

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

**Pathology-Toxicology
Project No. 885S70**

**Division of Biological Research
G. D. Searle & Co., P. O. Box 5110, Chicago, Illinois 60680**

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

K. S. Rao, T. B. Martinez, R. D. Hemm and R. G. McConnell

Department of Pathology-Toxicology
Division of Biological Research
G. D. Searle & Co.

November 29, 1971

Pathology-Toxicology
Project No. 885S70

TABLE OF CONTENTS

	<u>PAGE</u>
INTRODUCTION	1
METHODS	1
Material evaluated	1
Animals, housing, and diet	1
Compound administration	2
Statistical procedures	2
Physical examination and observations	2
Clinical laboratory procedures	2
Postmortem examination procedures	4
RESULTS	5
ANTEMORTEM OBSERVATIONS	5
Growth, food consumption and survival	5
Physical and behavioral signs	5
Clinical laboratory findings	5
Hematology	5
Clinical chemistry	10
Urinalysis	10
POSTMORTEM OBSERVATIONS	10
Organ and body weights	10
Gross and microscopic findings	10
SUMMARY AND CONCLUSIONS	16
REFERENCES	18
APPENDIX TABLES OF VALUES OF INDIVIDUAL MICE	19
POSTMORTEM REPORTS ON INDIVIDUAL ANIMALS	22

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

K. S. Rao, T. B. Martinez, R. D. Hemm and R. G. McConnell

Division of Biological Research
Department of Pathology-Toxicology

G. D. Searle & Co.

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 male mice for two consecutive weeks.

METHODS:

Material evaluated.

SC-19192 is a fine white powder with the 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 male mice (Ha/ICR strain) 4 weeks old were utilized. 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 5 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 mice that spilled was not used for food consumption calculations.

Compound administration.

Ten male mice were assigned randomly to control and treated groups. SC-19192 was administered 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 mice after two weeks treatment. Blood specimens were collected terminally from the abdominal aorta of the overnight fasted

ether anesthetized mice after two weeks of treatment. Urine specimens were collected terminally from mice 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
Bilirubin	Malloy & Evelyn ^{7,8}
Glucose	Nelson & Somogyi ⁹

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 mice were immediately autopsied, and entire organs or representative tissue blocks from stomach, small and large intestine, lung, heart, liver, kidney, spleen, pancreas, gall bladder, pituitary, thyroid-parathyroid, adrenal, testis, ventral and dorsal prostate, seminal vesicle, mammary gland, urinary bladder, lymph node (mesenteric), nerve (brachial plexus), brain, bone marrow smear (femoral), salivary gland (submandibular), eye (right), and thymus were removed following gross examination. Underlined organs were weighed fresh.

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.

Tissues examined microscopically at each dosage level are listed in Table 5. The histopathology scoring system is described on page 13.

RESULTS

ANTEMORTEM OBSERVATIONS.

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 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 mice are tabulated in the Appendix. Individual hematologic values for control or treated mice were not remarkable; means for treated groups were in close agreement with control values except the total white cell counts which were significantly lower in the treated group. However, the relatively low white cell count of $6.78 \times 10^3/\text{cmm}$ observed in the treated group is within the normal range of variability for mice.¹⁰

Table 1

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

Body Weight, Weight Gain and Food Intake

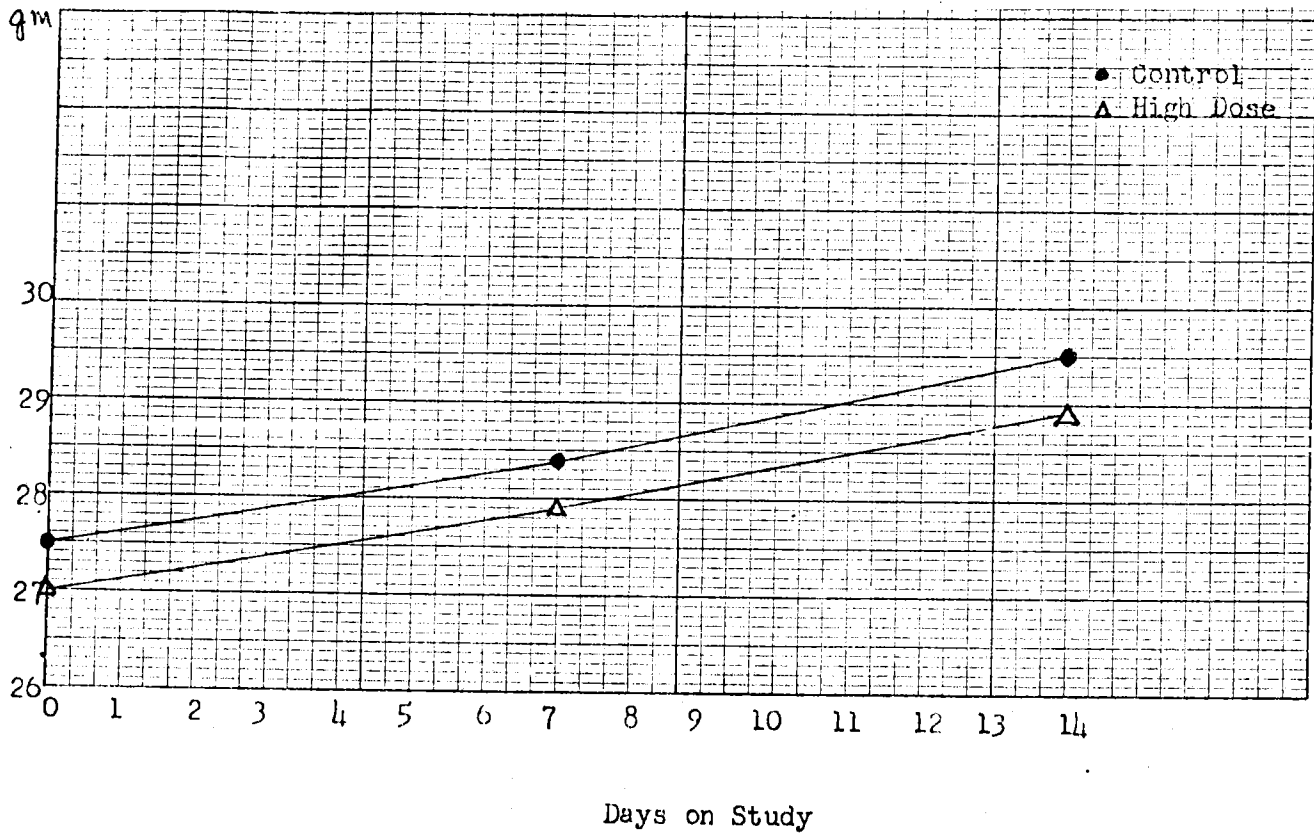
(Mean Values for Groups of 10 Mice)

Treatment Group	Days of Treatment		
	0	7	14
Body Weight, grams			
Control	27.5	28.4	29.5
High Dose	27.0	27.9	28.9
Weight Gain, grams per day			
Control		0.13	0.16
High Dose		0.13	0.14
Food Intake, grams per mouse per day			
Control		8.0	7.4
High Dose		7.6	7.3
Food Intake, grams per Kg. per day			
Control		280.3	251.9
High Dose		272.8	251.2

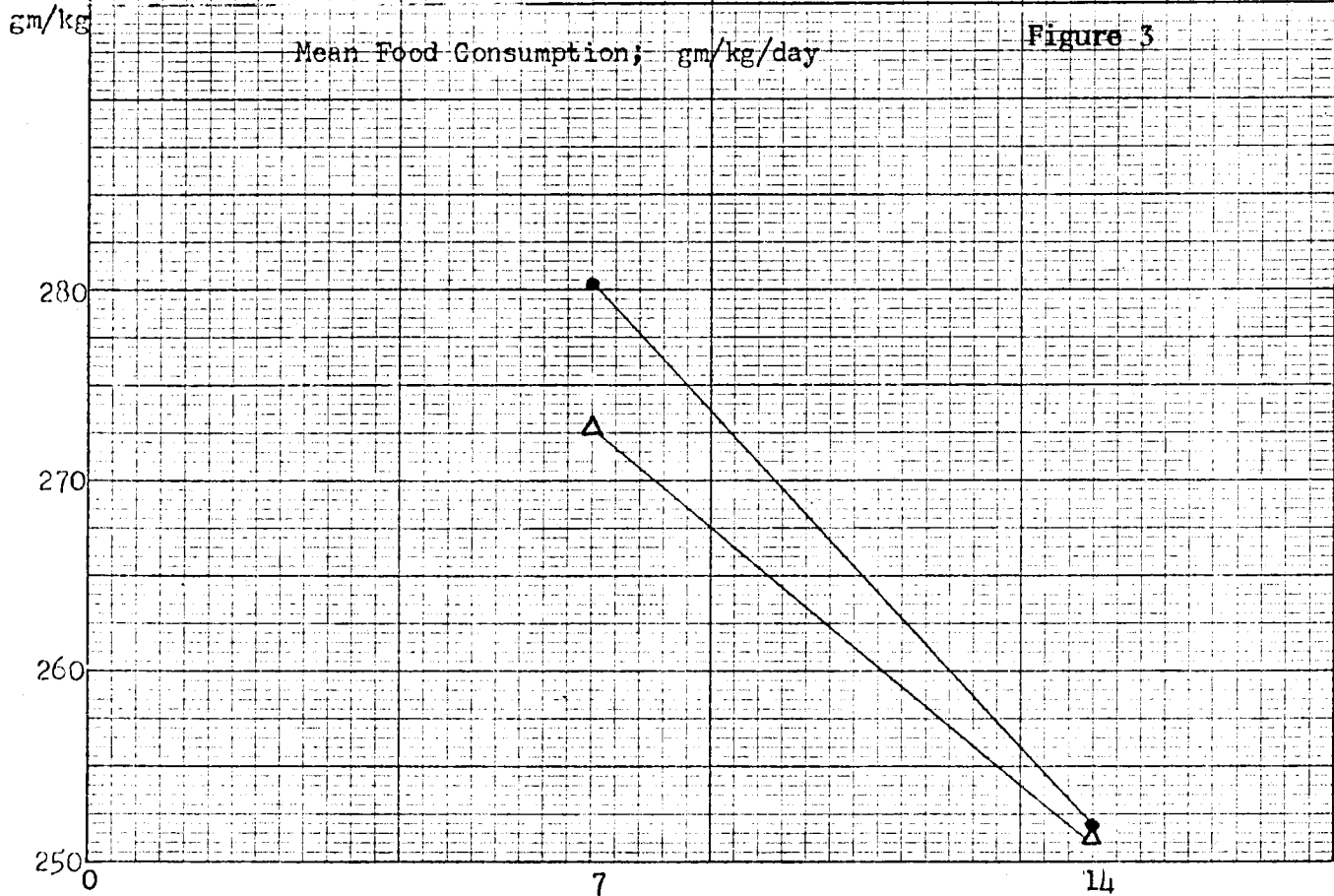
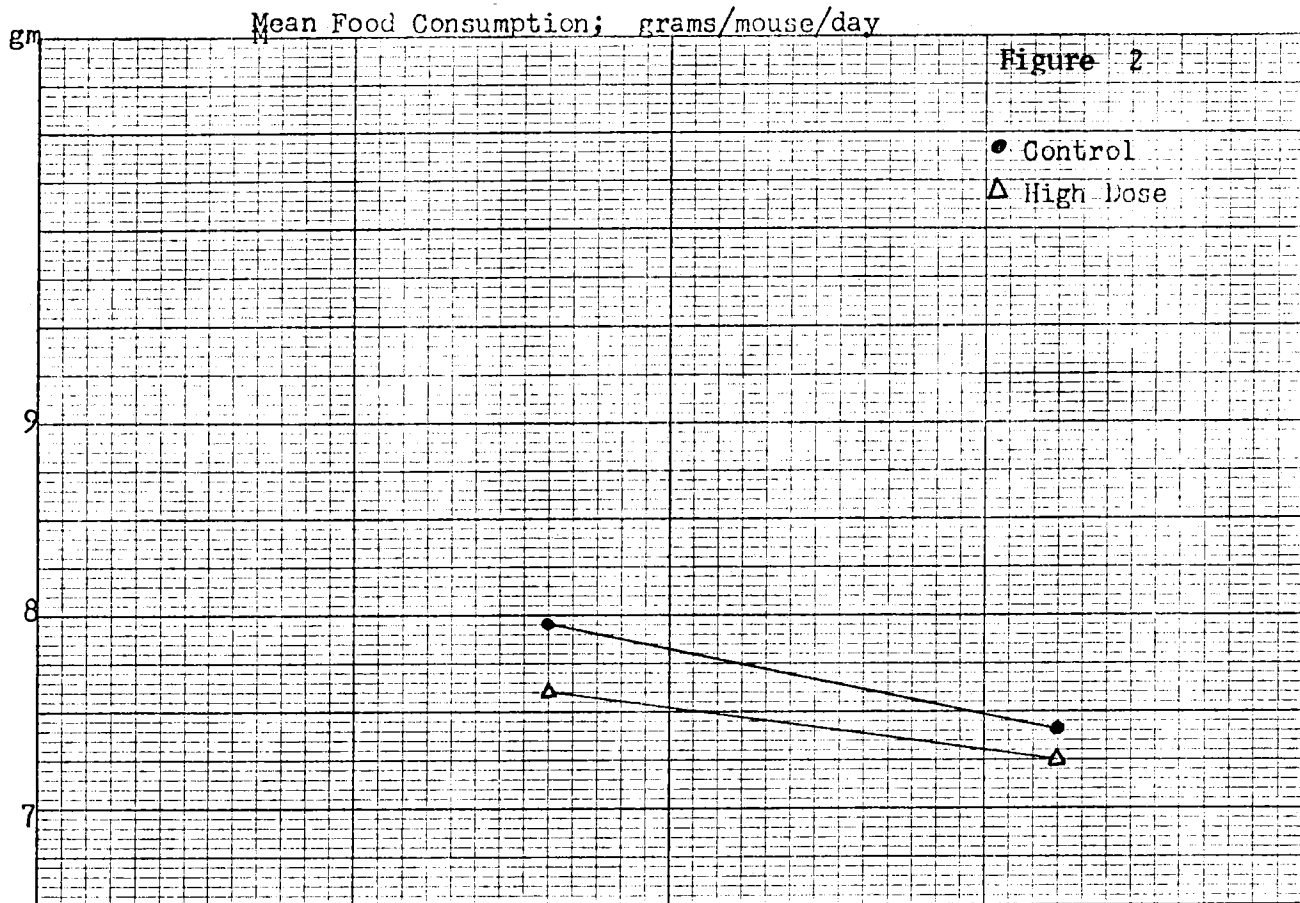
Figure 1

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

Mean Body Weight



1 YEAR BY WEEKS 46 3
X 180 DIVISIONS
KEUFFEL & ESSER CO.



Days on Study

Table 2

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

Hematology Data

(Arithmetic Means for 10 Mice Per Group Are Shown)

Treatment Group	2 Weeks of Treatment		
	Hgb. (g%)	Hct. (%)	RBC $\times 10^6/\text{cmm}$
Control	14.97 ± 0.40	46.3 ± 0.84	8.117 ± 0.26
High Dose	14.99 ± 0.67	46.3 ± 1.65	8.149 ± 0.31

White Cell Data

Treatment Group	2 Weeks of Treatment				
	WBC $\times 10^3/\text{cmm}$	PMN (%)	Differential Lym. (%)	Mon. (%)	Eos. (%)
Control	9.93 ± 1.19	28.3	68.7	2.8	0.2
High Dose	$6.78 \pm 0.43^*$	25.4	73.6	1.7	1.1

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

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 blood glucose which was significantly decreased in treated groups. However, the low blood glucose of 196 mg% observed in treated groups following two weeks of treatment is within the normal range for mice.¹⁰

Urinalysis. The results of urinalysis (pH, specific gravity, blood, protein, glucose, ketones, microscopic) showed no evidence of any 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 a statistically significant increase in mean absolute and relative seminal vesicle weight was apparent in treated animals, such a change was within the limits of variability for historical controls of comparable strain and age and is not regarded as treatment related.

Gross and microscopic findings.

Complete gross and microscopic findings for each animal are presented in the Appendix. Those organs examined microscopically are presented in Table 5; histopathological findings are summarized in Table 6.

Treatment related alterations of the various organs examined were not apparent; no alterations of the seminal vesicle were apparent in the treated group.

Table 3

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

Post-Treatment Blood Serum Biochemistry

Treatment Group	BUN mg%	GPT I.U.	Bilirubin mg%	Sugar mg%
Control	2.043±0.31	^a 31.0±17.35	^c 0.047±0.02	235.1±18.68
High Dose	1.727±0.25	^b 34.8±6.06	0.027±0.01	196.4±4.96*

^a 3 Mice Only

^b 9 Mice Only

^c 4 Mice Only

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

Table 4

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

Final Body and Fresh Organ Weights At Autopsy

Treatment Group	Final B. Wt. g	Heart mg	Liver g	Kidneys mg	Adrenals mg	Thyroids mg	Pituitary mg	Testes mg	Sem. Vesicle mg	Ven. Prostate mg
Control	29.5 ±0.64	145.42 ±7.16	1.701 ±0.08	488.45 ±11.70	6.41 ±1.36	3.22 ±1.10	1.05 ±0.29	214.1 ±7.66	29.14 ±2.85	10.99 ±2.40
High Dose	29.1 ±0.32	147.32 ±6.51	1.561 ±0.07	468.24 ±10.92	6.85 ±0.90	2.75 ±0.53	1.73 ±0.32	216.7 ±4.12	38.32 ±3.28*	14.22 ±2.03

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

HISTOPATHOLOGY SCORING SYSTEM

The scoring system employed here attempts to treat objectively two morphologic aspects of the disease process, namely the intensity (severity) of response and the extent (expanse) of tissue involvement.

Extent of the tissue alteration is expressed thus:

small: <0.3 mm diameter (one high dry field)
medium: 0.3-1.2 mm diameter (one medium power field)
large: >1.2 mm diameter (> one medium power field)

Intensity of the tissue alteration is expressed as mild, moderate, or severe.

Lesions are routinely described verbally employing the aforementioned terms for expressing intensity and extent of damage; such descriptions are later graded numerically and tabulated, thus facilitating comparisons among groups of animals.

No.	Score		Diffuse lesions
	Description	Focal Lesions*	
1	MINIMAL	mild intensity over small or medium area, or moderate intensity over a small area	
2	MODERATE	mild intensity over a large area, or moderate intensity over a medium area	
3	MARKED	moderate intensity over a large area, or severe intensity over a small or medium area	involves 15-25% of the tissue section
4	EXTREME	severe intensity over a large area	involves >25% of the tissue section

* Multiple discrete focal lesions are graded by a rough summation of the areas involved, and average intensity of response.

Table 5

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

Tissues Examined Microscopically*

Organ	Control	High Dose
Stomach	10/10	6/10
Large intestine	10/10	6/10
Small intestine	10/10	10/10
Lung	10/10	10/10
Heart	10/10	10/10
Kidney	10/10	10/10
Liver	10/10	10/10
Gall bladder	3/10	1/10
Spleen	10/10	10/10
Pancreas	10/10	10/10
Pituitary	5/10	8/10
Adrenal	10/10	10/10
Thyroid	8/10	10/10
Parathyroid	3/10	4/10
Urinary bladder	9/10	10/10
Breast	10/10	10/10
Testis	10/10	10/10
Lymph node	2/10	8/10
Seminal vesicle	10/10	10/10
Thymus	9/10	10/10
Prostate	10/10	10/10
Salivary gland	8/10	10/10
Eye	0/10	10/10
Parathyroid gland	3/10	4/10
Bone with marrow	9/10	10/10
Nerve; peripheral	0/10	10/10

* Organs examined/total number of animals necropsied.

Table 6

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

Histopathology Summary*

Organ	Control		High Dose	
	Incidence	Ave.	Incidence	Ave.
Kidney				
Chronic interstitial nephritis	3/10	2.0	2,1,3 1/10	1.0
				1

* Includes all non-neoplastic lesions occurring more than once per group.

Various incidental disease processes were evident; neither the intensity nor the incidence of these lesions were affected by administration of SC-19192.

SUMMARY AND CONCLUSIONS

A two week oral toxicity study was conducted employing intragastric (IG) administration of SC-19192 to weanling male mice (Ha/ICR strain). 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 groups. Physical examination findings were unremarkable throughout the study.

Findings for hematology, clinical chemistry and urinalysis were generally unremarkable. Treated mice had a significantly lower white cell count and a lower blood glucose level. However, these relatively lower values observed in the treated group are within the normal range of variability for mice.

Mean organ weights in general were comparable between the control and experimental animals. The mean seminal vesicle weight in the treated group was increased significantly. Such a change was within the limit of variability for historical controls of comparable strain and age and is not regarded as treatment related. However, on microscopic examination no alterations of the seminal vesicles were apparent in the treated group.

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

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

REFERENCES

1. Bray's Clinical Laboratory Methods; Bauer, Todd, and Ackermann;
1962 edit., pg. 106-107.
2. Ibid., pg. 99-100.
3. Instruction and Service Manual for the Model "B" Coulter Counter,
5th edit., April, 1969.
4. J. G. Miale, Laboratory Medicine Hematology, 1967, C. V. Mosby.
5. "Urograph", Quantitative Urea Nitrogen Assay System, General
Diagnostics, May, 1963.
6. S. Reitman and S. Frankel, Am. J. Clin. Path. 28:56 (1957).
7. H. T. Malloy and K. A. Evelyn, J. Biol. Chem. 119:480 (1937)
8. Standard Methods of Clinical Chemistry, Vol. I (1953), pg. 11.
9. R. Schoenfeld and C. Lowell, Clin. Chem. 10:533 (1964).
10. S. Schermer; The Blood Morphology of Laboratory Animals; 3rd edit., 1967,
pg. 65.

APPENDIX TABLES OF VALUES

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

Hematology Data**Terminal**

Treatment Group & Mouse No.	Hgb. (g%)	Hct. (%)	RBC x10 ⁶ /cmm	WBC x10 ³ /cmm	Differential					
					PMN		Lym. %	Mon. %	Eos. %	Bas. %
					%	%				
					bands	seg.				
Control										
1CM	15.2	47	9.11	11.5	0	25	72	2	0	
2CM	14.1	45	6.83	12.1	0	29	67	2	0	
3CM	15.2	47	8.44	18.8	0	30	65	5	0	
4CM	13.7	44	7.84	8.2	0	34	61	5	0	
5CM	16.7	50	8.49	9.6	0	24	74	2	0	
6CM	15.2	46	8.11	8.5	0	42	54	4	0	
7CM	14.9	47	8.58	7.3	0	26	69	5	0	
8CM	14.9	46	8.38	10.7	0	42	53	5	0	
9CM	12.8	41	6.64	7.3	0	22	78	0	0	
10CM	17.0	50	8.75	5.3	0	14	86	0	0	
High Dose										
11HM	9.4	32	5.72	8.5	0	8	91	1	0	
12HM	15.8	48	8.69	5.8	0	23	76	0	0	
13HM	16.4	50	9.23	7.0	0	31	61	1	0	
14HM	14.3	45	7.99	4.2	0	24	72	2	0	
15HM	14.9	48	8.16	6.2	0	12	86	1	0	
16HM	15.6	48	7.76	8.6	0	22	76	1	0	
17HM	15.2	46	8.11	7.1	0	29	69	2	0	
18HM	15.5	48	8.89	5.9	0	23	74	3	0	
19HM	15.6	49	8.08	7.9	0	41	55	2	0	
20HM	17.2	49	8.86	6.6	0	27	70	3	0	

Appendix Table 2

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

Clinical Chemistry Data

Terminal

Treatment Group & Mouse No.	BUN mg.%	GPT	Bili- rubin mg.%	Glucose mg.%
<u>Control</u>				
1CM	2.85	QNS	.08	194
2CM	3.85	QNS	.06	307
3CM	2.69	33	QNS	257
4CM	1.78	0	QNS	108
5CM	2.89	QNS	QNS	257
6CM	1.18	QNS	QNS	275
7CM	1.16	QNS	QNS	295
8CM	1.16	QNS	QNS	221
9CM	1.86	60	.04	191
10CM	1.01	QNS	.01	246
<u>High Dose</u>				
11HM	3.12	26	.01	197
12HM	0.92	49	0	175
13HM	1.21	47	0	210
14HM	1.35	24	.04	198
15HM	3.02	43	.04	189
16HM	1.38	35	.06	230
17HM	1.81	25	.02	191
18HM	2.10	1	.04	185
19HM	1.42	63	.04	194
20HM	0.94	QNS	.02	205

QNS = Quantity not sufficient.

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

UrinalysisTerminal

Treatment Group & Mouse No.	pH	Sp. Gr.	Protein	Sugar	Acetone	Bili-rubin	Occ. Blood	RBC/HPF	WBC/HPF	Bacteria	Crystals
<u>Control</u>											
1CM	QNS	1.000									
2CM	8	1.011	1	0	0	0	0				
3CM	8	1.016	1	0	0	0	0				
4CM	8	1.015	1	0	0	0	0	0	0-2	2-3	0-1
5CM	7	1.025	1	0	0	0	0	1-3	3-5	2	0
6CM								8-10	4-6	2	0-1
7CM	8	1.025	1	0	0	0	0	0-1	0	2	0
8CM	QNS	1.005									
9CM	7	1.029	1	0	0	0	0	6-8	1-3	3	2
10CM	6	1.048	2	0	0	0	0				
<u>High Dose</u>											
11HM	7	1.047	2	0	0	0	0-1	0-2	0	2	1
12HM	9	1.012	0	0	0	0	0	0-1	0	1	3
13HM	8	1.025	1	0	0	0	0	0	0-1	2	1-2
14HM	8	1.021	1	0	0	0	0	4-6	0	2	2
15HM	6	1.028	1	0	0	0	0	0-1	3-5	2	1
16HM	8	1.031	1	0	0	0	0	0	0-1	3	0
17HM	7	1.024	1	0	0	0	0	0	0-1	2-3	0-1
18HM	7	1.016	0	0	0	0	0	0	0	1-2	1-2
19HM	7	1.008	1	0	0	0	0	0	0	2	1-2
20HM	7	1.032	1	0	0	0	0	0	1-3	2	1-2

QNS = Quantity not sufficient.

**APPENDIX TABLES OF INDIVIDUAL
POSTMORTEM FINDINGS**

(Dr. Hemm)

Male Mouse No. 1CM

Control

Path. No. 87427

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Pituitary - Not examined microscopically.

Thyroid - Not examined microscopically.

Parathyroid - Not examined microscopically.

Thymus - Not examined microscopically.

Gall bladder - Not examined microscopically.

Male Mouse No. 2CM

Control

Path. No. 87428

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Parathyroid - Not examined microscopically.

Lymph node - Not examined microscopically.

Male Mouse No. 3CM

Control

Path. No. 87429

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Thyroid - Not examined microscopically.

Parathyroid - Not examined microscopically.

Gall bladder - Not examined microscopically.

Male Mouse No. 4CM

Control

Path. No. 87430

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Lung - Moderate focal pulmonary adenomatosis. Single, moderate sized focus of alveolar cell metaplasia forming small cysts lined by cuboidal epithelium; notable surrounding areas of atelectasis. Notable intra-alveolar mucus deposition with foam cell aggregates and sloughing of detritic material; the remainder of the lung is unremarkable.

Liver - Moderate focal hepatocyte necrosis. Multiple widely scattered, discrete foci of hepatocyte necrosis with accompanying chronic inflammatory cell infiltration, occupy roughly 20% of the tissue section. Occasional widely scattered foci of chronic inflammatory cell infiltration of the portal triads. Single, large discrete hepatic abscess consisting of a central focus of hepatocyte necrosis with marked accompanying polymorphonuclear cell infiltration.

Bone Marrow - Not examined microscopically.

Lymph node - Not examined microscopically.

Gall bladder - Not examined microscopically.

Male Mouse No. 5CM

Control

Path. No. 87431

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Pituitary - Not examined microscopically.

Parathyroid - Not examined microscopically.

Salivary gland - Not examined microscopically.

Lymph node - Not examined microscopically.

Gall bladder - Not examined microscopically.

Male Mouse No. 6CM

Control

Path. No. 87432

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Parathyroid - Not examined microscopically.

Lymph node - Not examined microscopically.

Gall bladder - Not examined microscopically.

Male Mouse No. 7CM

Control

Path. No. 87433

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Kidney - Moderate unilateral, chronic interstitial nephritis. Multiple (3) moderate sized, discrete foci of severe tubular dilatation with accompanying chronic inflammatory cell infiltration occupy roughly 15-20% of the tissue section, unilaterally. Affected tubules are lined by thin atrophic epithelium and exhibit marked dilatation; notable intraluminal deposition of mucoid or hyaline droplet material. Areas surrounding dilated tubules exhibit moderate to severe fibrosis and chronic inflammatory cell infiltration, predominantly lymphocytic in nature. Occasional adjacent tubules exhibit advanced hydropic or albuminous degeneration; few adjoining foci of glomerulosclerosis. The kidney is otherwise unremarkable, bilaterally.

Pituitary - Not examined microscopically.

Parathyroid - Not examined microscopically.

Lymph node - Not examined microscopically.

Gall bladder - Not examined microscopically.

Male Mouse No. 8CM

Control

Path. No. 87434

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Kidney - Minimal focal chronic interstitial nephritis. Single small unilateral focus of tubular dilatation surrounded by mild chronic inflammatory cell infiltration; otherwise unremarkable.

Pituitary - Not examined microscopically.

Parathyroid - Moderate diffuse enlargement; otherwise unremarkable.

Lymph node - Not examined microscopically.

Gall bladder - Not examined microscopically.

Male Mouse No. 9CM

Control

Path. No. 87435

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Pituitary - Not examined microscopically.

Salivary gland - Not examined microscopically.

Lymph node - Not examined microscopically.

Gall bladder - Not examined microscopically.

Male Mouse No. 10CM

Control

Path. No. 87436

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Kidney - Marked unilateral, chronic interstitial nephritis. Multiple (3-4) widely scattered discrete foci of peritubular chronic inflammatory cell infiltration, predominantly lymphocytic in nature, with accompanying fibrosis occupy roughly 25% of the tissue section. Multiple widely scattered foci of severe tubular dilatation with intraluminal deposition of mucinous or hyaline droplet material. Occasional adjoining foci of glomerulosclerosis. Single small

Male Mouse No. 10CM (cont.) Control

Path. No. 87436

Microscopic:

focus of chronic inflammatory cell infiltration immediately underlying the lining epithelium of the renal pelvis occupies roughly 2% of the tissue section.

Parathyroid - Not examined microscopically.

Lymph node - Not examined microscopically.

Gall bladder - Not examined microscopically.

Male Mouse No. 11HM

High Dose

Path. No. 87437

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Spleen - Moderate diffuse extramedullary hematopoiesis. Moderate to severe increase in hematopoietic activity is present throughout the red pulp of the tissue section; notable extension of erythroid and myeloid hematopoietic colonies from the splenic capsule into the red pulp surrounding Malpighian corpuscles.

Pituitary - Not examined microscopically.

Parathyroid - Not examined microscopically.

Lymph node - Not examined microscopically.

Gall bladder - Not examined microscopically.

Male Mouse No. 12HM

High Dose

Path. No. 87438

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Large intestine - Not examined microscopically.

Gall bladder - Not examined microscopically.

Male Mouse No. 13HM

High Dose

Path. No. 87439

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Parathyroid - Not examined microscopically.

Gall bladder - Not examined microscopically.

Male Mouse No. 14HM

High Dose

Path. No. 87440

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Large intestine - Not examined microscopically.

Pituitary - Not examined microscopically.

Parathyroid - Not examined microscopically.

Male Mouse No. 15HM

High Dose

Path. No. 87441

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Parathyroid - Not examined microscopically.

Male Mouse No. 16HM

High Dose

Path. No. 87442

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Parathyroid - Multiple (3) large unilocular cysts lined by pale cuboidal epithelium occupy roughly 40% of the organ; the cysts are filled with pale mucoid material; otherwise unremarkable.

Lymph node - Not examined microscopically.

Male Mouse No. 17HM

High Dose

Path. No. 87443

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Lung - Not examined microscopically.

Parathyroid - Not examined microscopically.

Male Mouse No. 18HM

High Dose

Path. No. 87444

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Large intestine - Not examined microscopically.

Parathyroid - Not examined microscopically.

Male Mouse No. 19HM

High Dose

Path. No. 87445

Gross:

All organs examined were grossly normal and unremarkable.

Male Mouse No. 20HM

High Dose

Path. No. 87446

Gross:

All organs examined were grossly normal and unremarkable.

Microscopic:

Large intestine - Not examined microscopically.

Lung - Minimal focal chronic interstitial pneumonia. Single, small discrete focus of mild peribronchiolar chronic inflammatory cell infiltration, predominantly lymphocytic in nature, occupies roughly 5% of the tissue section. Adjacent alveoli exhibit compensatory alveolar emphysema with notable septal thickening by chronic inflammatory cell infiltration and fibrosis. Occasional foci of cuboidal metaplasia of alveolar lining cells. The remainder of the lung is unremarkable.

Male Mouse No. 20HM (cont.) High Dose

Path. No. 87446

Microscopic:

Kidney - Minimal unilateral chronic interstitial nephritis. Single unilateral small discrete subcapsular focus of chronic inflammatory cell infiltration, predominantly lymphocytic in nature, surrounding a solitary large dilated proximal tubule, occupies roughly 5% of the tissue section, unilaterally. Mild intraluminal deposition of pale staining, homogeneous material within the dilated tubule; 2 small discrete foci of chronic inflammatory cell infiltration immediately underlining the lining epithelium of the renal pelvis. Occasional widely scattered foci of glomerular atrophy.