

SC-19192: TWO WEEK ORAL TOXICITY STUDY IN THE RAT

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INTRODUCTION:

The commercial grade finished product of SC-18862, a nutritive artificial sweetening agent, may contain from 0-1% of a degradation product, SC-19192. This degradation 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, preclinical testing of SC-19192 for its potential toxicity was performed. In this study, SC-19192 was administered daily as an aqueous suspension intragastrically to young adult albino rats of both sexes for two consecutive weeks. It was the objective of the study to investigate the initial tolerance and evaluate the toxic potential of a single dose of SC-19192 to rats for further toxicity studies of longer duration.

METHODS:

Material evaluated.

SC-19192 is a fine white powder with chemical name (2S, 5S-5-benzyl-3, 6-dioxo-2-piperazineacetic acid). Lot No. TJT-12-32 was employed throughout this study.

Animals, housing and diet.

Twenty young adult (11 week old) albino rats, 10 of each sex, of the Charles River CD strain were employed. They were housed individually in suspended wire mesh cages, and acclimated to the laboratory environment for 1 week, and placed on treatment at the age of 12 weeks. Basal diet consisted of Rockland Rat-Mouse Complete Diet in raw meal form (Teklad, Inc., Winfield, Iowa). Fresh basal powdered diet was continuously available in individual feeder jars. Group mean food consumption determination was performed twice weekly. Food spillage by individual animals was recorded at these intervals and food consumption data from the rat that spilled was not used for food consumption calculations. Food and water was available ad libitum. Animal rooms were air-conditioned and temperature was maintained at 70°F. continuously. Artificial fluorescent lighting was provided uninterrupted for a 14 hour interval daily.

Compound administration.

Animals were separated according to sex and assigned individual cages by a standard randomization procedure. Ten rats, five of each sex, were assigned randomly to control and treated groups. SC-19192 was administered to the treated group intragastrically as a 5% aqueous suspension once each day for two weeks. The daily dosage employed was 1 g/kg. body weight. Controls received an equal volume of vehicle only.

Statistical procedures.

The means and standard errors of various measured parameters were calculated for each group. The significance of differences between control and compound-treated group means was tested using student's t-test with $p < 0.05$.

Physical examination 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 body weight measurement. Naked eye examinations of eyes were performed terminally prior to autopsy.

Clinical laboratory procedures.

Hematologic and clinical chemistry examinations, and urinalysis were performed terminally on all rats after two weeks of treatment. Blood specimens were collected terminally from the abdominal aorta of the overnight fasted ether anesthetized rats after two weeks of treatment. Urine specimens were collected terminally from rats housed individually in metabolism cages for 7-8 hours.

Hematology. The following parameters were measured.

<u>Parameter</u>	<u>Method</u>
Packed cell volume	Micro method ¹
Hemoglobin	Cyanmethemoglobin ²
Total RBC Count	Coulter Counter ³
Total WBC Count	Coulter Counter ³
Differential WBC Count	Smear ⁴

Clinical chemistry. Determinations of the following parameters were made on serum separated following blood clotting.

<u>Parameter</u>	<u>Method</u>
Blood (serum) urea nitrogen	Urograph method ⁵
Glutamic pyruvic transaminase	Reitman and Frankel ⁶

<u>Parameter</u>	<u>Method</u>
Alkaline phosphatase	Klein et al. ⁷
Bilirubin	Malloy & Evelyn ^{8,9}
Glucose	Nelson & Somogyi ¹⁰
Sodium	Autoanalyzer ¹¹
Potassium	Autoanalyzer ¹¹

Urinalysis. The following parameters were measured.

<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)

Postmortem examination procedures.

All animals from the two groups were fasted overnight, anesthetized with ether, and exsanguinated via the abdominal aorta. The rats were immediately autopsied, and entire organs or representative tissue blocks of control and treated groups from stomach, small and large intestine, lung, heart, liver, kidney, spleen, pancreas, pituitary, thyroid-parathyroid, adrenal, testis, ovary, ventral and dorsal prostate, seminal vesicle, mammary gland, urinary bladder, salivary gland (submandibular) were removed following gross examination. Underlined organs were weighed fresh.

The following tissues only from the treated group were removed: lymph node (mesenteric), nerve (brachial plexus), brain, bone marrow smear (femoral), eye (right), and thymus.

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 SC-19192 treated groups were embedded in paraffin, sectioned, and stained. Coronal sections of brain at the level of the optic chiasm (cerebrum) and the trapezoid body (cerebellum) were examined microscopically after luxol fast blue-PAS-hematoxylin staining. Sections of all other tissues were stained with hematoxylin-eosin and examined microscopically.

Smears of femoral marrow were air-dried, stained with Giemsa solution, and stored for subsequent examination when indicated.

Stained glass mounted tissues from all 20 rats were shipped to Microscopy for Biological Research, Ltd., for microscopic examination.

Tissues examined microscopically at each dosage level are listed in Table 5.

RESULTS

ANTEMORTEM OBSERVATION.

Growth, food consumption and survival.

Group mean body weight and food consumption are presented in Table 1 and Figs. 1 and 2. No significant variations in body weight or food consumption were observed between the control and treated group males. However, the body weight gain in the treated females was significantly lower at one week of treatment compared to control females (Table 1). Mean relative food

consumption (gm/kg/day) of treated females (fig. 2) was reduced proportionally to the depressed body weight gain.

Survival was 100% both in control and treated groups. No deaths occurred among the 20 animals studied.

Physical and behavioral signs.

No adverse physical or behavioral effects were apparent in treated animals. General posture and locomotion, behavior and level of motor activity, pelage, body orifices and excretions were unremarkable throughout the study.

Clinical laboratory findings.

Hematology. Arithmetic means \pm S. E. of hematology parameters evaluated are presented in Table 2. Values for individual rats are tabulated in the Appendix. Individual hematologic values for control or treated rats were not remarkable; means of all hematologic parameters evaluated for treated groups were in close agreement with control values.

Clinical chemistry. Mean serum biochemistry values are presented in Table 3; individual values are tabulated in the Appendix. All the clinical chemistry parameters evaluated were comparable between control and treated groups, except serum potassium which was significantly decreased in treated group males and females. However, the low serum potassium observed in treated animals following two weeks of treatment is within the normal range for rats of Charles River CD strain.

Urinalysis. The results of urinalysis (pH, specific gravity, blood, protein, glucose, ketones, microscopic) showed no evidence of any

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Body Weight, Weight Gain and Food consumption
(Mean Values for Groups of 5 Rats)

Treatment Group	Days of Treatment		
	0	7	14
Body Weight, Grams			
<u>Males</u>			
Control	310.8	334.8	364.4
High Dose	302.0	334.8	357.2
<u>Females</u>			
Control	219.6	234.4	246.4
High Dose	231.2	234.4	246.4
Weight Gain, Grams per Day			
<u>Males</u>			
Control	3.4	4.2	
High Dose	4.7	3.2	
<u>Females</u>			
Control	2.1	1.7	
High Dose	0.46*	1.7	
Food Intake, Grams per Rat per Day			
<u>Males</u>			
Control		23.3	22.8
High Dose		23.9	21.6
<u>Females</u>			
Control		18.3	16.6
High Dose		16.6	15.5
Food Intake, Grams per Kg per Day			
<u>Males</u>			
Control		69.6	62.6
High Dose		71.3	60.5
<u>Females</u>			
Control		78.2	67.5
High Dose		70.9	63.0

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

Figure 1

SC-19192: 2 WEEK ORAL TOXICITY STUDY IN THE RAT

Mean Body Weight

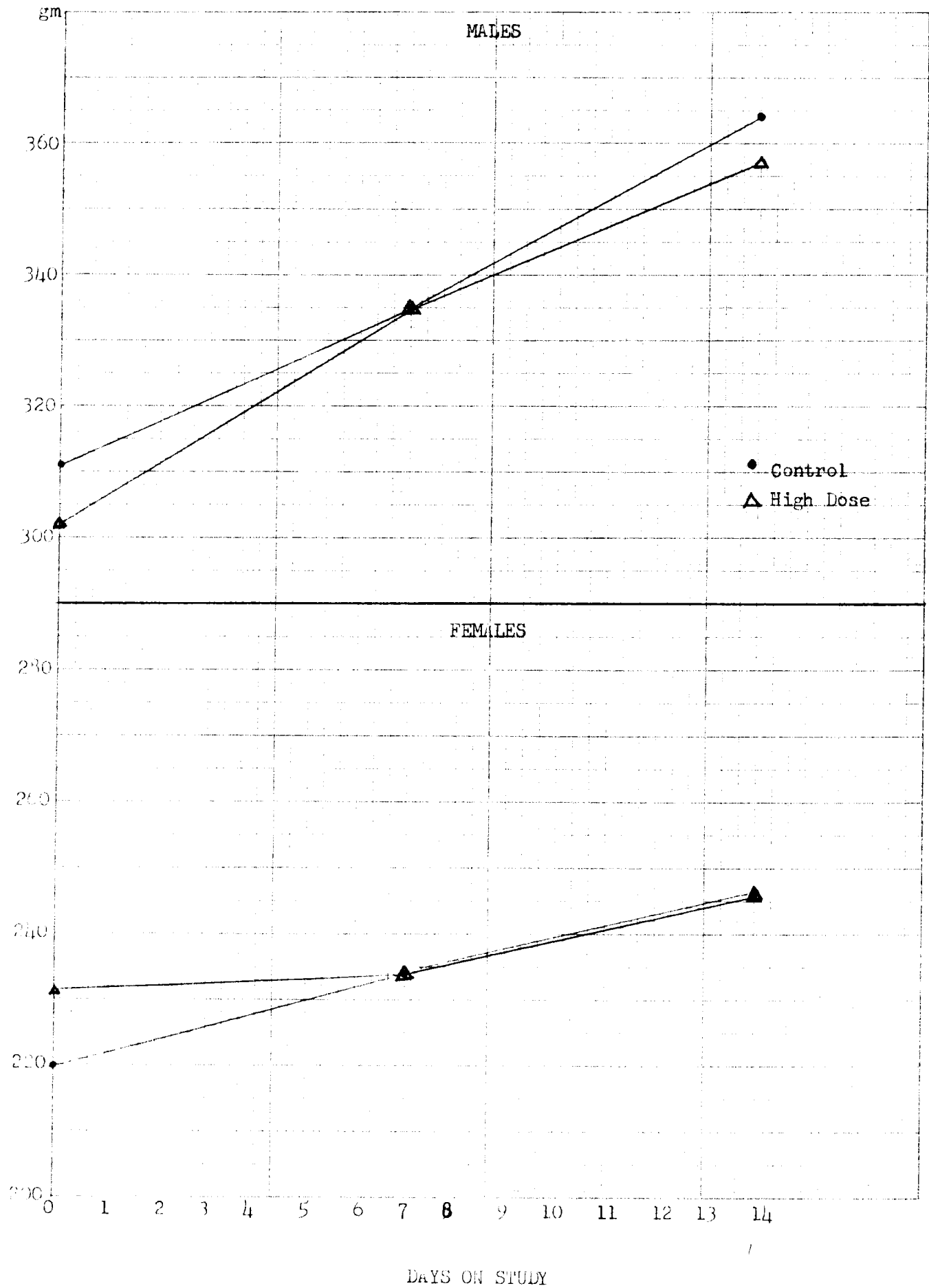


Figure 2

SC-19192: 2 WEEK ORAL TOXICITY STUDY IN THE RAT

Mean Food Consumption; gm/kg/day

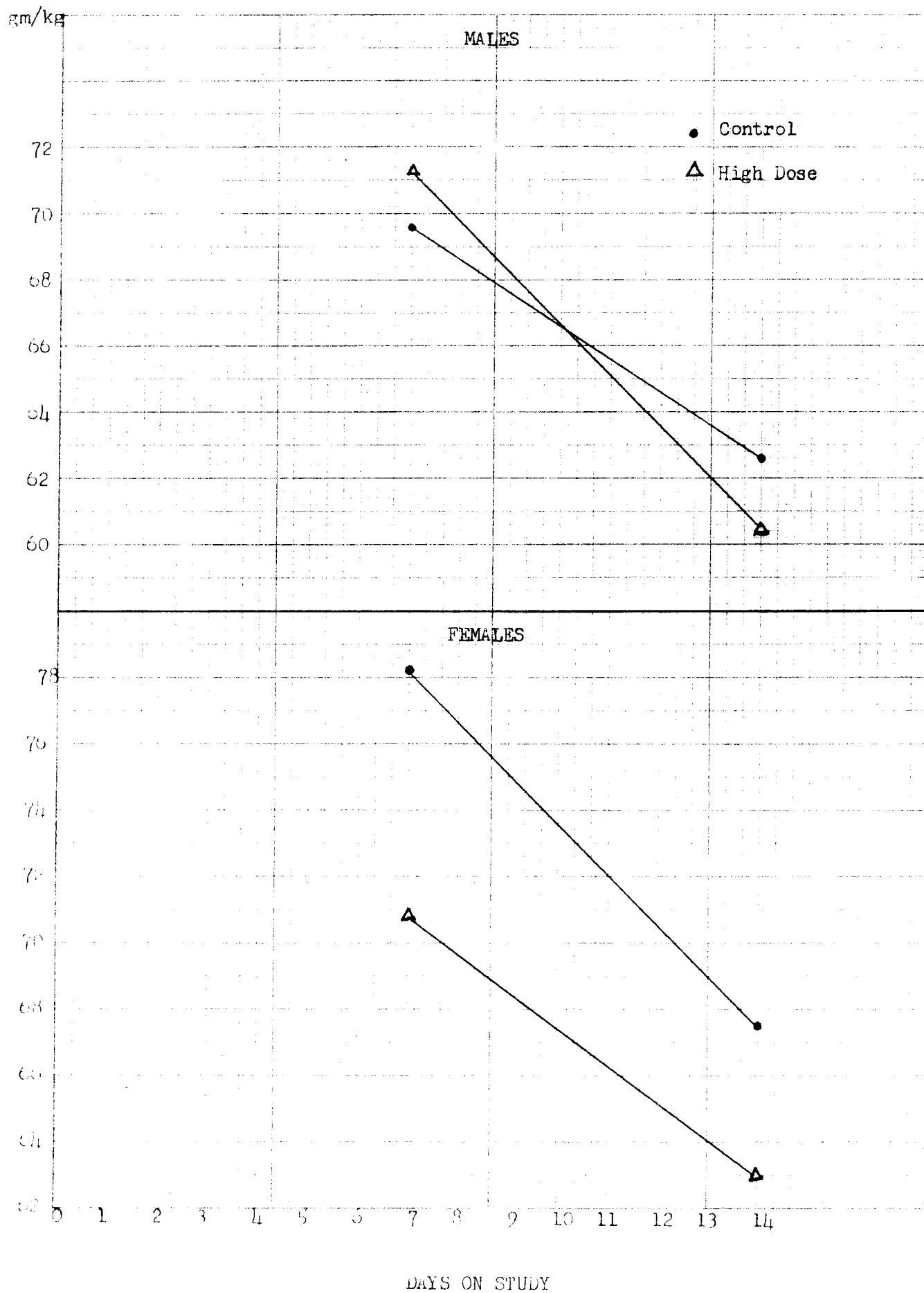


Table 2

SC-19192: TWO WEEK ORAL TOXICITY STUDY IN THE RAT

Hematology: Red Cell Data
(Mean Values for Groups of 5 Rats)

Treatment Group	2 Weeks of Treatment		
	Hgb (g%)	Hct (%)	RBC $\times 10^6$ /cmm
Males			
Control	15.82 \pm 0.19	46.8 \pm 0.58	7.53 \pm 0.04
High Dose	15.64 \pm 0.25	48.2 \pm 0.74	7.93 \pm 0.18
Females			
Control	15.18 \pm 0.34	45.6 \pm 0.75	7.15 \pm 0.20
High Dose	15.76 \pm 0.13	45.8 \pm 0.66	7.34 \pm 0.07

White Cell Data

Treatment Group	2 Weeks of Treatment				
	WBC $\times 10^6$ /cmm	Differential			
		PMN (%)	LYM(%)	Mon (%)	Eos (%)
Males					
Control	16.86 \pm 0.99	17.0	81.6	0	1.2
High Dose	16.68 \pm 1.43	25.4	72.6	0.6	1.4
Females					
Control	12.94 \pm 1.06	18.4	80.4	0.4	0.8
High Dose	14.76 \pm 1.35	23.4	75.4	0.4	0.4

treatment related effect. Results of urinalysis performed on individual rats are presented in the Appendix.

POSTMORTEM OBSERVATIONS

Organ and body weights.

Mean organ and terminal body weight values are given in Table 4; individual values are given in the Appendix. No unequivocal compound related effect on terminal body and organ weight was evident. Although significant increase in prostate gland weight and a decrease in heart weight was apparent in treated males, such changes were within the limit of variability for historical controls of comparable strain and age and is not regarded as treatment related.

Gross and microscopic findings.

The organs examined microscopically are presented in Table 5. The histopathologic report from Dr. Mauro, MBR, on complete gross and microscopic findings for each animal is presented in its entirety in the appendix. Summary of pathologic conditions is presented in Tables 6-8. The conclusions thereof are reproduced below.

Treatment related alterations of the various organs examined were not apparent; no alterations of the prostate gland and heart were apparent in the treated group showing a statistically significant change in absolute and relative organ weight.

Various incidental disease processes, like slight inflammatory lesions of the lung and liver were evident; neither the intensity nor the incidence of these lesions were affected by the administration of SC-19192.

Table 3

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Post-Treatment Blood Serum Biochemistry

(Mean Values for Groups of 5 Rats)

Treatment Group	BUN mg%	R-F Units	Alk. P'ase Bodansky Units	Bilirubin mg%	Sugar ^a mg%	Na ⁺ meq/L	K ⁺ meq/L
Males							
Control	11.58 ± 1.58	32.86 ± 4.85	4.064 ± 0.37	0.172 ± 0.04	167 ± 12.59	138.2 ± 0.97	7.26 ± 0.20
High Dose	9.3 ± 0.51	22.22 ± 1.76	3.176 ± 0.17	0.128 ± 0.05	153.4 ± 3.44	138.8 ± 0.20	6.08 ± 0.14*
Females							
Control	9.24 ± 0.61	26.88 ± 3.05	2.236 ± 0.18	0.128 ± 0.05	165.4 ± 3.79	139.0 ± 0.32	5.78 ± 0.16
High Dose	8.64 ± 0.70	23.22 ± 3.17	2.298 ± 0.31	0.124 ± 0.05	173.8 ± 8.0	139.4 ± 1.21	5.12 ± 0.16*

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

Table 4

SC-19192: TWO WEEK ORAL TOXICITY STUDY IN THE RAT

Final Body and Fresh Organ Weights at Autopsy

(Mean Values for Groups of 5 Rats)

Group	Final Body Weight (g)	Heart (g)	Liver (g)	Kidneys (g)	Adrenals (mg)	Thyroids (mg)	Pituitary (mg)	Testis (g)	Sem. Ves. (mg)	Prostate (mg)	Ovaries (mg)	Uterus (mg)
Males												
Control	364.4 ± 13.14	1.226 ± 0.06	13.134 ± 0.67	2.504 ± 0.09	51.0 ± 1.51	18.68 ± 2.89	12.06 ± 1.14	2.994 ± 0.11	216.9 ± 19.27	447.2 ± 26.21		
High Dose	357.2 ± 14.09	1.048* ± 0.05	13.202 ± 1.24	2.586 ± 0.19	56.44 ± 5.65	19.58 ± 1.17	15.34 ± 2.03	3.232 ± 0.12	219.0 ± 20.28	525.2* ± 22.35		
Females												
Control	246.4 ± 5.85	0.861 ± 0.03	8.39 ± 0.28	1.746 ± 0.05	66.88 ± 5.31	17.48 ± 1.46	14.54 ± 1.30				85.18 ± 6.67	488.0 ± 45.45
High Dose	246.4 ± 6.79	0.869 ± 0.05	8.134 ± 0.16	1.738 ± 0.06	72.86 ± 4.89	19.46 ± 2.70	13.18 ± 0.74				91.74 ± 2.69	487.66 ± 73.21

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

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	<u>Tissues Examined Microscopically</u>		
	TOTAL	CONTROL	HIGH
NO. ANIMALS EXAMINED	20	10	10
LUNG	20	10	10
BRONCHUS	20	10	10
HEART	20	10	10
ARTERY	7	0	7
KIDNEY	20	10	10
BILE DUCT	19	10	9
LIVER	19	10	9
SPLEEN	20	10	10
BRAIN	10	0	10
MENINGES	10	0	10
STOMACH	20	10	10
COLON	19	10	9
INTESTINE	19	10	9
PANCREAS	20	10	10
ISLET	20	10	10
ADRENAL CORTEX	20	10	10
ADRENAL MEDULLA	19	10	9
PITUITARY	20	10	10
THYROID	20	10	10
PARATHYROID	7	4	3
LYMPH NODE	9	0	9
SALIVARY GLAND	20	10	10
THYMUS	10	0	10
TESTIS	10	5	5
SEMINAL VESICLE	10	5	5
PROSTATE	10	5	5
BLADDER	20	10	10
OVARY	10	5	5
UTERUS	10	5	5
OVIDUCT	2	2	0
BONE	20	10	10
BONE MARROW	20	10	10
MUSCLE	20	10	10
SKIN AND SUBCUTIS	20	10	10
MAMMARY GLAND	20	10	10
EYE	20	10	10
VAGINA	5	4	5
EPIDIDYMIS	1	1	0
NERVE	10	0	10
TOTALS	600	276	324

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Summary of Pathological Conditions by Group (Males)

	TOTAL	CONTROL	HIGH
LUNG			
CHRONIC MURINE BRONCHITIS	8/ 10	4/ 5	4/ 5
HEART			
CHRONIC INFLAMMATION	1/ 10	0/ 5	1/ 5
KIDNEY			
CALCIFICATION	0/ 10	0/ 5	0/ 5
KIDNEY			
CHRONIC INFLAMMATION	1/ 10	0/ 5	1/ 5
BILE DUCT			
CHRONIC INFLAMMATION	0/ 10	0/ 5	0/ 5
LIVER			
CHRONIC INFLAMMATION	8/ 10	4/ 5	4/ 5
ADRENAL CORTEX			
VACUOLIZATION	1/ 10	1/ 5	0/ 5
PROSTATE			
CHRONIC INFLAMMATION	1/ 10	1/ 5	0/ 5

SC-19192: TWO WEEK ORAL TOXICITY STUDY IN THE RAT

Summary of Pathological Conditions by Group (Female)

	TOTAL	CONTROL	HIGH
LUNG			
CHRONIC MURINE BRONCHITIS	8/ 10	4/ 5	4/ 5
HEART			
CHRONIC INFLAMMATION	0/ 10	0/ 5	0/ 5
KIDNEY			
CALCIFICATION	1/ 10	1/ 5	0/ 5
KIDNEY			
CHRONIC INFLAMMATION	1/ 10	0/ 5	1/ 5
BILE DUCT			
CHRONIC INFLAMMATION	1/ 9	0/ 5	1/ 4
LIVER			
CHRONIC INFLAMMATION	6/ 9	4/ 5	2/ 4
ADRENAL CORTEX			
VACUOLIZATION	0/ 10	0/ 5	0/ 5
VAGINA			
ACUTE INFLAMMATION	1/ 9	0/ 4	1/ 5

SC-19192: TWO WEEK ORAL TOXICITY STUDY IN THE RAT

Summary of Pathological Conditions by Group (Totals)

	TOTAL	CONTROL	HIGH
LUNG			
CHRONIC MURINE BRONCHITIS	16/ 20	8/ 10	8/ 10
HEART			
CHRONIC INFLAMMATION	1/ 20	0/ 10	1/ 10
KIDNEY			
CALCIFICATION	1/ 20	1/ 10	0/ 10
KIDNEY			
CHRONIC INFLAMMATION	2/ 20	0/ 10	2/ 10
BILE DUCT			
CHRONIC INFLAMMATION	1/ 19	0/ 10	1/ 9
LIVER			
CHRONIC INFLAMMATION	14/ 19	8/ 10	6/ 9
ADRENAL CORTEX			
VACUOLIZATION	1/ 20	1/ 10	0/ 10
PROSTATE			
CHRONIC INFLAMMATION	1/ 10	1/ 5	0/ 5
VAGINA			
ACUTE INFLAMMATION	1/ 9	0/ 4	1/ 5

SUMMARY AND CONCLUSIONS.

A two week oral toxicity study was conducted employing intra-gastric (IG) administration of SC-19192 to 11 week old Charles River CD strain male and female albino rats. SC-19192 was administered daily (IG) in water suspension at a dosage level of 1 g/kg. body weight. Physical examinations were performed periodically and hematology, clinical chemistry and urinalysis exams were done on specimens collected terminally (exsanguination) after two weeks of treatment. All animals were promptly necropsied and representative tissues from control and SC-19192 treated animals processed for microscopic examination.

Survival in both control and treated groups was 100%. Food consumption and body weight gain were comparable between the control and treated males. A moderate decrease in relative food consumption with a proportionate decrease in body weight gain (gm/rat/day) occurred in the SC-19192 treated females. Physical examination findings were unremarkable throughout the study.

Findings for hematology, clinical chemistry and urinalysis were generally unremarkable. Treated rats of both sexes had a significantly lower serum potassium level. However, these relatively lower values observed in the treated group are within the normal range of variability for rats of Charles River CD strain.

Mean organ weights in general were comparable between the control and experimental animals. A significant increase in prostate gland weight and a decrease in heart weight in treated males was apparent. Such changes were within the limit of variability for historical controls of comparable

strain and age and are not regarded as treatment related. However, on microscopic examination, no alterations in the prostate gland and heart were apparent in the treated males.

Postmortem gross and histopathological findings were unremarkable. Although evidence of incidental disease was observed in several organs, no indication of compound related alterations were present.

It is concluded from the above data that daily intragastric administration of 1 g/kg SC-19192 to young adult rats for 2 weeks caused no biologically meaningful alterations in clinical laboratory or postmortem findings.

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APPENDIX TABLES OF VALUES OF INDIVIDUAL RATS

Appendix Table 1

SC-19192: TWO WEEK ORAL TOXICITY STUDY IN THE RAT

Post-Treatment Hematology Data

(Individual Values)

Treatment Group	Hgb (g%)	Hct (%)	RBC x10 ⁶ /cmm	WBC x10 ³ /cmm	Differential				
					PMN %	Lym %	Mon %	Eos %	Bas %
Males									
Control									
1CM	15.8	48	7.60	18.3	9	90	0	1	0
2CM	15.8	45	7.60	13.4	22	76	0	2	0
3CM	15.9	48	7.53	19.2	24	75	0	1	0
4CM	15.2	46	7.40	16.9	18	81	0	1	0
5CM	16.4	47	7.52	16.5	12	86	0	1	0
High Dose									
6HM	14.7	46	7.53	12.4	15	84	1	0	0
7HM	15.8	47	8.49	16.0	19	79	1	1	0
8HM	16.2	50	8.21	18.6	19	78	1	2	0
9HM	15.6	49	7.68	20.8	24	74	0	2	0
10HM	15.9	49	7.75	15.6	50	48	0	2	0
Females									
Control									
11CF	15.8	47	7.44	11.2	25	74	0	1	0
12CF	14.3	45	6.80	13.6	16	82	1	1	0
13CF	15.8	47	7.38	16.7	22	77	0	1	0
14CF	15.6	46	7.59	10.8	18	81	1	0	0
15CF	14.4	43	6.55	12.4	11	88	0	1	0
High Dose									
16HF	16.2	46	7.30	11.9	14	86	0	0	0
17HF	15.8	44	7.30	11.1	26	73	1	0	0
18HF	15.5	45	7.55	16.8	18	82	0	0	0
19HF	15.8	48	7.40	16.5	29	69	0	0	0
20HF	15.5	46	7.15	17.5	30	67	1	2	0

Appendix Table 2

SC-19192: TWO WEEK ORAL TOXICITY STUDY IN THE RAT

Post-Treatment Blood Plasma Biochemistry

(Individual Values)

Treatment Group	BUN mg%	GPT R-F Units	Alk. P'ase Bod.U.	Bili- rubin mg%	Glucose mg%	Na ⁺ meq/L	K ⁺ meq/L
<u>Males</u>							
<u>Control</u>							
1CM	7.5	42.9	3.69	0.22	166	136	7.9
2CM	12.4	46.4	5.34	<0.20	158	139	7.4
3CM	14.4	25.0	4.27	0.22	173	136	7.3
4CM	15.3	25.0	3.15	0.22	208	139	6.9
5CM	8.3	25.0	3.87	0.42	130	141	6.8
<u>High Dose</u>							
6HM	8.8	25.0	3.78	0.24	146	139	6.3
7HM	11.1	16.7	2.86	<0.20	145	139	6.3
8HM	8.6	25.0	2.85	<0.20	157	139	5.9
9HM	9.7	25.0	3.16	<0.20	156	138	6.3
10HM	8.3	19.4	3.23	<0.20	163	139	5.6
<u>Females</u>							
<u>Control</u>							
11CF	11.1	25.0	2.05	<0.20	158	140	6.1
12CF	9.7	19.4	1.93	0.24	166	139	5.9
13CF	9.0	32.1	2.50	<0.20	156	138	6.0
14CF	9.1	35.7	2.76	0.40	176	139	5.7
15CF	7.3	22.2	1.94	0.30	171	139	5.2
<u>High Dose</u>							
16HF	7.3	19.4	3.48	0.22	163	141	5.6
17HF	9.7	35.7	1.63	<0.20	162	137	5.1
18HF	9.6	22.2	2.29	<0.20	167	136	4.7
19HF	6.6	19.4	2.07	<0.20	172	141	5.3
20HF	10.0	19.4	2.02	0.20	205	142	4.9

Appendix Table 3

SC-19192: TWO WEEK ORAL TOXICITY STUDY IN THE RAT

Post-Treatment Urinalysis

(Individual Values)

Treatment Group	pH	Sp.Gr.	Protein	Sugar	Acetone	Bilirubin	Occ Blood
<u>Males</u>							
<u>Control</u>							
1CM	9	1.056	2	0	0	0	1
2CM	8	1.038	1	0	0	0	0
3CM	9	1.044	1	0	0	0	0
4CM	8	1.064	2	0	0	0	0
5CM	8	1.054	1	0	0	0	0
<u>High Dose</u>							
6HM	8	1.035	1	0	0	0	0
7HM	8	1.033	1	0	0	0	0
8HM	8	1.036	1	0	0	0	0-1
9HM	9	1.033	3	0	0	0	0-1
10HM	8	1.038	1	0	0	0	0
<u>Females</u>							
<u>Control</u>							
11CF	9	1.038	1	0	0	0	0
12CF	8	1.033	1	0	0	0	0
13CF	8	1.048	1	0	0	0	0
14CF	8	1.042	1	0	0	0	0
15CF	8	1.022	0	0	0	0	0
<u>High Dose</u>							
16HF	8	1.029	1	0	0	0	0
17HF	7	1.052	1	0	0	0	0
18HF	9	1.048	2	0	0	0	0
19HF	8	1.020	0	0	0	0	0
20HF	7	1.008	0	0	0	0	0

Appendix Table 3 (cont.)

SC-19192: TWO WEEK ORAL TOXICITY STUDY IN THE RAT

Post-Treatment Urinalysis

(Individual Values)

Treatment Group	RBC/ HPF	WBC/ HPF	Bacteria 0+4	Crystals 0+4
<u>Males</u>				
<u>Control</u>				
1CM	8-10	0	3	3-4
2CM	0	0	4	3-4
3CM	0	0	2-3	3-4
4CM	0-1	0	1-2	3-4
5CM	0	0	1	4
<u>High Dose</u>				
6HM	0	0-1	4	2-3
7HM	0	0	4	4
8HM	0-1	0	2	4
9HM	0-1	0-1	4	2
10HM	0	0-1	2-3	2-3
<u>Females</u>				
<u>Control</u>				
11CF	0-1	0	4	3-4
12CF	0	0-1	4	2-3
13CF	0-1	0	1	4
14CF	0	0	4	3-4
15CF	0	0	4	1-2
<u>High Dose</u>				
16HF	0-1	0	4	3-4
17HF	0	0-2	4	4
18HF	0	0	3	4
19HF	0	0-1	4	1-2
20HF	0	0	4	1

Appendix Table 5

SC-19192: TWO WEEK ORAL TOXICITY STUDY IN THE RAT

Individual Body and Organ Weights

Treatment Group	Body Weight gm	Heart gm	Liver gm	Kidneys gm	Adrenals gm	Thyroids gm	Pituitary gm	R. Sem. Vesicle			Ven. Prostate			Ovaries gm	Uterus gm
								Testes gm	mgm	mgm	mgm	mgm	mgm		
Males															
Control															
1CM	330.	1.040	11.12	2.261	51.0	16.4	10.0	3.152	265.4	357.2					
2CM	384.	1.131	12.89	2.630	51.4	18.0	11.2	2.758	248.7	480.0					
3CM	404.	1.400	14.80	2.671	46.6	12.4	16.5	3.351	225.2	455.2					
4CM	354.	1.280	12.49	2.310	50.0	29.6	11.2	2.861	166.2	512.4					
5CM	350.	1.277	14.37	2.647	56.0	17.0	11.4	2.850	179.2	431.4					
High Dose															
6HM	392.	1.114	15.78	3.085	62.8	20.0	15.5	3.243	253.7	602.0					
7HM	350.	1.084	13.04	2.514	46.2	21.5	21.7	3.411	271.6	462.7					
8HM	350.	0.965	11.38	2.330	58.8	21.0	17.3	3.418	163.5	518.0					
9HM	382.	1.183	16.13	2.917	72.8	20.4	10.0	3.316	221.5	528.7					
10HM	312.	0.893	9.68	2.082	41.6	15.0	12.2	2.772	184.8	514.8					
Females															
Control															
11CF	240.	0.802	7.82	1.714	77.6	17.2	11.5				81.1	447.4			
12CF	248.	0.800	7.68	1.621	50.4	17.5	12.6				81.5	510.0			
13CF	254.	0.900	9.09	1.765	78.2	19.6	19.0				105.8	340.3			
14CF	262.	0.854	8.86	1.694	68.2	20.8	15.4				92.0	529.1			
15CF	228.	0.948	8.51	1.934	60.0	12.3	14.2				65.5	613.2			
High Dose															
16HF	232.	0.807	8.13	1.932	88.5	17.6	15.6				98.3	526.4			
17HF	258.	0.755	8.73	1.813	69.3	17.4	11.5				87.2	409.2			
18HF	228.	0.931	7.93	1.596	58.5	17.7	13.8				88.7	404.1			
19HF	260.	1.026	8.06	1.644	76.5	14.6	13.2				86.3	755.4			
20HF	254.	0.827	7.82	1.707	71.5	30.0	11.8				98.2	343.2			

REPORT IN TOTO OF MICROSCOPIC EXAMINATION OF TISSUES

from

Dr. J. Mauro

Microscopy for Biological Research, Ltd.

MICROSCOPY for BIOLOGICAL RESEARCH, Ltd.

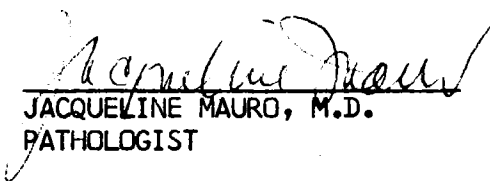
COMPUTER PARK EAST, ALBANY, NEW YORK 12205

PROJECT P-T 884S70

SC-19192

PREPARED FOR: G. D. SEARLE & COMPANY

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JACQUELINE MAURO, M.D.
PATHOLOGIST

DATE SUBMITTED: DECEMBER 15, 1971



MICROSCOPY FOR BIOLOGICAL RESEARCH, LTD.

G. D. SEARLE & COMPANY

PROJECT P-T 884S70

SC-19192

INTRODUCTION

ON DECEMBER 2, 1971, PREPARED SLIDES FROM 20 RATS WERE RECEIVED FOR HISTOPATHOLOGICAL EVALUATION.

THE RATS WERE NUMBERED AND DISTRIBUTED AMONG GROUPS AS FOLLOWS:

<u>GROUP</u>	<u>PATHOLOGY NUMBER</u>	<u>ANIMAL NUMBER</u>
CONTROL	87407 - 87411, 87412 - 87416.	1CM - 5CM, 11CF - 15CF.
HIGH	87417 - 87421, 87422 - 87426.	6HM - 10HM, 16HF - 20HF.

THE TISSUES SUBMITTED FOR EVALUATION INCLUDED: LUNG, BRONCHUS, HEART, ARTERY, KIDNEY, BILE DUCT, LIVER, SPLEEN, BRAIN, MENINGES, STOMACH, COLON, INTESTINE, PANCREAS, ISLET, ADRENAL CORTEX, ADRENAL MEDULLA, PITUITARY, THYROID, PARATHYROID, LYMPH NODE, SALIVARY GLAND, THYMUS, TESTIS, SEMINAL VESICLE, PROSTATE, BLADDER, OVARY, UTERUS, OVIDUCT, BONE, BONE MARROW, MUSCLE, SKIN AND SUBCUTIS, MAMMARY GLAND, EYE, VAGINA, EPIDIDYMIS, NERVE. ALL TISSUES WERE STAINED WITH HEMATOXYLIN AND EOSIN WITH THE EXCEPTION OF BONE, BONE MARROW, CEREBRUM, CEREBELLUM, MENINGES, NERVE, AND OCCASIONALLY ARTERY. THESE NEURAL TISSUES WERE STAINED WITH LUXOL FAST BLUE-PERIODIC ACID SCHIFF-HEMATOXYLIN.

MAY-GRUNWALD GIEMSA STAINED BONE AND BONE MARROW SECTIONS WERE RECEIVED.

ALL TISSUE SECTIONS WERE THEN SUBJECTED TO MICROSCOPIC REVIEW.

MICROSCOPY FOR BIOLOGICAL RESEARCH, LTD.

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PROJECT P-T 884S70

SC-19192

SUMMARY

RANDOM SPORADIC CONDITIONS WERE PRESENT, THE MOST COMMON BEING SLIGHT INFLAMMATORY LESIONS OF THE LUNG AND LIVER. THESE DO NOT APPEAR TO BE DRUG RELATED OCCURRING WITH EQUAL FREQUENCY IN BOTH CONTROL AND HIGH DOSE GROUPS.

ALL THE LESIONS SEEN ARE THOSE KNOWN TO OCCUR COMMONLY IN THE RAT.

MICROSCOPY FOR BIOLOGICAL RESEARCH, LTD.

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PROJECT P-T 884S70

SC-19192

OIL RED O

INTRODUCTION

OIL RED O STAINED SECTIONS OF HEART, KIDNEY, LIVER, AND
ADRENAL WERE RECEIVED AND EVALUATED ON THE FOLLOWING ANIMALS:

<u>GROUP</u>	<u>PATHOLOGY NUMBER</u>	<u>ANIMAL NUMBER</u>
CONTROL	87407 - 87411, 87412 - 87416.	1CM - 5CM, 11CF - 15CF.
HIGH	87417 - 87421, 87422 - 87426.	6HM - 10HM, 16HF - 20HF.

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PROJECT P-T 884S70

SC-19192

OIL RED O

TABLES OF FINDINGS

CONTROL

<u>PATH./AN. NO.</u>	<u>HEART</u>	<u>KIDNEY</u>	<u>LIVER</u>	<u>ADRENAL</u>
87407 - 1CM	N	N	N	N
87408 - 2CM	N	N	N	N
87409 - 3CM	N	N	N	N
87410 - 4CM	N	N	N	TRACE
87411 - 5CM	N	N	N	N
87412 - 11CF	N	N	N	TRACE
87413 - 12CF	N	N	N	TRACE
87414 - 13CF	N	N	N	TRACE
87415 - 14CF	N	N	N	TRACE
87416 - 15CF	N	N	N	TRACE

HIGH

<u>PATH./AN. NO.</u>	<u>HEART</u>	<u>KIDNEY</u>	<u>LIVER</u>	<u>ADRENAL</u>
87417 - 6HM	N	N	N	TRACE
87418 - 7HM	N	N	N	TRACE
87419 - 8HM	N	N	N	N
87420 - 9HM	N	N	N	N
87421 - 10HM	N	N	N	TRACE
87422 - 16HF	N	N	N	TRACE
87423 - 17HF	N	N	N	TRACE
87424 - 18HF	N	N	N	TRACE
87425 - 19HF	N	N	N	TRACE
87426 - 20HF	N	N	N	TRACE

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SC-19192

OIL RED O

SUMMARY

THE CONTROL SLIDE WAS ONLY A TRACE POSITIVE. SIX
CONTROL ADRENAL GLANDS AND EIGHT DOSE ADRENAL GLANDS WERE
A TRACE POSITIVE.

BECAUSE OF THE PALE STAINING OF THE CONTROL SECTION,
THE RELEVANCE OF THESE FINDINGS IS QUESTIONABLE.

MICROSCOPY FOR BIOLOGICAL RESEARCH, LTD.

SUMMARY OF PATHOLOGICAL CONDITIONS BY GROUP

TABLE BB 2
NON-NEOPLASTIC MALE

	TOTAL	CONTROL	HIGH
LUNG			
CHRONIC MURINE BRONCHITIS	8/ 10	4/ 5	4/ 5
HEART			
CHRONIC INFLAMMATION	1/ 10	0/ 5	1/ 5
KIDNEY			
CALCIFICATION	0/ 10	0/ 5	0/ 5
KIDNEY			
CHRONIC INFLAMMATION	1/ 10	0/ 5	1/ 5
BILE DUCT			
CHRONIC INFLAMMATION	0/ 10	0/ 5	0/ 5
LIVER			
CHRONIC INFLAMMATION	8/ 10	4/ 5	4/ 5
ADRENAL CORTEX			
VACUOLIZATION	1/ 10	1/ 5	0/ 5
PROSTATE			
CHRONIC INFLAMMATION	1/ 10	1/ 5	0/ 5

MICROSCOPY FOR BIOLOGICAL RESEARCH, LTD.

SUMMARY OF PATHOLOGICAL CONDITIONS BY GROUP

TABLE BB 3
NON-NEOPLASTIC FEMALE

	TOTAL	CONTROL	HIGH
LUNG			
CHRONIC MURINE BRONCHITIS	8/ 10	4/ 5	4/ 5
HEART			
CHRONIC INFLAMMATION	0/ 10	0/ 5	0/ 5
KIDNEY			
CALCIFICATION	1/ 10	1/ 5	0/ 5
KIDNEY			
CHRONIC INFLAMMATION	1/ 10	0/ 5	1/ 5
BILE DUCT			
CHRONIC INFLAMMATION	1/ 9	0/ 5	1/ 4
LIVER			
CHRONIC INFLAMMATION	6/ 9	4/ 5	2/ 4
ADRENAL CORTEX			
VACUOLIZATION	0/ 10	0/ 5	0/ 5
VAGINA			
ACUTE INFLAMMATION	1/ 9	0/ 4	1/ 5

MICROSCOPY FOR BIOLOGICAL RESEARCH, LTD.

SUMMARY OF PATHOLOGICAL CONDITIONS BY GROUP

TABLE BB 1
NON-NEOPLASTIC TOTALS

	TOTAL	CONTROL	HIGH
LUNG			
CHRONIC MURINE BRONCHITIS	16/ 20	8/ 10	8/ 10
HEART			
CHRONIC INFLAMMATION	1/ 20	0/ 10	1/ 10
KIDNEY			
CALCIFICATION	1/ 20	1/ 10	0/ 10
KIDNEY			
CHRONIC INFLAMMATION	2/ 20	0/ 10	2/ 10
BILE DUCT			
CHRONIC INFLAMMATION	1/ 19	0/ 10	1/ 9
LIVER			
CHRONIC INFLAMMATION	14/ 19	8/ 10	6/ 9
ADRENAL CORTEX			
VACUOLIZATION	1/ 20	1/ 10	0/ 10
PROSTATE			
CHRONIC INFLAMMATION	1/ 10	1/ 5	0/ 5
VAGINA			
ACUTE INFLAMMATION	1/ 9	0/ 4	1/ 5

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NON-NEOPLASTIC PATHOLOGICAL SUMMARY

TABLE A 1

MALE GROUP CONTROL

8	8	8	8	8
7	7	7	7	7
4	4	4	4	4
0	0	0	1	1
7	8	9	0	1

LUNG

CHRONIC MURINE BRONCHITIS

1	1	1	0	1
---	---	---	---	---

HEART

CHRONIC INFLAMMATION

0	0	0	0	0
---	---	---	---	---

KIDNEY

CALCIFICATION

0	0	0	0	0
---	---	---	---	---

KIDNEY

CHRONIC INFLAMMATION

0	0	0	0	0
---	---	---	---	---

BILE DUCT

CHRONIC INFLAMMATION

0	0	0	0	0
---	---	---	---	---

LIVER

CHRONIC INFLAMMATION

1	1	0	1	1
---	---	---	---	---

ADRENAL CORTEX

VACUOLIZATION

0	1	0	0	0
---	---	---	---	---

PROSTATE

CHRONIC INFLAMMATION

0	0	1	0	0
---	---	---	---	---

MICROSCOPY FOR BIOLOGICAL RESEARCH, LTD.

NON-NEOPLASTIC PATHOLOGICAL SUMMARY

TABLE B 1

FEMALE GROUP CONTROL

8	8	8	8	8
7	7	7	7	7
4	4	4	4	4
1	1	1	1	1
2	3	4	5	6

LUNG

CHRONIC MURINE BRONCHITIS

1	0	1	1	1
---	---	---	---	---

HEART

CHRONIC INFLAMMATION

0	0	0	0	0
---	---	---	---	---

KIDNEY

CALCIFICATION

0	0	0	0	1
---	---	---	---	---

KIDNEY

CHRONIC INFLAMMATION

0	0	0	0	0
---	---	---	---	---

BILE DUCT

CHRONIC INFLAMMATION

0	0	0	0	0
---	---	---	---	---

LIVER

CHRONIC INFLAMMATION

0	1	1	1	1
---	---	---	---	---

ADRENAL CORTEX

VACUOLIZATION

0	0	0	0	0
---	---	---	---	---

VAGINA

ACUTE INFLAMMATION

0	0	0	0	NE
---	---	---	---	----

MICROSCOPY FOR BIOLOGICAL RESEARCH, LTD.

NON-NEOPLASTIC PATHOLOGICAL SUMMARY

TABLE C 1

MALE GROUP HIGH

3	8	8	8	8
7	7	7	7	7
4	4	4	4	4
1	1	1	2	2
7	8	9	0	1

LUNG

CHRONIC MURINE BRONCHITIS

1	1	1	0	1
---	---	---	---	---

HEART

CHRONIC INFLAMMATION

0	0	0	1	0
---	---	---	---	---

KIDNEY

CALCIFICATION

0	0	0	0	0
---	---	---	---	---

KIDNEY

CHRONIC INFLAMMATION

0	0	0	1	0
---	---	---	---	---

BILE DUCT

CHRONIC INFLAMMATION

0	0	0	0	0
---	---	---	---	---

LIVER

CHRONIC INFLAMMATION

1	1	1	0	1
---	---	---	---	---

ADRENAL CORTEX

VACUOLIZATION

0	0	0	0	0
---	---	---	---	---

PROSTATE

CHRONIC INFLAMMATION

0	0	0	0	0
---	---	---	---	---

MICROSCOPY FOR BIOLOGICAL RESEARCH, LTD.

NON-NEOPLASTIC PATHOLOGICAL SUMMARY

TABLE D 1

FEMALE GROUP HIGH

8	8	8	8	8
7	7	7	7	7
4	4	4	4	4
2	2	2	2	2
2	3	4	5	6

LUNG

CHRONIC MURINE BRONCHITIS

0	1	1	1	1
---	---	---	---	---

HEART

CHRONIC INFLAMMATION

0	0	0	0	0
---	---	---	---	---

KIDNEY

CALCIFICATION

0	0	0	0	0
---	---	---	---	---

KIDNEY

CHRONIC INFLAMMATION

0	1	0	0	0
---	---	---	---	---

BILE DUCT

CHRONIC INFLAMMATION

0	1	0	0	NE
---	---	---	---	----

LIVER

CHRONIC INFLAMMATION

1	0	1	0	NE
---	---	---	---	----

ADRENAL CORTEX

VACUOLIZATION

0	0	0	0	0
---	---	---	---	---

VAGINA

ACUTE INFLAMMATION

1	0	0	0	0
---	---	---	---	---

MICROSCOPY FOR BIOLOGICAL RESEARCH, LTD.

SUMMARY OF ORGANS EXAMINED

	TOTAL	CONTROL	HIGH
NO. ANIMALS EXAMINED	20	10	10
LUNG	20	10	10
BRONCHUS	20	10	10
HEART	20	10	10
ARTERY	7	0	7
KIDNEY	20	10	10
BILE DUCT	19	10	9
LIVER	19	10	9
SPLEEN	20	10	10
BRAIN	10	0	10
MENTINGES	10	0	10
STOMACH	20	10	10
COLON	19	10	9
INTESTINE	19	10	9
PANCREAS	20	10	10
ISLET	20	10	10
ADRENAL CORTEX	20	10	10
ADRENAL MEDULLA	19	10	9
PITUITARY	20	10	10
THYROID	20	10	10
PARATHYROID	7	4	3
LYMPH NODE	9	0	9
SALIVARY GLAND	20	10	10
THYMUS	10	0	10
TESTIS	10	5	5
SEMINAL VESICLE	10	5	5
PROSTATE	10	5	5
BLADDER	20	10	10
OVARY	10	5	5
UTERUS	10	5	5
OVIDUCT	2	2	0
BONE	20	10	10
BONE MARROW	20	10	10
MUSCLE	20	10	10
SKIN AND SUBCUTIS	20	10	10
MAMMARY GLAND	20	10	10
EYE	20	10	10
VAGINA	9	4	5
EPIIDYIMIS	1	1	0
NERVE	10	0	10
TOTALS	600	276	324

12-10-71

G. D. SEARLE & CO.

PROJECT P-T NO. 384S70

GROUP CONTROL

THE SPECIES TESTED WAS RAT

12-10-71

PATHOLOGY NUMBER 87407

ANIMAL NUMBER 1CM

MALE

GROUP

CONTROL

P-T NO. 884570

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
KIDNEY
BILE DUCT
LIVER
SPLEEN
STOMACH
COLON
INTESTINE
PANCREAS
ISLET
ADRENAL CORTEX
ADRENAL MEDULLA
PITUITARY
THYROID
SALIVARY GLAND
TESTIS
SEMINAL VESICLE
PROSTATE
BLADDER
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

LUNG

CHRONIC MURINE BRONCHITIS - THERE IS MASSIVE PERIBRONCHIAL LYMPHOCYTIC INFILTRATE AND PATCHY FOCI OF INTERSTITIAL INFLAMMATION AND FIBROSIS.

LIVER

CHRONIC INFLAMMATION - THE INTERSTITIAL TISSUES SHOW INFILTRATION BY MONONUCLEAR CELLS AND INCREASE IN FIBROUS STROMA.

12-10-71

PATHOLOGY NUMBER 87408

ANIMAL NUMBER 2CM

MALE

GROUP CONTROL

P-T NO. 884570

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
KIDNEY
BILE DUCT
LIVER
SPLEEN
STOMACH
COLON
INTESTINE
PANCREAS
ISLET
ADRENAL CORTEX
ADRENAL MEDULLA
PITUITARY
THYROID
SALIVARY GLAND
TESTIS
SEMINAL VESICLE
PROSTATE
BLADDER
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE
EPIDIDYMIS

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

LUNG

CHRONIC MURINE BRONCHITIS - THERE IS MASSIVE PERIBRONCHIAL LYMPHOCYTIC INFILTRATE AND PATCHY FOCI OF INTERSTITIAL INFLAMMATION AND FIBROSIS.

LIVER

CHRONIC INFLAMMATION - THE INTERSTITIAL TISSUES SHOW INFILTRATION BY MONONUCLEAR CELLS AND INCREASE IN FIBROUS STROMA.

ADRENAL CORTEX

VACUOLIZATION - PARENCHYMAL CELLS CONTAIN NUMEROUS SMALL VACUOLES.

12-10-71

PATHOLOGY NUMBER 87409

ANIMAL NUMBER 3CM

MALE

GROUP

CONTROL

P-T NO. 884S70

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
KIDNEY
BILE DUCT
LIVER
SPLEEN
STOMACH
COLON
INTESTINE
PANCREAS
ISLET
ADRENAL CORTEX
ADRENAL MEDULLA
PITUITARY
THYROID
PARATHYROID
SALIVARY GLAND
TESTIS
SEMINAL VESICLE
PROSTATE
BLADDER
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

LUNG

CHRONIC MURINE BRONCHITIS - THERE IS MASSIVE PERIBRONCHIAL LYMPHOCYTIC INFILTRATE AND PATCHY FOCI OF INTERSTITIAL INFLAMMATION AND FIBROSIS.

PROSTATE

CHRONIC INFLAMMATION - THE INTERSTITIAL TISSUES SHOW INFILTRATION BY MONONUCLEAR CELLS AND INCREASE IN FIBROUS STROMA.

12-10-71

PATHOLOGY NUMBER 87410

ANIMAL NUMBER 40M

MALE

GROUP

CONTROL

P-T NO. 884S70

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
KIDNEY
BILE DUCT
LIVER
SPLEEN
STOMACH
COLON
INTESTINE
PANCREAS
ISLET
ADRENAL CORTEX
ADRENAL MEDULLA
PITUITARY
THYROID
SALIVARY GLAND
TESTIS
SEMINAL VESICLE
PROSTATE
BLADDER
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

LIVER

CHRONIC INFLAMMATION - THE INTERSTITIAL TISSUES
SHOW INFILTRATION BY MONONUCLEAR CELLS AND INCREASE IN
FIBROUS STROMA.

12-10-71

PATHOLOGY NUMBER 87411

ANIMAL NUMBER 504

MALE

GROUP

CONTROL

P-T NO. 884S70

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
KIDNEY
BILE DUCT
LIVER
SPLEEN
STOMACH
COLON
INTESTINE
PANCREAS
ISLET
ADRENAL CORTEX
ADRENAL MEDULLA
PITUITARY
THYROID
PARATHYROID
SALIVARY GLAND
TESTIS
SEMINAL VESICLE
PROSTATE
BLADDER
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

LUNG

CHRONIC MURINE BRONCHITIS - THERE IS MASSIVE PERIBRONCHIAL LYMPHOCYTIC INFILTRATE AND PATCHY FOCI OF INTERSTITIAL INFLAMMATION AND FIBROSIS.

LIVER

CHRONIC INFLAMMATION - THE INTERSTITIAL TISSUES SHOW INFILTRATION BY MONONUCLEAR CELLS AND INCREASE IN FIBROUS STROMA.

12-10-71

PATHOLOGY NUMBER 87412

ANIMAL NUMBER 11CF

FEMALE GROUP CONTROL

P-T NO. 884S70

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
KIDNEY
BILE DUCT
LIVER
SPLEEN
STOMACH
COLON
INTESTINE
PANCREAS
ISLET
ADRENAL CORTEX
ADRENAL MEDULLA
PITUITARY
THYROID
PARATHYROID
SALIVARY GLAND
BLADDER
OVARY
UTERUS
OVIDUCT
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE
VAGINA

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

LUNG

CHRONIC MURINE BRONCHITIS - THERE IS MASSIVE
PERIBRONCHIAL LYMPHOCYTIC INFILTRATE AND PATCHY FOCI OF
INTERSTITIAL INFLAMMATION AND FIBROSIS.

12-10-71

PATHOLOGY NUMBER 87413

ANIMAL NUMBER 12CF

FEMALE

GROUP CONTROL

P-T NO. 884570

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
KIDNEY
BILE DUCT
LIVER
SPLEEN
STOMACH
COLON
INTESTINE
PANCREAS
ISLET
ADRENAL CORTEX
ADRENAL MEDULLA
PITUITARY
THYROID
PARATHYROID
SALIVARY GLAND
BLADDER
OVARY
UTERUS
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE
VAGINA

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

LIVER

CHRONIC INFLAMMATION - THE INTERSTITIAL TISSUES
SHOW INFILTRATION BY MONONUCLEAR CELLS AND INCREASE IN
FIBROUS STROMA.

12-10-71

PATHOLOGY NUMBER 87414

ANIMAL NUMBER 13CF

FEMALE

GROUP

CONTROL

P-T NO. 884S70

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
KIDNEY
BILE DUCT
LIVER
SPLEEN
STOMACH
COLON
INTESTINE
PANCREAS
ISLET
ADRENAL CORTEX
ADRENAL MEDULLA
PITUITARY
THYROID
SALIVARY GLAND
BLADDER
OVARY
UTERUS
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE
VAGINA

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

LUNG

CHRONIC MURINE BRONCHITIS - THERE IS MASSIVE PERIBRONCHIAL LYMPHOCYTIC INFILTRATE AND PATCHY FOCI OF INTERSTITIAL INFLAMMATION AND FIBROSIS.

LIVER

CHRONIC INFLAMMATION - THE INTERSTITIAL TISSUES SHOW INFILTRATION BY MONONUCLEAR CELLS AND INCREASE IN FIBROUS STROMA.

12-10-71

PATHOLOGY NUMBER 87415

ANIMAL NUMBER 14CF

FEMALE

GROUP

CONTROL

P-T NO. 884570

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
KIDNEY
BILE DUCT
LIVER
SPLEEN
STOMACH
COLON
INTESTINE
PANCREAS
ISLET
ADRENAL CORTEX
ADRENAL MEDULLA
PITUITARY
THYROID
SALIVARY GLAND
BLADDER
OVARY
UTERUS
OVIDUCT
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE
VAGINA

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

LUNG

CHRONIC MURINE BRONCHITIS - THERE IS MASSIVE PERIBRONCHIAL LYMPHOCYTIC INFILTRATE AND PATCHY FOCI OF INTERSTITIAL INFLAMMATION AND FIBROSIS.

LIVER

CHRONIC INFLAMMATION - THE INTERSTITIAL TISSUES SHOW INFILTRATION BY MONONUCLEAR CELLS AND INCREASE IN FIBROUS STROMA.

12-10-71

PATHOLOGY NUMBER 87416

ANIMAL NUMBER 15CF

FEMALE

GROUP CONTROL

P-T NO. 884S70

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
KIDNEY
BILE DUCT
LIVER
SPLEEN
STOMACH
COLON
INTESTINE
PANCREAS
ISLET
ADRENAL CORTEX
ADRENAL MEDULLA
PITUITARY
THYROID
SALIVARY GLAND
BLADDER
OVARY
UTERUS
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

LUNG

CHRONIC MURINE BRONCHITIS - THERE IS MASSIVE PERIBRONCHIAL LYMPHOCYTIC INFILTRATE AND PATCHY FOCI OF INTERSTITIAL INFLAMMATION AND FIBROSIS.

KIDNEY

CALCIFICATION - FOCAL CALCIFICATION IS PRESENT IN THE TUBULAR EPITHELIUM.

LIVER

CHRONIC INFLAMMATION - THE INTERSTITIAL TISSUES SHOW INFILTRATION BY MONONUCLEAR CELLS AND INCREASE IN FIBROUS STROMA.

12-10-71

G. D. SEAPLE & CO.

PROJECT P-T NO. 894S70

GROUP HIGH

THE SPECIES TESTED WAS RAT

12-10-71

PATHOLOGY NUMBER 87417

ANIMAL NUMBER 6HM

MALE

GROUP HIGH

P-T NO. 884570

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
ARTERY
KIDNEY
BILE DUCT
LIVER
SPLEEN
BRAIN
MENINGES
STOMACH
COLON
INTESTINE
PANCREAS
ISLET
ADRENAL CORTEX
ADRENAL MEDULLA
PITUITARY
THYROID
LYMPH NODE
SALIVARY GLAND
THYMUS
TESTIS
SEMINAL VESICLE
PROSTATE
BLADDER
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE
NERVE

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

LUNG

CHRONIC MURINE BRONCHITIS - THERE IS MASSIVE PERIBRONCHIAL LYMPHOCYTIC INFILTRATE AND PATCHY FOCI OF INTERSTITIAL INFLAMMATION AND FIBROSIS.

LIVER

CHRONIC INFLAMMATION - THE INTERSTITIAL TISSUES SHOW INFILTRATION BY MONONUCLEAR CELLS AND INCREASE IN FIBROUS STROMA.

12-10-71

PATHOLOGY NUMBER 87418

ANIMAL NUMBER 7HM

MALE

GROUP HIGH

P-T NO. 384S70

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
ARTERY
KIDNEY
BILE DUCT
LIVER
SPLEEN
BRAIN
MENINGES
STOMACH
COLON
INTESTINE
PANCREAS
ISLET
ADRENAL CORTEX
ADRENAL MEDULLA
PITUITARY
THYROID
PARATHYROID
LYMPH NODE
SALIVARY GLAND
THYMUS
TESTIS
SEMINAL VESICLE
PROSTATE
BLADDER
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE
NERVE

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

LUNG

CHRONIC MURINE BRONCHITIS - THERE IS MASSIVE PERIBRONCHIAL LYMPHOCYTIC INFILTRATE AND PATCHY FOCI OF INTERSTITIAL INFLAMMATION AND FIBROSIS.

LIVER

CHRONIC INFLAMMATION - THE INTERSTITIAL TISSUES SHOW INFILTRATION BY MONONUCLEAR CELLS AND INCREASE IN FIBROUS STROMA.

12-10-71

PATHOLOGY NUMBER 87420

ANIMAL NUMBER 944

MALE

GROUP HIGH

P-T NO. 884S70

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
ARTERY
KIDNEY
BILE DUCT
LIVER
SPLEEN
BRAIN
MENINGES
STOMACH
COLON
INTESTINE
PANCREAS
ISLET
ADRENAL CORTEX
ADRENAL MEDULLA
PITUITARY
THYROID
LYMPH NODE
SALIVARY GLAND
THYMUS
TESTIS
SEMINAL VESICLE
PROSTATE
BLADDER
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE
NERVE

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

HEART

CHRONIC INFLAMMATION - THE INTERSTITIAL TISSUES
SHOW INFILTRATION BY MONONUCLEAR CELLS AND INCREASE IN
FIBROUS STROMA.

KIDNEY

CHRONIC INFLAMMATION - THE INTERSTITIAL TISSUES
SHOW INFILTRATION BY MONONUCLEAR CELLS AND INCREASE IN
FIBROUS STROMA.

12-10-71

PATHOLOGY NUMBER 87421

ANIMAL NUMBER 10HM

MALE

GROUP HIGH

P-T NO. 884S70

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
ARTERY
KIDNEY
BILE DUCT
LIVER
SPLEEN
BRAIN
MENINGES
STOMACH
PANCREAS
ISLET
ADRENAL CORTEX
PITUITARY
THYROID
PARATHYROID
SALIVARY GLAND
THYMUS
TESTIS
SEMINAL VESICLE
PROSTATE
BLADDER
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE
NERVE

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

LUNG

CHRONIC MURINE BRONCHITIS - THERE IS MASSIVE PERIBRONCHIAL LYMPHOCYTIC INFILTRATE AND PATCHY FOCI OF INTERSTITIAL INFLAMMATION AND FIBROSIS.

LIVER

CHRONIC INFLAMMATION - THE INTERSTITIAL TISSUES SHOW INFILTRATION BY MONONUCLEAR CELLS AND INCREASE IN FIBROUS STROMA.

12-10-71

PATHOLOGY NUMBER 87422

ANIMAL NUMBER 16HF

FEMALE

GROUP HIGH

P-T NO. 884570

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
KIDNEY
BILE DUCT
LIVER
SPLEEN
BRAIN
MENINGES
STOMACH
COLON
INTESTINE
PANCREAS
ISLET
ADRENAL CORTEX
ADRENAL MEDULLA
PITUITARY
THYROID
LYMPH NODE
SALIVARY GLAND
THYMUS
BLADDER
OVARY
UTERUS
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE
VAGINA
NERVE

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

LIVER

CHRONIC INFLAMMATION - THE INTERSTITIAL TISSUES
SHOW INFILTRATION BY MONONUCLEAR CELLS AND INCREASE IN
FIBROUS STROMA.

VAGINA

ACUTE INFLAMMATION - ACCUMULATIONS OF
NEUTROPHILS ARE PRESENT WITHIN THE INTERSTITIAL TISSUE.

12-10-71

PATHOLOGY NUMBER 87423

ANIMAL NUMBER 174F

FEMALE

GROUP HIGH

P-T NO. 384570

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
ARTERY
KIDNEY
BILE DUCT
LIVER
SPLEEN
BRAIN
MENINGES
STOMACH
COLON
INTESTINE
PANCREAS
ISLET
ADRENAL CORTEX
ADRENAL MEDULLA
PITUITARY
THYROID
LYMPH NODE
SALIVARY GLAND
THYMUS
BLADDER
OVARY
UTERUS
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE
VAGINA
NERVE

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

LUNG

CHRONIC MURINE BRONCHITIS - THERE IS MASSIVE PERIBRONCHIAL LYMPHOCYTIC INFILTRATE AND PATCHY FOCI OF INTERSTITIAL INFLAMMATION AND FIBROSIS.

KIDNEY

CHRONIC INFLAMMATION - THE INTERSTITIAL TISSUES SHOW INFILTRATION BY MONONUCLEAR CELLS AND INCREASE IN FIBROUS STROMA.

BILE DUCT

CHRONIC INFLAMMATION - THERE IS INFILTRATION BY
MONONUCLEAR CELLS IN THE MUCOSA AND SUBMUCOSA.

12-10-71

PATHOLOGY NUMBER 87424

ANIMAL NUMBER 18HF

FEMALE GROUP HIGH

P-T NO. 884S70

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
KIDNEY
BILE DUCT
LIVER
SPLEEN
BRAIN
MENINGES
STOMACH
COLON
INTESTINE
PANCREAS
ISLET
ADRENAL CORTEX
ADRENAL MEDULLA
PITUITARY
THYROID
LYMPH NODE
SALIVARY GLAND
THYMUS
BLADDER
OVARY
UTERUS
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE
VAGINA
NERVE

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

LUNG

CHRONIC MURINE BRONCHITIS - THERE IS MASSIVE PERIBRONCHIAL LYMPHOCYTIC INFILTRATE AND PATCHY FOCI OF INTERSTITIAL INFLAMMATION AND FIBROSIS.

LIVER

CHRONIC INFLAMMATION - THE INTERSTITIAL TISSUES SHOW INFILTRATION BY MONONUCLEAR CELLS AND INCREASE IN FIBROUS STROMA.

12-10-71

PATHOLOGY NUMBER 87425

ANIMAL NUMBER 19HF

FEMALE

GROUP HIGH

P-T NO. 884S70

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
ARTERY
KIDNEY
BILE DUCT
LIVER
SPLEEN
BRAIN
MENINGES
STOMACH
COLON
INTESTINE
PANCREAS
ISLET
ADRENAL CORTEX
ADRENAL MEDULLA
PITUITARY
THYROID
LYMPH NODE
SALIVARY GLAND
THYMUS
BLADDER
OVARY
UTERUS
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE
VAGINA
NERVE

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

LUNG

CHRONIC MURINE BRONCHITIS - THERE IS MASSIVE
PERIBRONCHIAL LYMPHOCYTIC INFILTRATE AND PATCHY FOCI OF
INTERSTITIAL INFLAMMATION AND FIBROSIS.

12-10-71

PATHOLOGY NUMBER 87426

ANIMAL NUMBER 20HF

FEMALE

GROUP HIGH

P-T NO. 884S70

TISSUES EXAMINED

LUNG
BRONCHUS
HEART
ARTERY
KIDNEY
SPLEEN
BRAIN
MENINGES
STOMACH
COLON
INTESTINE
PANCREAS
ISLET
ADRENAL CORTEX
ADRENAL MEDULLA
PITUITARY
THYROID
PARATHYROID
LYMPH NODE
SALIVARY GLAND
THYMUS
BLADDER
OVARY
UTERUS
BONE
BONE MARROW
MUSCLE
SKIN AND SUBCUTIS
MAMMARY GLAND
EYE
VAGINA
NERVE

ALL ORGANS WERE HISTOLOGICALLY NOT REMARKABLE, EXCEPT

LUNG

CHRONIC MURINE BRONCHITIS - THERE IS MASSIVE
PERIBRONCHIAL LYMPHOCYTIC INFILTRATE AND PATCHY FOCI OF
INTERSTITIAL INFLAMMATION AND FIBROSIS.