B29HF	0.13	35	24	62	59	
D03HF	0.16	49	75	93	57	

Appendix Table 3 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988S73

CLINICAL CHEMISTRY

TREATMENT DAY 735
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	GLUCOSE MG/DL	PHENYLAL MG/DL	NA MMOL/L	K MMOL/L	CA MMOL/L
CONTROL					
B01CF	130	2.4	141	3.7	2.8
B02CF	102	2.3	138	3.4	3.0
B06CF	107	2.9	145	4.5	QNS
B11CF	151	2.5	115	3.5	2.7
B16CF	114	2.3	139	3.7	2.7
B18CF	64	2.7	142	4.0	2.6
LOW					
B21LF	96	2.1	148	3.9	2.9
B24LF	89	3.0	150	3.1	2.9
B25LF	108	2.8	QNS	QNS	QNS
B27LF	112	2.4	151	3.4	QNS
D11LF	103	2.4	QNS	QNS	QNS
D26LF	112	2.8	127	3.8	QNS
MEDIUM					
B04MF	138	2.1	145	4.0	3.0
B05MF	132	2.4	147	4.1	2.7
B07MF	120	2.0	147	3.7	2.9
B19MF	96	2.7	145	3.9	2.9
B23MF	106	1.9	143	3.3	QNS
B28MF	157	2.7	161	4.1	QNS
HIGH					
B12HF	154	2.5	150	3.4	QNS
B13HF	125	1.8	144	3.6	QNS
B14HF	124	2.2	144	3.5	2.7
B20HF	129	2.3	143	3.4	2.9
B29HF	129	2.1	148	3.0	2.8
D03HF	149	1.8	144	4.5	2.8

QNS = Quantity not sufficient for analysis.

Appendix Table 3 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

CLINICAL CHEMISTRY

TREATMENT DAY 735
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	TTL PROT G/DL	PROTEIN ELECTROPHORESIS					ALB/GLOB RATIO	
		ALB %	ALPHA1 %	ALPHA2 %	ALPHA3 %	BETA1&2 %		GAMMA %
CONTROL								
801CF	8.2	47.8	17.3	3.0	5.4	15.9	11.0	0.89
902CF	8.6	34.4	22.9	5.9	5.4	20.3	11.4	0.54
806CF	7.6	44.1	20.4	5.1	4.6	16.5	9.8	0.81
811CF	7.3	44.8	16.9	4.6	5.5	16.4	11.6	0.78
816CF	8.3	40.1	16.4	5.3	4.2	20.1	13.7	0.67
918CF	7.6	40.2	17.1	4.3	4.2	17.5	16.4	0.65
LOW								
921LF	8.6	46.9	18.8	4.5	3.9	14.0	11.9	0.91
824LF	9.6	36.2	16.1	2.6	5.5	19.3	20.1	0.53
825LF	7.6	43.4	14.8	5.5	4.6	16.2	15.8	0.77
827LF	7.6	39.9	14.6	3.2	11.7	18.4	12.5	0.67
D11LF	8.1	37.3	16.6	5.9	6.3	21.4	12.5	0.62
D26LF	8.0	38.4	17.5	5.6	4.9	15.9	17.9	0.63
MEDIUM								
804MF	7.9	45.6	17.4	4.3	5.4	17.6	9.9	0.84
905MF	7.8	40.3	14.1	4.4	4.5	16.2	20.2	0.67
307MF	7.4	51.8	12.0	4.0	5.8	15.8	11.1	1.03
919MF	6.7	31.1	21.4	6.3	11.1	13.6	17.2	0.46
823MF	8.5	50.3	18.1	3.8	4.3	15.5	9.5	1.00
828MF	7.7	51.4	14.7	5.4	4.6	15.6	8.7	1.08
HIGH								
812HF	6.6	53.3	10.6	4.9	4.1	17.6	9.6	1.20
813HF	6.6	49.3	12.1	4.2	4.1	16.9	13.2	0.94
914HF	7.3	52.8	12.3	3.6	4.5	16.0	10.7	1.12
820HF	7.2	52.7	8.8	2.9	5.2	16.2	13.7	1.15
829HF	7.4	47.5	13.1	2.4	2.4	17.4	18.0	0.90
D03HF	7.3	47.4	17.8	2.3	1.5	12.3	19.9	0.87

Appendix Table 4
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988573

URINALYSIS									
TREATMENT DAY 42									
INDIVIDUAL VALUES FOR MALES									
TREATMENT GROUP AND ANIMAL NO	PH	SP GRAV	GLUCOSE	KETONES	PROTEIN	BILI	OC BLOOD	UROBILI	
CONTROL									
A02CM	9.0	1.034	0	0	0	0	0	0	0
A04CM	8.5	1.018	0	0	0	0	0	0	0
A06CM	9.0	1.015	0	0	0	0	0	0	0
A07CM	8.0	1.018	0	0	0	0	0	0	0
A10CM	8.5	1.014	0	0	0	0	0	0	0
A11CM	8.0	1.018	0	0	0	0	0	0	0
LOW									
A05LM	8.0	1.015	0	0	0	0	0	0	0
A13LM	8.0	1.026	0	0	0	0	0	0	0
A17LM	8.5	1.026	0	0	0	0	0	0	0
A20LM	8.5	1.035	0	0	0	0	0	0	0
A23LM	8.5	1.035	0	0	0	0	0	0	0
A26LM	8.5	1.035	0	0	0	0	0	0	0
MEDIUM									
A08MM	9.0	1.035	0	0	0	0	0	0	0
A14MM	8.0	1.028	0	0	0	0	0	0	0
A16MM	8.5	1.014	0	0	0	0	1	0	0
A18MM	8.5	1.035	0	0	0	0	0	0	0
A22MM	8.0	1.024	0	0	0	0	0	0	0
A25MM	9.0	1.032	0	0	0	0	0	0	0
HIGH									
A01HM	9.0	1.035	0	0	0	0	0	0	0
A03HM	8.5	1.022	0	0	0	0	0	0	0
A09HM	8.5	1.024	0	0	0	0	0	0	0
A24HM	8.0	1.034	0	0	0	0	0	0	0
A28HM	8.0	1.028	0	0	0	0	0	0	0
A29HM	8.5	1.030	0	0	0	0	0	0	0

Appendix Table 4 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

TREATMENT GROUP AND ANIMAL NO	URINALYSIS						
	TREATMENT DAY 42						
	INDIVIDUAL VALUES FOR MALES						
	MICROSCOPIC FINDINGS						
	RBC AVE#/HPF	WBC AVE#/HPF	CASTS AVE#/LPF	CRYSTALS	BACTERIA	PHENYLKE PKU	
CONTROL							
A02CM	0	0	0	0	2	0	
A04CM	0	0	0	0	4	0	
A06CM	0	0	0	1	1	0	
A07CM	0	0	0	0	0	0	
A10CM	0	0	0	0	1	0	
A11CM	0	0	0	1	1	1	
LOW							
A05LM	0	0	0	2	2	0	
A13LM	0	0	0	1	0	0	
A17LM	0	0	0	1	1	0	
A20LM	0	0	0	1	2	0	
A23LM	0	0	0	2	3	0	
A26LM	0	0	0	0	0	0	
MEDIUM							
A08MM	0	0	0	0	1	0	
A14MM	0	0	0	2	2	0	
A16MM	0	0	0	0	1	0	
A18MM	0	0	0	0	1	0	
A22MM	0	0	0	0	2	0	
A25MM	0	0	0	1	1	0	
HIGH							
A01HM	0	0	0	0	2	0	
A03HM	0	0	0	1	1	0	
A09HM	0	0	0	1	1	0	
A24HM	0	0	0	1	2	0	
A28HM	0	0	0	1	1	1	
A29HM	0	0	0	0	1	0	

Appendix Tab14 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

URINALYSIS

TREATMENT DAY 42
 INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	PH	SP GRAV	GLUCOSE	KETONES	PROTEIN	BILI	OC BLOOD	UROBILI
CONTROL								
801CF	9.0	1.017	0	0	0	0	0	0
802CF	8.5	1.022	0	0	0	0	0	0
806CF	8.5	1.030	0	0	0	0	0	0
809CF	9.0	1.030	0	0	0	0	0	0
910CF	8.5	1.032	0	0	0	0	0	0
811CF	8.0	1.022	0	0	0	0	0	0
LOW								
808LF	8.0	1.032	0	0	0	0	0	0
915LF	8.0	1.020	0	0	0	0	0	0
821LF	9.0	1.024	0	0	0	0	0	0
924LF	8.0	1.035	0	0	0	0	0	0
825LF	8.5	1.028	0	0	0	0	0	0
827LF	9.0	1.020	0	0	0	0	0	0
MEDIUM								
804MF	8.0	1.017	0	0	0	0	0	0
805MF	7.0	1.034	0	0	0	0	0	0
807MF	7.0	1.022	0	0	0	0	0	0
819MF	9.0	1.035	0	0	1	0	0	0
823MF	9.0	1.022	0	0	0	0	0	0
828MF	8.0	1.034	0	0	0	0	0	0
HIGH								
803HF	8.5	1.020	0	0	0	0	0	0
812HF	9.0	1.030	0	0	0	0	0	0
813HF	9.0	1.035	0	0	0	0	1	0
814HF	9.0	1.028	0	0	0	0	0	0
920HF	8.0	1.028	0	0	0	0	0	0
829HF	8.5	1.032	0	0	0	0	0	0

SC-19192; 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

URINALYSIS

TREATMENT DAY 42
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	MICROSCOPIC FINDINGS					BACTERIA	PHENYLKE PKU
	RBC AVE#/HPF	WBC AVE#/HPF	CASIS AVE#/LPF	CRYSTALS			
CONTROL							
B01CF	0	0	0	0	2	1	0
B02CF	0	0	0	2	2	0	0
B06CF	0	0	0	1	1	0	0
B09CF	0	0	0	1	1	0	0
B10CF	0	0	0	0	0	0	0
B11CF	0	0	0	1	2	0	0
LOW							
B08LF	0	0	0	2	1	0	0
B15LF	0	0	0	0	2	0	0
B21LF	0	0	0	2	1	0	0
B24LF	0	0	0	1	1	0	0
B25LF	0	0	0	1	0	0	0
B27LF	0	0	0	1	2	0	0
MEDIUM							
B04MF	0	0	0	1	1	0	0
B05MF	0	0	0	0	0	0	0
B07MF	0	0	0	2	2	1	0
B19MF	0	0	0	2	2	0	0
B23MF	0	0	0	0	0	0	0
B28MF	0	0	0	1	1	0	0
HIGH							
B03HF	0	0	0	0	0	0	0
B12HF	0	0	0	1	1	0	0
B13HF	0	0	0	0	0	0	0
B14HF	0	0	0	2	2	0	0
B20HF	0	0	0	1	2	0	0
B29HF	0	0	0	0	0	0	0

Appendix Table 4 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PI#0988S73

URINALYSIS

TREATMENT DAY 91
 INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	PH	SP GRAV	GLUCOSE	KETONES	PROTEIN	BILI	OC BLOOD
CONTROL							
A02CM	9.0	1.032	0	0	0	0	0
A04CM	8.0	1.032	0	0	0	0	0
A06CM	8.0	1.024	0	0	0	0	0
A07CM	8.0	1.028	0	0	0	0	0
A10CM	8.5	1.019	0	0	0	0	0
A11CM	8.5	1.035	0	0	0	0	0
LOW							
A05LM	8.0	1.026	0	0	0	0	0
A13LM	8.5	1.022	0	0	0	0	0
A17LM	8.0	1.022	0	0	0	0	0
A20LM	7.0	1.035	0	0	0	0	0
A23LM	6.0	1.035	0	0	0	0	0
A26LM	8.5	1.035	0	0	0	0	0
MEDIUM							
A08MM	8.0	1.035	0	0	0	0	0
A14MM	8.5	1.035	0	0	0	0	0
A16MM	8.0	1.024	0	0	0	0	0
A18MM	8.0	1.035	0	0	0	0	0
A22MM	8.0	1.032	0	0	0	0	0
A25MM	8.0	1.030	0	0	0	0	0
HIGH							
A01HM	8.0	1.035	0	0	0	0	0
A03HM	9.0	1.017	0	0	0	0	0
A09HM	7.0	1.035	0	0	0	0	0
A24HM	8.0	1.032	0	0	0	0	0
A28HM	7.5	1.032	0	0	0	0	0
A29HM	7.5	1.028	0	0	0	0	0

Appendix Table 4 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0908S73

URINALYSIS

TREATMENT DAY 91
 INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	MICROSCOPIC FINDINGS					PHENYLKE PKU
	RBC AVE#/HPF	WBC AVE#/HPF	CASTS AVE#/LPF	CRYSTALS	BACTERIA	
CONTROL						
A02CM	0	0	0	2	1	0
A04CM	0	0	0	1	1	0
A06CM	0	0	0	2	1	0
A07CM	0	0	0	0	0	0
A10CM	0	0	0	0	0	0
A11CM	0	0	0	2	1	0
LOW						
A05LM	0	0	0	0	0	0
A13LM	0	0	0	1	2	0
A17LM	0	0	0	0	1	0
A20LM	0	0	0	2	1	0
A23LM	0	0	0	0	1	0
A26LM	0	0	0	2	2	0
MEDIUM						
A08MM	0	0	0	1	2	0
A14MM	0	0	0	1	1	0
A16MM	0	0	0	1	2	0
A18MM	0	0	0	1	1	0
A22MM	0	0	0	2	2	0
A25MM	0	0	0	3	1	0
HIGH						
A01HM	0	0	0	3	2	0
A03HM	0	0	0	0	0	0
A09HM	0	0	0	3	2	0
A24HM	0	0	0	0	0	0
A28HM	0	0	0	0	1	0
A29HM	0	0	0	2	2	0

Appendix Table 4 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0980S73

TREATMENT GROUP AND ANIMAL NO	URINALYSIS							
	TREATMENT DAY 93							
	INDIVIDUAL VALUES FOR FEMALES							
PH	SP GRAV	GLUCOSE	KETONES	PROTEIN	BILI	OC BLOOD		
CONTROL								
B01CF	8.0	1.018	0	0	0	0		
B02CF	8.5	1.027	0	0	0	0		
B06CF	8.5	1.032	0	0	0	0		
B09CF	8.5	1.032	0	0	0	0		
B10CF	8.0	1.028	0	0	0	0		
B11CF	8.0	1.035	0	0	0	0		
LOW								
B08LF	7.5	1.018	0	0	0	0		
B15LF	8.0	1.035	0	0	0	0		
B21LF	7.0	1.035	0	0	0	0		
B24LF	8.0	1.016	0	0	0	0		
B25LF	9.0	1.035	0	0	0	0		
B27LF	9.0	1.035	0	0	0	0		
MEDIUM								
B04MF	8.0	1.035	0	0	0	0		
B05MF	8.0	1.028	0	0	0	0		
B07MF	8.0	1.022	0	0	0	0		
B19MF	8.5	1.042	0	0	0	0		
B23MF	9.0	1.034	0	0	0	0		
B28MF	8.5	1.035	0	0	0	0		
HIGH								
B03HF	6.0	1.035	0	0	0	0		
B12HF	8.0	1.028	0	0	0	0		
B13HF	8.0	1.034	0	0	0	0		
B14HF	6.0	1.016	0	0	0	0		
B20HF	8.0	1.028	0	0	0	0		
B29HF	7.0	1.018	0	0	0	0		

Appendix Table 4 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

TREATMENT GROUP AND ANIMAL NO	URINALYSIS					
	TREATMENT DAY 93					
	INDIVIDUAL VALUES FOR FEMALES					
	-----MICROSCOPIC FINDINGS-----					
	RBC AVE#/HPF	WBC AVE#/HPF	CASTS AVE#/LPF	CRYSTALS	BACTERIA	PHENYLKE PKU
CONTROL						
B01CF	0	0	0	1	1	0
B02CF	0	0	0	0	0	0
B06CF	0	0	0	1	1	0
B09CF	0	0	0	1	0	0
B10CF	0	0	0	1	1	1
B11CF	0	0	0	1	2	0
LOW						
B08LF	0	0	0	2	2	0
B15LF	0	0	0	1	1	0
B21LF	0	0	0	1	1	0
B24LF	0	0	0	2	1	0
B25LF	0	0	0	2	1	0
B27LF	0	0	0	1	1	0
MEDIUM						
B04MF	0	0	0	0	0	0
B05MF	0	0	0	2	1	0
B07MF	0	0	0	3	1	0
B19MF	0	0	0	2	1	0
B23MF	0	0	0	1	1	0
B28MF	0	0	0	0	0	0
HIGH						
B03HF	0	0	0	0	0	0
B12HF	0	0	0	0	2	0
B13HF	0	0	0	1	1	0
B14HF	0	0	0	2	2	0
B20HF	0	0	0	2	1	0
B29HF	0	0	0	1	1	0

Appendix Table 4 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

URINALYSIS										
TREATMENT DAY 189										
INDIVIDUAL VALUES FOR MALES										
TREATMENT GROUP AND ANIMAL NO	PH	SP GRAV	GLUCOSE	KETONES	PROTEIN	BILI	OC BLOOD	UROBILI		
CONTROL										
A02CM	8.0	1.070	0	0	3	0	0	0		
A04CM	6.5	1.030	0	0	0	0	0	0		
A06CM	6.5	1.025	0	0	0	0	0	0		
A07CM	8.0	1.033	0	0	1	0	0	0		
A10CM	8.5	1.038	0	0	0	0	0	0		
A11CM	7.5	1.028	0	0	0	0	0	0		
LOW										
A05LM	8.0	1.034	0	0	0	0	1	0		
A13LM	7.0	1.039	0	0	1	0	0	0		
A17LM	7.5	1.055	0	0	2	0	0	0		
A20LM	7.0	1.045	0	0	2	0	0	0		
A23LM	8.0	1.065	0	0	3	0	0	0		
A26LM	7.5	1.035	0	0	0	0	0	0		
MEDIUM										
A08MM	8.0	1.042	0	0	1	0	0	0		
A14MM	7.0	1.042	0	0	3	0	0	0		
A16MM	7.0	1.050	0	0	1	0	0	0		
A18MM	7.5	1.090	0	0	3	0	0	0		
A22MM	7.5	1.033	0	0	0	0	0	0		
A25MM	8.0	1.090	0	0	2	0	0	0		
HIGH										
A01HM	7.5	1.070	0	0	1	0	0	0		
A03HM	8.0	1.080	0	0	0	0	0	0		
A09HM	5.0	1.080	0	0	1	0	0	0		
A24HM	6.0	1.060	0	0	1	0	0	0		
A28HM	8.0	1.031	0	0	0	0	0	0		
A29HM	6.0	1.085	0	0	0	0	0	0		

Appendix Table 4 (cont.)
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PI#0988S73

TREATMENT GROUP AND ANIMAL NO	URINALYSIS						PHENYLKE PKU
	TREATMENT DAY 189						
	INDIVIDUAL VALUES FOR MALES						
	MICROSCOPIC FINDINGS						
	RBC AVE#/HPF	WBC AVE#/HPF	CASTS AVE#/LPF	CRYSTALS	BACTERIA		
CONTROL							
A02CM	0	0	0	1	1	0	
A04CM	0	0	0	0	0	0	
A06CM	0	0	0	0	0	0	
A07CM	0	0	0	0	0	0	
A10CM	0	0	0	1	1	0	
A11CM	0	0	0	0	0	0	
LOW							
A05LM	0	0	0	0	0	0	
A13LM	0	0	0	0	0	0	
A17LM	0	0	0	1	2	0	
A20LM	0	0	0	0	0	0	
A23LM	0	0	0	0	1	0	
A26LM	0	0	0	1	2	0	
MEDIUM							
A08MM	0	0	0	0	0	0	
A14MM	0	0	0	0	2	0	
A16MM	0	0	0	0	1	0	
A18MM	0	0	0	3	4	0	
A22MM	0	0	0	0	0	0	
A25MM	0	0	0	0	0	0	
HIGH							
A01HM	0	0	0	0	0	0	
A03HM	0	0	0	0	0	0	
A09HM	0	0	0	1	1	0	
A24HM	0	0	0	0	0	0	
A28HM	0	0	0	0	1	0	
A29HM	0	0	0	0	0	0	

Appendix Table 4 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

URINALYSIS

TREATMENT DAY 190
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	PH	SP GRAV	GLUCOSE	KETONES	PROTEIN	BILI	OC 9L000	UROBILI
CONTROL								
B01CF	8.0	1.026	0	0	0	0	0	0
B02CF	8.5	1.028	0	0	0	0	0	0
B06CF	9.0	1.018	0	0	0	0	0	0
B09CF	7.5	1.032	0	0	0	0	0	0
B10CF	9.0	1.030	0	0	0	0	0	0
B11CF	7.0	1.033	0	0	0	0	0	0
LOW								
B08LF	8.5	1.035	0	0	0	0	0	0
B15LF	7.0	1.030	0	0	1	0	0	0
B21LF	7.5	1.028	0	0	1	0	0	0
B24LF	8.5	1.035	0	0	0	0	0	0
B25LF	8.0	1.026	0	0	0	0	0	0
B27LF	7.0	1.024	0	0	0	0	0	0
MEDIUM								
B04MF	8.5	1.032	0	0	0	0	0	0
B05MF	6.0	1.035	0	0	0	0	0	0
B07MF	7.0	1.032	0	0	0	0	0	0
B19MF	7.0	1.024	0	0	1	0	0	0
B23MF	8.0	1.032	0	0	0	0	0	0
B28MF	9.0	1.022	0	0	0	0	0	0
HIGH								
B03HF	7.5	1.035	0	0	0	0	0	0
B12HF	6.0	1.035	0	0	0	0	0	0
B13HF	7.0	1.024	0	0	0	0	0	0
B14HF	6.0	1.022	0	0	0	0	0	0
B20HF	7.5	1.035	0	0	0	0	0	0
B29HF	8.0	1.018	0	0	0	0	0	0

Appendix Table 4 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0986S73

URINALYSIS

TREATMENT DAY 190
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	-----MICROSCOPIC FINDINGS-----					BACTERIA	PHENYLKE PKU
	RBC AVE#/HPF	WBC AVE#/HPF	CASTS AVE#/LPF	CRYSTALS			
CONTROL							
B01CF	0	0	0	0	0	0	0
B02CF	0	0	0	0	2	2	0
B06CF	0	0	0	0	0	0	0
B09CF	0	0	0	0	0	2	0
B10CF	0	0	0	0	1	1	0
B11CF	0	0	0	0	0	0	0
LOW							
B0ALF	0	0	0	0	0	0	0
B15LF	0	0	0	0	0	0	0
B21LF	0	0	0	0	0	0	0
B24LF	0	0	0	0	0	0	0
B25LF	0	0	0	0	0	1	0
B27LF	0	0	0	0	0	0	0
MEDIUM							
B04MF	0	0	0	0	1	2	0
B05MF	0	0	0	0	0	0	0
B07MF	0	0	0	0	0	1	0
B19MF	0	0	0	0	0	1	0
B23MF	0	0	0	0	0	2	0
B28MF	0	0	0	0	0	1	0
HIGH							
B03HF	0	0	0	0	0	2	0
B12HF	0	0	0	0	0	0	0
B13HF	0	0	0	0	0	2	0
B14HF	0	0	0	0	0	0	0
B20HF	0	0	0	0	0	0	0
B29HF	0	0	0	0	0	0	0

Appendix Table 4 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

URINALYSIS										
TREATMENT DAY 364										
INDIVIDUAL VALUES FOR MALES										
TREATMENT GROUP AND ANIMAL NO	PH	SP GRAV	GLUCOSE	KETONES	PROTEIN	BILI	OC BLOOD	UROBILI		
CONTROL										
A02CM	6.0	1.060	0	0	2	0	0	1		
A04CM	6.0	1.041	0	0	2	0	0	0		
A06CM	7.0	1.083	0	0	4	0	0	1		
A07CM	7.0	1.027	0	0	2	0	0	0		
A10CM	7.0	1.043	0	0	2	0	1	0		
A11CM	7.5	1.068	0	0	2	0	0	0		
LOW										
A05LM	6.0	1.032	0	0	1	0	1	0		
A13LM	6.0	1.042	0	0	2	0	0	0		
A17LM	6.0	1.053	0	0	3	0	0	0		
A20LM	6.0	1.010	0	0	1	0	0	0		
A23LM	6.0	1.057	0	0	3	0	0	0		
A26LM	8.0	1.037	0	0	0	0	0	0		
MEDIUM										
A08MM	6.5	1.064	0	0	2	0	0	0		
A14MM	6.5	1.032	0	0	3	0	0	0		
A16MM	6.0	1.023	0	0	0	0	0	0		
A18MM	6.5	1.041	0	0	3	0	0	0		
A22MM	6.5	1.039	0	0	3	0	0	0		
A25MM	6.0	1.068	0	0	2	0	3	0		
HIGH										
A01HM	6.0	1.053	0	0	1	0	1	1		
A03HM	6.0	1.060	0	0	1	0	0	1		
A09HM	6.0	1.052	0	0	2	0	3	0		
A24HM	6.0	1.035	0	0	1	0	0	0		
A28HM	6.0	1.036	0	0	0	0	0	0		
A29HM	6.0	1.054	0	0	1	0	0	0		

Appendix Table 4 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988S73

URINALYSIS

TREATMENT DAY 364
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	-----MICROSCOPIC FINDINGS-----					PHENYLKE PKU
	RBC AVE#/HPF	WBC AVE#/HPF	CASTS AVE#/LPF	CRYSTALS	BACTERIA	
CONTROL						
A02CM	0	0	0	0	1	0
A04CM	0	0	0	0	1	0
A06CM	3	0	0	0	2	0
A07CM	3	3	0	1	1	0
A10CM	0	0	0	2	2	0
A11CM	0	0	0	2	2	0
LOW						
A05LM	0	0	1	0	1	0
A13LM	0	0	0	2	1	0
A17LM	0	0	0	0	1	1
A20LM	0	2	0	1	1	0
A23LM	0	0	0	1	1	0
A26LM	0	17	0	1	1	0
MEDIUM						
A08MM	0	0	0	0	1	0
A14MM	0	0	0	0	1	0
A16MM	0	0	0	1	2	0
A18MM	0	0	0	0	1	0
A22MM	0	2	0	2	2	0
A25MM	15	3	0	2	1	0
HIGH						
A01HM	15	3	0	0	1	0
A03HM	0	3	0	0	1	0
A09HM	25	25	0	1	4	0
A24HM	0	0	0	1	1	0
A28HM	0	0	0	1	1	0
A29HM	0	0	0	1	0	0

Appendix Table 4 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0980S73

URINALYSIS

TREATMENT DAY 364
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	PH	SP GRAV	GLUCOSE	KETONES	PROTEIN	BILI	OC BLOOD	UROBILI
CONTROL								
B01CF	7.0	1.014	0	0	0	0	0	0
B02CF	7.0	1.022	0	0	0	0	0	0
B06CF	6.5	1.016	0	0	0	0	0	0
B09CF	7.5	1.032	0	0	2	0	1	0
B10CF	6.0	1.032	0	0	3	0	0	0
B11CF	7.0	1.030	0	0	0	0	1	0
LOW								
B08LF	6.0	1.018	0	0	0	0	0	0
B15LF	6.0	1.018	0	0	3	0	0	0
B21LF	6.5	1.022	0	0	0	0	0	0
B24LF	6.0	1.010	0	0	0	0	0	0
B25LF	6.5	1.020	0	0	0	0	1	0
B27LF	6.0	1.032	0	0	0	0	0	0
MEDIUM								
B04MF	6.0	1.022	0	0	0	0	0	0
B05MF	6.0	1.034	0	0	0	0	0	0
B07MF	6.5	1.035	0	0	1	0	0	0
B19MF	6.0	1.034	0	0	0	0	0	0
B23MF	6.0	1.024	0	0	0	0	1	0
B28MF	7.0	1.016	0	0	1	0	0	0
HIGH								
B03HF	6.0	1.018	0	0	0	0	0	0
B12HF	6.0	1.020	0	0	0	0	0	0
B13HF	6.0	1.035	0	0	0	0	0	0
B14HF	6.0	1.035	0	0	0	0	0	0
B20HF	6.0	1.035	0	0	0	0	0	0
B29HF	6.5	1.028	0	0	0	0	0	0

Appendix Table 4 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

TREATMENT GROUP AND ANIMAL NO	URINALYSIS					
	TREATMENT DAY 364					
	INDIVIDUAL VALUES FOR FEMALES					
	MICROSCOPIC FINDINGS					
	RBC AVE#/HPF	WBC AVE#/HPF	CASTS AVE#/LPF	CRYSTALS	BACTERIA	PHENYLKE PKU
CONTROL						
B01CF	0	0	0	0	1	0
B02CF	0	0	0	0	1	0
B06CF	0	0	0	2	1	0
B09CF	0	3	2	0	1	0
B10CF	0	0	0	0	1	0
B11CF	0	0	2	0	1	0
LOW						
B08LF	0	0	0	0	0	0
B15LF	0	0	0	0	0	0
B21LF	0	0	0	0	0	0
B24LF	3	0	0	0	1	0
B25LF	0	0	0	1	2	0
B27LF	0	0	0	0	0	0
MEDIUM						
B04MF	0	0	0	1	2	0
B05MF	0	0	0	0	1	0
B07MF	0	0	0	0	0	0
B19MF	0	0	0	1	1	0
B23MF	0	0	0	0	1	0
B28MF	0	0	0	0	0	0
HIGH						
B03HF	0	0	0	0	1	0
B12HF	0	0	0	0	4	0
B13HF	0	0	0	0	0	0
B14HF	0	0	0	0	1	0
B20HF	0	0	0	0	1	0
B29HF	0	0	0	0	1	0

Appendix Table 4 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988573

URINALYSIS

TREATMENT DAY 546
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	PH	SP GRAV	PROTEIN	BILI	OC BLOOD	UROBILI
CONTROL						
A02CM	6.0	1.048	2	0	0	0
A04CM	6.0	1.025	1	0	0	0
A06CM	7.0	1.028	2	0	0	0
A07CM	6.5	1.030	0	0	0	0
A10CM	6.5	1.035	2	0	0	0
A11CM	7.0	1.020	1	0	0	0
LOW						
A05LM	7.0	1.035	0	0	0	0
A13LM	6.0	1.027	1	0	0	0
A17LM	7.0	1.030	0	0	0	0
A20LM	6.0	1.018	1	0	0	0
A23LM	7.0	1.020	0	0	0	0
A26LM	8.5	1.034	3	0	0	0
MEDIUM						
A08MM	6.0	1.035	1	0	0	0
A14MM	6.0	1.020	2	0	0	0
A16MM	6.0	1.022	0	0	0	0
A18MM	6.5	1.016	0	0	0	0
A22MM	6.0	1.035	1	0	0	0
A25MM	6.0	1.028	0	0	0	0
HIGH						
A01HM	6.0	1.042	1	0	0	0
A03HM	7.0	1.012	0	0	1	0
A09HM	7.0	1.034	0	0	0	0
A24HM	6.0	1.018	2	0	0	0
A28HM	6.0	1.035	0	0	0	0
A29HM	7.0	1.014	1	0	0	0

Appendix Table 4 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0908S73

URINALYSIS

TREATMENT DAY 546
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	MICROSCOPIC FINDINGS					BACTERIA	PHENYLKE PKU
	RBC AVE#/HPF	WBC AVE#/HPF	CASTS AVE#/LPF	CRYSTALS			
CONTROL							
A02CH	0	1	0	0	1	0	
A04CH	0	1	0	0	1	0	
A06CH	0	0	0	1	1	0	
A07CH	0	1	0	0	1	0	
A10CH	0	0	0	1	1	0	
A11CH	0	0	0	1	0	0	
LOW							
A05LM	0	0	0	1	1	0	
A13LM	0	0	0	1	1	0	
A17LM	0	0	0	1	1	0	
A20LM	4	2	0	0	1	0	
A23LM	0	0	0	0	1	0	
A26LM	0	2	0	0	2	0	
MEDIUM							
A08MM	0	2	0	0	2	0	
A14MM	0	0	0	1	1	0	
A16MM	0	1	0	0	1	0	
A18MM	0	0	0	1	1	0	
A22MM	0	3	0	1	1	0	
A25MM	1	2	0	1	1	0	
HIGH							
A01HM	0	0	0	1	0	0	
A03HM	0	0	0	0	0	0	
A09HM	0	1	0	1	1	0	
A24HM	0	2	0	0	1	0	
A28HM	0	1	0	0	1	0	
A29HM	0	0	0	0	1	0	

Appendix Table 4 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

URINALYSIS

TREATMENT DAY 547
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	PH	SP GRAV	PROTEIN	BILI	OC BLOOD	UROBILI
CONTROL						
B01CF	7.0	1.031	1	0	0	0
B02CF	7.0	1.024	1	0	0	0
B06CF	7.0	1.008	1	0	0	0
B09CF	6.0	1.023	0	0	0	0
B10CF	7.0	1.033	2	0	0	0
B11CF	8.0	1.022	0	0	0	0
LOW						
B08LF	7.0	1.046	1	0	0	0
B21LF	6.5	1.024	0	0	0	0
B24LF	7.5	1.029	1	0	0	0
B25LF	6.0	1.026	0	0	0	0
B27LF	7.5	1.027	1	0	0	0
D11LF	7.5	1.018	0	0	0	0
MEDIUM						
B04MF	6.0	1.052	1	0	0	0
B05MF	6.0	1.042	0	0	0	0
B07MF	6.0	1.042	0	0	0	0
B19MF	6.0	1.033	0	0	0	0
B23MF	7.0	1.026	1	0	0	0
B28MF	7.0	1.050	2	0	0	0
HIGH						
B03HF	6.0	1.048	0	0	0	0
B12HF	6.0	1.032	0	0	0	0
B13HF	6.0	1.060	1	0	0	0
B14HF	6.0	1.038	0	0	0	0
B20HF	6.0	1.044	0	0	0	0
B29HF	6.0	1.034	1	0	0	0

Appendix Table 4 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0988S73

URINALYSIS

TREATMENT DAY 547
INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	MICROSCOPIC FINDINGS					BACTERIA	PHENYLKE PKU
	RBC AVE#/HPF	WBC AVE#/HPF	CASTS AVE#/LPF	CRYSTALS			
CONTROL							
901CF	0	0	0	0	1	0	
902CF	0	1	0	1	1	0	
906CF	0	0	0	0	1	0	
909CF	0	2	0	0	1	0	
910CF	0	1	0	0	1	0	
911CF	0	0	0	2	2	0	
LOW							
908LF	0	0	0	1	1	0	
921LF	0	1	0	0	1	0	
924LF	0	0	0	0	1	0	
925LF	0	0	0	0	1	0	
927LF	20	1	0	0	0	0	
011LF	0	1	0	0	1	0	
MEDIUM							
804MF	0	0	0	0	2	0	
805MF	2	1	0	1	1	0	
907MF	0	0	0	0	1	0	
819MF	0	1	0	1	1	0	
823MF	0	0	0	0	1	0	
828MF	0	1	0	1	2	0	
HIGH							
903HF	0	1	0	0	1	0	
812HF	0	1	0	0	1	0	
813HF	0	0	0	1	1	0	
814HF	0	0	0	1	1	0	
920HF	0	0	0	1	0	0	
829HF	0	0	0	0	1	0	

Appendix Table 4 (cont.)

SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988573

URINALYSIS

TREATMENT DAY 734
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	PH	SP GRAV	GLUCOSE	KETONES	PROTEIN	BILI	OC BLOOD
CONTROL							
A02CM	6.0	1.030	3	0	3	0	3
A06CM	6.0	1.020	0	0	3	0	3
A12CM	7.0	1.010	0	0	3	0	0
A15CM	7.0	1.008	0	0	3	0	0
A27CM	7.0	1.025	0	0	3	0	0
E02CM	6.0	1.035	0	0	3	0	0
LOW							
A05LM	6.0	1.026	0	0	3	0	0
A13LM	6.0	1.026	0	0	3	0	0
A20LM	6.0	1.032	0	0	3	0	0
A26LM	6.0	1.033	0	0	3	0	0
E15LM	7.5	1.023	0	0	3	0	0
E18LM	7.5	1.026	0	0	3	0	0
MEDIUM							
A06MM	6.0	1.035	0	0	3	0	0
A18MM	6.0	1.023	0	0	3	0	3
A22MM	6.0	1.021	0	0	3	0	0
A25MM	6.0	1.020	0	0	3	0	0
E10MM	7.0	1.020	0	0	2	0	3
E17MM	6.0	1.040	0	0	3	0	0
HIGH							
A01HM	6.0	1.048	0	0	1	0	0
A09HM	6.0	1.016	0	0	1	0	0
A29HM	6.0	1.034	0	0	1	0	0
E12HM	6.0	1.042	0	0	1	0	0
E14HM	6.0	1.035	0	0	1	0	0
E21HM	6.0	1.032	0	0	1	0	0

Appendix Table 4 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

TREATMENT GROUP AND ANIMAL NO	URINALYSIS						
	TREATMENT DAY 734						
	INDIVIDUAL VALUES FOR MALES						
	MICROSCOPIC FINDINGS						
	RBC AVE#/HPF	WBC AVE#/HPF	CASTS AVE#/LPF	CRYSTALS	BACTERIA	PHENYLKE PKU	
CONTROL							
A02CM	5	3	1	1	1	0	
A06CM	2	2	0	1	1	0	
A12CM	0	2	0	1	3	0	
A15CM	0	0	0	1	2	0	
A27CM	0	4	0	1	3	0	
E02CM	3	0	0	1	1	0	
LOW							
A05LM	1	2	0	1	2		
A13LM	0	0	0	1	2		
A26LM	0	5	0	1	2		
E15LM	0	2	1	4	4		
E18LM	0	2	0	4	4		
MEDIUM							
A08MM	0	1	0	1	1		
A18MM	5	20	0	1	4		
A22MM	2	5	1	1	2		
A25MM	0	7	0	2	4		
E10MM	5	5	0	1	3		
E17MM	0	3	0	2	3		
HIGH							
A01HM	0	1	0	1	4	0	
A09HM	0	1	0	1	1	0	
A29HM	2	3	0	1	1	0	
E12HM	0	1	0	1	1	0	
E14HM	0	4	0	1	2	0	
E21HM	0	1	0	1	1	0	

Appendix Table 4 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAI; PI#0988S73

TREATMENT GROUP AND ANIMAL NO	URINALYSIS					
	TREATMENT DAY 735					
	INDIVIDUAL VALUES FOR FEMALES					
	MICROSCOPIC FINDINGS					
	RBC AVE#/HPF	WBC AVE#/HPF	CASTS AVE#/LPF	CRYSTALS	BACTERIA	PHENYLKE PKU
CONTROL						
B01CF	1	10	0	1	2	0
B02CF	0	6	0	1	2	0
B06CF	2	8	0	1	4	0
B11CF	0	3	0	1	2	0
B16CF	4	10	1	1	3	0
B18CF	0	2	0	1	2	0
LOW						
B21LF	0	4	0	1	4	
B24LF	0	2	0	2	4	
B25LF	0	1	0	1	1	
B27LF	0	0	0	1	1	
D11LF	0	0	0	1	2	
D26LF	0	4	0	1	1	
MEDIUM						
B04MF	3	0	0	1	2	
B05MF	0	0	0	1	1	
B07MF	0	0	0	1	1	
B19MF	0	0	0	1	1	
B23MF	0	2	0	1	1	
B28MF	0	0	0	2	3	
HIGH						
B12HF	0	0	0	1	1	0
B13HF	0	0	0	1	1	0
B14HF	0	0	0	1	1	0
B20HF	0	0	0	1	1	0
B29HF	0	0	0	1	2	0
D03HF	1	3	0	3	4	0

Table 9
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

TREATMENT GROUP	AUTOPSY ORGAN WEIGHTS							
	TREATMENT DAY 805							
	ARITHMETIC MEANS WITH STANDARD ERRORS							
	BODY WTS G	HEART G	KIDNEYS G	LIVER G	ADRENALS MG	THYROID MG	PITU MG	
M A L E S								
CONTROL	560 21	1.96 0.05	4.96 0.36	17.2 0.8	103.0 8.8	51.7 8.6	23.2 2.1	
LOW	538 21	1.82 0.06	4.44 0.27	16.5 0.6	116.3 38.5	35.3 * 4.1	29.6 11.5	
MEDIUM	536 23	1.75 * 0.05	4.63 0.37	15.6 0.7	65.1 5.8	32.1 * 2.0	36.8 13.9	
HIGH	522 29	1.53 * 0.03	4.25 0.48	15.6 0.7	66.1 5.6	37.1 3.6	16.0 1.9	
F E M A L E S								
CONTROL	466 21	1.36 0.03	2.69 0.06	14.1 0.6	101.8 8.4	34.6 3.5	63.3 17.2	
LOW	400 * 17	1.31 0.06	2.58 0.09	12.2 * 0.4	109.3 19.3	35.2 3.2	77.2 19.7	
MEDIUM	412 * 16	1.27 0.04	2.69 0.11	12.9 0.5	153.4 48.1	38.7 7.1	56.7 21.5	
HIGH	343 * 10	1.12 * 0.03	2.61 0.06	11.9 * 0.4	131.4 38.2	25.6 2.0	91.3 41.1	

* MEAN DIFFERS SIGNIFICANTLY FROM CONTROL ($P < 0.05$)

* LESS THAN 100% OF GROUP SIZE WAS AVAILABLE, BUT SUFFICIENT NUMBERS WERE PRESENT
FOR VALID STATISTICAL ANALYSIS

Appendix Table 5
 SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT: PT#0908S73

AUTOPSY ORGAN WEIGHTS

TREATMENT DAY 805
 INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	BODY WTS G	HEART G	KIDNEYS G	LIVER G	ADRENALS MG	THYROIDS MG	PITU MG	VEN PROS MG	SEM VES MG	TESTES G
CONTROL										
A02CM	400	2.04	3.57	14.7	202.3	37.2	LOST	321	911	2.23
A12CM	511	1.87	3.75	14.4	142.9	25.5	12.9	273	322	2.65
A15CM	529	1.65	4.11	14.3	71.3	41.3	14.5	307	79	6.53
A27CM	587	1.94	4.85	15.7	115.2	62.3	10.0	384	635	2.48
C25CM	480	2.08	8.58	19.0	123.5	52.5	13.5	563	485	2.02
C26CM	608	1.88	5.03	16.5	175.6	33.1	28.1	667	256	4.08
C30CM	475	1.61	3.54	11.2	86.7	23.7	12.0	282	116	2.37
E13CM	630	1.70	4.20	16.4	90.7	50.7	17.0	573	274	3.69
E16CM	412	1.62	3.20	11.4	81.5	28.9	25.7	302	173	2.46
E25CM	654	2.14	7.11	21.8	83.7	48.6	17.1	714	378	3.89
E30CM	546	2.06	6.84	22.3	87.2	56.3	14.1	626	336	2.65
G01CM	559	1.80	4.20	16.7	60.0	21.5	28.0	570	450	3.33
G23CM	686	2.28	6.70	23.2	66.5	51.0	10.0	955	436	3.29
L01CM	628	1.92	6.71	22.9	73.7	60.0	46.8	696	451	2.98
L09CM	737	1.78	3.92	18.5	83.4	40.5	20.5	893	316	3.69
L20CM	472	2.34	3.84	16.5	103.2	32.8	23.2	219	151	2.34
L23CM	536	2.19	6.15	19.2	80.0	194.5	20.8	649	355	3.77
L25CM	668	2.11	3.53	15.4	88.4	48.0	25.7	634	360	3.53
L29CM	527	2.15	4.47	16.4	141.5	73.0	24.2	364	276	2.76
LOW										
A05LM	389	2.28	5.21	14.4	85.2	30.6	195.5	1210	242	2.42
A13LM	601	2.06	4.27	17.2	681.3	31.0	11.1	306	862	3.33
A26LM	616	2.05	5.11	20.0	95.0	45.2	32.6	78	179	2.30
C22LM	425	2.13	3.32	14.3	185.6	32.0	52.5	1065	300	1.83
C27LM	465	1.66	7.40	17.6	75.6	90.3	16.1	470	168	2.68
C28LM	494	1.73	5.00	16.0	77.2	31.1	12.1	607	206	2.36
E15LM	521	1.57	3.47	14.5	61.5	24.5	13.5	316	265	3.41
G09LM	653	1.56	3.77	18.6	57.5	42.4	22.0	385	346	3.23
G25LM	615	1.82	3.67	15.2	42.5	22.2	14.0	582	315	3.70
J08LM	566	1.80	4.76	19.6	80.3	22.2	23.2	705	345	3.14
J09LM	531	1.79	5.69	20.2	101.8	38.6	10.9	442	207	2.03
J16LM	672	1.66	3.84	19.5	62.1	27.9	3.2	421	270	LOST
J17LM	607	1.56	3.18	13.8	52.8	23.8	1.9	407	312	2.45
L03LM	525	1.89	4.06	15.5	54.2	36.3	17.4	2070	344	2.51
L17LM	465	1.57	3.70	13.1	75.2	29.7	17.5	456	234	3.08
L28LM	456	2.05	4.59	13.8	72.5	37.5	14.7	747	344	2.51

Appendix Table 5 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

AUTOPSY ORGAN WEIGHTS

TREATMENT DAY 805
INDIVIDUAL VALUES FOR MALES

TREATMENT GROUP AND ANIMAL NO	BODY WTS G	HEART G	KIDNEYS G	LIVER G	ADRENALS MG	THYROID MG	PITUITARY MG	VEN PROS MG	SEM VES MG	TESTES G
MEDIUM										
A08MM	523	1.62	3.93	15.2	70.7	35.0	19.1	611	1780	3.01
A22MM	480	1.81	7.39	20.6	89.1	48.2	20.9	570	734	2.74
A25MM	549	1.78	5.31	17.1	56.0	31.1	24.0	232	90	3.15
C01MM	364	2.09	9.40	19.3	151.1	38.4	13.8	429	274	0.90
C05MM	622	1.72	3.92	13.5	74.2	28.0	16.7	383	179	3.25
C07MM	538	1.70	6.02	16.6	61.1	15.0	5.5	851	286	2.56
C18MM	400	1.32	3.46	9.9	62.4	17.1	271.6	295	153	2.84
E10MM	380	1.84	3.19	13.1	52.1	40.2	10.8	517	225	2.43
E17MM	692	1.47	3.63	14.9	67.5	34.2	87.5	1393	317	3.04
E20MM	421	1.87	3.20	10.8	60.6	35.2	20.8	326	222	3.60
E24MM	614	1.73	3.68	13.9	56.0	27.9	13.8	879	253	3.21
G03MM	531	1.77	3.57	14.3	42.1	20.2	11.2	1083	358	3.27
G21MM	698	2.11	5.54	21.9	83.0	24.5	72.0	88	388	2.83
G22MM	640	1.69	4.35	16.2	65.0	42.8	30.0	937	360	3.47
J10MM	517	1.37	3.76	13.9	42.0	34.3	11.8	643	303	3.28
J14MM	573	2.01	3.40	12.6	50.6	30.9	14.2	508	297	3.44
L08MM	544	1.71	5.40	20.6	30.3	31.7	15.7	658	381	2.57
L16MM	477	1.87	4.70	15.6	71.9	43.3	18.1	661	401	3.42
L18MM	625	1.83	4.19	16.1	49.7	31.1	22.6	645	453	3.30
HIGH										
A01MM	453	1.44	4.14	18.7	44.1	14.1	0.8	507	201	2.88
A09MM	450	1.51	3.88	12.1	103.5	63.4	15.8	546	198	3.25
A29MM	536	1.36	3.30	13.6	91.5	44.5	22.6	431	645	3.89
C02MM	668	1.46	1.46	16.1	76.3	36.2	14.6	610	365	3.17
C24MM	485	1.74	3.86	15.4	80.0	50.6	20.0	1407	471	3.46
E14MM	706	1.66	11.74	21.4	117.0	70.9	25.9	937	313	3.14
E21MM	557	1.68	4.57	15.7	55.5	17.1	2.9	334	339	3.86
G17MM	370	1.34	3.76	13.0	40.1	23.0	14.0	744	348	2.85
G30MM	459	1.36	3.98	14.5	73.5	39.0	19.0	378	196	2.83
J06MM	696	1.75	4.88	19.2	66.5	34.0	26.5	1052	382	3.75
J07MM	467	1.52	3.82	14.7	52.3	38.8	12.0	320	214	2.77
J12MM	367	1.60	3.62	13.4	72.0	21.4	3.0	354	150	2.64
J22MM	579	1.49	4.46	18.0	41.6	24.4	13.3	433	305	3.51
J30MM	374	1.38	3.19	12.4	46.9	41.7	11.0	444	156	1.26
L04MM	672	1.57	4.37	20.1	90.4	24.8	25.3	572	330	3.85
L22MM	645	1.57	4.25	16.4	51.5	51.2	14.7	815	379	3.71
L24MM	577	1.56	4.15	15.8	54.7	40.0	20.0	626	460	3.30
L27MM	338	1.52	3.00	10.4	32.2	32.5	27.0	369	96	3.24

Appendix Table 5 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PI#0988S73

AUTOPSY ORGAN WEIGHTS

TREATMENT DAY 805

INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	BODY WTS G	HEART G	KIDNEYS G	LIVER G	ADRENALS MG	THYROID MG	PITUITARY MG	OVARIES MG	UTERUS MG
CONTROL									
B06CF	554	1.39	2.73	13.5	83.1	30.0	86.8	50.0	2146
B11CF	500	1.46	2.61	14.0	76.1	32.4	18.8	102.7	722
B16CF	462	1.41	2.90	14.4	151.1	31.9	89.2	72.1	1738
D06CF	383	1.29	2.30	11.2	99.5	24.0	20.0	108.5	828
D12CF	453	1.27	3.10	16.0	153.0	33.0	20.0	129.0	771
D18CF	486	1.51	2.57	13.4	79.3	31.5	19.0	43.5	1035
D19CF	455	1.36	2.60	13.7	30.5	35.0	26.0	115.0	662
F13CF	463	1.43	2.52	12.8	146.5	49.9	26.1	76.1	650
F15CF	513	1.31	2.77	16.5	116.6	35.8	50.9	102.0	455
F16CF	451	1.15	2.56	12.6	65.9	34.8	85.4	74.5	NOT AV
F17CF	312	1.15	2.56	10.3	171.5	37.5	18.0	36.7	535
F26CF	314	1.20	2.26	11.5	106.0	46.8	26.6	55.0	1480
F30CF	479	1.57	3.15	15.4	104.0	50.0	63.4	268.0	1120
H10CF	491	1.16	2.37	13.7	58.0	25.9	25.6	104.0	765
H11CF	626	1.42	2.67	25.0	152.5	26.5	64.7	45.5	570
H19CF	376	1.06	2.30	10.5	50.3	15.5	415.4	111.9	961
H21CF	550	1.40	2.87	17.8	208.2	107.2	44.1	145.2	788
H30CF	412	1.18	1.90	9.4	71.1	36.4	26.2	54.7	714
K13CF	831	1.51	3.09	18.4	116.1	26.3	26.3	51.7	705
K25CF	479	1.54	2.93	14.8	70.0	20.0	221.2	107.6	1188
K29CF	432	1.32	2.49	13.0	78.4	31.0	28.8	62.5	1487
M04CF	458	1.53	3.02	14.7	71.7	21.5	20.5	38.9	1198
M10CF	411	1.50	3.03	12.7	100.0	23.2	90.3	1158.1	NOT AV
M15CF	352	1.50	2.95	16.2	92.7	27.0	118.8	90.8	1052
M22CF	402	1.26	2.94	11.1	93.1	37.5	100.7	136.2	1024

Appendix Table 5 (cont.)
SC-19192: 115 WEEK ORAL TUMORIGENICITY STUDY - RAT; PT#0988S73

AUTOPSY ORGAN WEIGHTS									
TREATMENT DAY 805									
INDIVIDUAL VALUES FOR FEMALES									
TREATMENT GROUP AND ANIMAL NO	BODY WTS G	HEART G	KIDNEYS G	LIVER G	ADRENALS MG	THYROID MG	PITU MG	OVARIES MG	UTERUS MG
LOW									
825LF	472	1.31	2.83	12.0	346.6	25.9	57.1	98.1	1159
827LF	406	1.26	2.50	10.0	46.4	28.1	7.7	394.6	731
011LF	361	1.30	2.18	9.5	75.5	34.5	25.5	104.5	130
026LF	392	1.52	2.61	12.6	71.0	33.2	50.0	243.9	748
030LF	299	1.46	2.61	11.7	111.0	36.5	48.8	40.0	336
F04LF	421	1.30	2.60	14.3	98.1	25.8	39.8	131.1	544
F08LF	338	1.31	2.30	9.8	65.9	33.9	31.1	36.2	835
F12LF	502	0.91	2.14	12.6	61.9	56.1	85.9	37.2	477
F20LF	332	0.97	2.40	11.8	91.3	25.2	30.1	57.3	547
K08LF	294	1.15	2.87	11.4	77.5	22.5	57.6	25.2	506
K27LF	433	1.49	2.41	14.9	184.7	66.9	247.6	29.0	NOT AV
M09LF	480	1.29	3.48	13.9	120.0	27.8	72.1	NOT AV	1017
M17LF	461	1.65	3.04	14.6	142.9	45.5	241.5	62.6	1918
M20LF	407	1.53	2.48	12.2	85.5	40.0	110.9	96.3	805
M23LF	401	1.10	2.20	11.6	61.4	25.5	51.9	47.9	751
MEDIUM									
304MF	454	1.16	2.19	11.7	108.3	24.1	45.0	32.9	687
805MF	413	1.20	2.60	12.9	76.1	23.2	10.0	123.9	1002
807MF	489	1.09	2.90	16.6	114.8	34.8	25.1	150.0	1083
823MF	485	1.23	2.76	14.4	54.8	43.2	57.1	40.0	1598
828MF	384	1.21	2.54	12.6	229.8	25.4	35.1	123.5	510
009MF	257	1.23	2.04	7.5	55.1	23.0	14.5	50.0	33
024MF	401	1.75	2.58	12.8	67.7	19.4	27.0	31.0	924
F02MF	365	1.34	3.26	14.0	199.2	29.1	38.1	146.5	1830
F10MF	362	1.12	2.63	12.4	90.6	40.1	22.9	64.0	1540
H28MF	447	1.47	2.82	14.6	78.3	31.5	20.2	35.2	761
K09MF	353	1.14	2.64	12.6	79.2	141.5	114.1	51.4	NOT AV
K14MF	501	1.25	2.73	13.2	83.4	36.1	20.0	138.9	779
K30MF	471	1.37	3.85	12.5	844.2	44.0	57.2	2550.4	793
M19MF	452	1.22	2.39	12.6	50.0	44.6	24.6	64.6	812
M28MF	416	1.07	2.36	15.0	199.2	27.8	365.3	64.4	419
M29MF	345	1.42	2.78	11.1	124.5	31.5	30.5	52.8	1410

Appendix Table 5 (cont.)

SC-191924 115 WEEK ORAL TUMORIGENICITY STUDY - RAY; PT#0988573

AUTOPSY ORGAN WEIGHTS

TREATMENT DAY 805

INDIVIDUAL VALUES FOR FEMALES

TREATMENT GROUP AND ANIMAL NO	BODY WTS G	HEART G	KIDNEYS G	LIVER G	ADRENALS MG	THYROIDS MG	PITU MG	OVARIES MG	UTERUS MG
HIGH									
B12HF	382	1.20	2.95	15.9	90.0	26.1	57.0	71.9	537
B13HF	293	1.04	2.41	11.3	50.0	23.4	5.8	71.2	718
B14HF	386	1.07	2.33	11.1	77.2	25.0	113.0	64.4	813
B20HF	395	1.01	2.53	10.9	63.8	42.3	19.5	78.2	1115
D03HF	304	1.55	2.69	10.0	50.0	22.5	23.5	3.0	655
D28HF	387	1.13	2.70	13.7	65.3	26.5	15.2	89.0	1301
F11HF	318	0.85	2.34	10.4	40.9	33.9	16.5	31.2	1480
F23HF	329	1.13	2.81	12.3	94.2	30.3	32.6	94.2	828
H05HF	375	1.02	2.62	12.1	82.6	23.1	7.4	38.7	1023
H07HF	284	0.95	2.40	10.4	60.8	18.8	15.8	112.0	903
H09HF	255	1.06	2.25	7.6	113.3	12.5	7.3	15.4	625
H15HF	319	0.99	2.17	10.3	56.0	44.9	17.9	1320.4	930
H18HF	307	1.08	2.67	10.0	87.1	30.0	139.5	87.5	639
H23HF	325	1.07	3.14	14.0	289.0	25.2	132.8	20.9	924
K05HF	321	1.23	2.25	11.3	35.5	13.1	10.8	50.1	374
K11HF	326	1.02	2.66	12.3	799.1	11.5	284.0	344.6	437
K24HF	340	1.18	3.28	11.4	113.0	25.4	25.3	53.1	1200
M02HF	358	1.27	2.72	13.6	77.3	17.0	102.5	30.5	864
M05HF	391	1.16	2.72	15.3	67.3	23.4	12.4	599.9	1741
M14HF	348	1.07	2.57	13.2	390.0	24.1	858.4	62.1	605
M30HF	451	1.42	2.66	13.1	57.0	38.3	20.0	67.0	813