International Research and Development Corporation

SPONSOR: 3M Company

COMPOUND: Fluorad® Fluorochemical FC-143

SUBJECT: Ninety Day Subacute Rhesus Monkey Toxicity Study.

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137-090

TABLE OF CONTENTS
(Continued)

Table No.		Page
5- 7.	Individual Hematological Values	18-20
8.	Means and Significance of Biochemical Values	21
9-11.	Individual Biochemical Values	22-24
12.	Means and Significance of Urinalysis Values	25
13-15.	Individual Urinalysis Values	26-28
16.	Summary of Gross Necropsy Observations	29-30
17.	Absolute and Relative Organ Weights	31-32
18.	Microscopic Observations	33-39

I. SYNOPSIS

In a ninety day oral study in rhesus monkeys, Fluorad® Fluorochemical FC-143 was administered at dosage levels of 0 (control, treated only with 0.5% Methocel®), 3, 10, 30 and 100 mg/kg/day. Two male and two female monkeys were initiated at each dosage level and also in a control group. The monkeys were observed twice daily for general physical appearance and behavior and pharmacotoxic signs. Body weights were recorded weekly. Hematological, biochemical and urinalysis studies were conducted once in the control period, at the end of the first and third months of study.

The monkeys treated with the higher dose, (100 mg/kg/day) all died during weeks 2 through 5 of the study. At the 30 mg/kg/day dosage level, three monkeys died during weeks 7-12. They all showed signs of toxicity in the gastrointestinal tract (anorexia, emesis, sometimes brown in color, black stools), pale face and gums, swollen face and eyes, slight to severe decreased activity and prostration. The monkeys of the 30 and 100 mg/kg/day dosage level showed body weight losses from the first week of the study.

Because of the early deaths of the monkeys at the 100 mg/kg/day dosage level, the clinical laboratory tests were not conducted.

The monkeys at the 30 mg/kg/day dosage level showed, in the first month of the study, slight increase in prothrombin time and in activated partial thromboplastin time (A.P.T.T.) values, as well as decreased alkaline phosphatase activity in the serum (statistically significant). Only one monkey from this dosage level in this period showed a low albumin value. At the end of the study, the only remaining monkey from the 30 mg/kg/day dosage level showed apparent anemia, low blood glucose, alkaline phosphatase, total protein and albumin values.

There was no mortality at the 10 mg/kg/day dosage level. One monkey had black stool on several days in week 12 and occasionally

anorexia and one monkey exhibited pale face and gums. At this dosage level there was a very slight increase in the activated P.T.T. values in the female monkeys during the first month of the study (not statistically significant). There were no changes in the other indices and no changes in the body weight. In single monkeys from the 3 and 10 mg/kg/day dosage levels, there were trends toward decreased alkaline phosphatase in the serum.

In the control and the 3 mg/kg/day dosage level there was no mortality, no changes in the body weights and no signs of toxicity. Soft stool, diarrhea or emesis were observed occasionally.

The mortality and the above mentioned signs of toxicity in the 30 and 100 mg/kg/day dosage levels were compound-related. There was a trend toward the same signs of toxicity in single monkeys at the 10 mg/kg/day dosage level. The 3 mg/kg/day dosage level seems to be free of signs of toxicity. There is an evident relationship between the administered doses and the degree of the toxicity.

No gross or microscopic lesions which were considered compound-related were seen in tissues other than the adrenals, bone marrow, spleen and lymph nodes for male and female monkeys at the 30 and 100 mg/kg/day dosage levels. Microscopically, the adrenals from male and female monkeys at the 30 and 100 mg/kg/day dosage levels had compound-related marked diffuse lipid depletion; the bone marrow from male and female monkeys at the 30 and 100 mg/kg/day dosage levels had compound-related slight to moderate hypocellularity; the spleen and lymph nodes from male and female monkeys at the 30 and 100 mg/kg/day dosage levels had compound related moderate atrophy of lymphoid follicles.

Statistically significant variations in sex group mean weights of a few organs occurred between the control and experimental groups. These variations were of unknown biological significance and were not accompanied by morphologic alterations.

II. COMPOUND

The compound was received from 3M Company, Saint Paul, Minnesota on October 24, 1977 as shown below:

Label	Description
Fluorad® Fluorochemical FC-143 3M Stock No. 98-0211-0008-0 Lot 340	white powder

III. CLINICAL STUDIES

A. METHODS:

1. General Procedure:

Ten male rhesus monkeys (weighing from 2.60 to 3.90 kilograms) and 10 females (weighing from 2.95 to 3.80 kilograms) were initiated on this study. The monkeys were purchased from Primate Imports Corporation, Port Washington, N. Y. 11050. The monkeys were housed individually in hanging wire mesh, "squeeze type" cages and maintained in a temperature, humidity and light controlled enviroment. Purina® Monkey Chow® was fed twice each day and fresh apples were fed 3 times a week. Water was available ad libitum.

During the conditioning period, the monkeys were tattooed on the inner surface of the thigh and intrapalpebral tuberculin tests were conducted. Tuberculin tests were conducted at bimonthly intervals during the treatment period. Also a complete physical examination was conducted by the staff veterinarian prior to initiation of compound administration. Only monkeys in good health were selected for the study.

This study was initiated on January 11, 1978. Terminal sacrifices were conducted on April 12, 1978.

2. Compound Administration:

At the end of the conditioning period the monkeys were divided into five groups on a random basis, so that the initial average body weights were similar:

Number of Monkeys		
Male	Female	Dosage Level
2	2	Control
2	2	3 mg/kg/day
2	2	10 mg/kg/day
2	2	30 mg/kg/day
2	2	100 mg/kg/day

The test compound, suspended in 0.5% Methocel®, was administered by gavage, 7 days each week. All doses were given in a constant volume. Also the same volume of 0.5% Methocel® was given to the vehicle control group. Individual daily doses were based upon the body weights obtained weekly.

3. Observations:

The monkeys were observed twice daily for general physical appearance and behavior and pharmacotoxic signs. Individual body weights were recorded weekly. General physical examinations were conducted in the control period and monthly during the study.

4. Clinical Laboratory Tests:

Blood and urine samples were obtained for analysis from all monkeys once during the control period and at 1 and 3 months of study. The monkeys were fasted overnight prior to the collection of blood and urine samples.

a. Hematology:

Hematological studies included: hemoglobin[1], hematocrit[2], erythrocyte count[3], total[3] and differential leucocyte counts, reticulocyte count[4], platelet count[5], prothrombin time[6], activated partial thromboplastin time[7] (A.P.T.T.). Mean corpuscular hemoglobin, mean corpuscular volume and mean corpuscular hemoglobin concentration were calculated.

b. Biochemistry:

Biochemical studies included: fasting blood glucose[8], blood urea nitrogen[8], serum alkaline phosphatase[8], serum glutamic oxalacetic and pyruvic transaminase activities[8], cholesterol[9], total protein[9], albumin[8], sodium[10], potassium[10], chloride[9], inorganic phosphate[9], γ-glutamyl transpeptidase[11] (γ-G.T.P.) and creatinine phosphokinase[9].

c. Urinalysis:

Urinalysis included: measurement of volume, pH[12] and specific gravity; description of color and appearance; qualitative tests for protein[12], glucose[12], ketones[12], occult blood[12] and microscopic examination of the sediment.

d. Statistical Analysis:

Analysis of body weights and clinical laboratory tests were performed. All statistical analyses compared the treatment groups with the control group, by sex. The tests were compared by analysis of variance (one-way classification) Bartlett's test for homogeneity and the appropriate t-test (for equal or unequal variances) as described by Steel and Torrie[13] using Dunnett's[14] multiple comparison tables to judge significance of differences.

B. RESULTS:

1. General Behavior, Appearance and Survival:

There was no mortality in monkeys at 0, 3 and 10 mg/kg/day dosage levels.

The monkeys from the control and 3 mg/kg/day dosage levels did not show any unusual behavior or signs of toxicity. Soft stool or moderate to marked diarrhea were noted occasionally. Frothy emesis was also noted occasionally.

At the 10 mg/kg/day dosage level the monkeys did not show any unusual signs of toxicity, except Monkey 7363. In week 7 its face appeared swollen and pale. It had been occasionally anorexic in week 4 and black stools appeared for several days in week 12 of the study.

At the 30 mg/kg/day dosage level, three monkeys died during weeks 7, 12 and 13 of the study. From week 4, the monkeys were anorexic. Slight to moderate and sometimes severe decreased activity was noted occasionally to frequently for the four monkeys. Emesis and ataxia were very rarely noted, for one monkey.

Swollen face, eyes and vulva, as well as pallor of the face and gums were noted. From week 6, for two monkeys, black stools were noted. Monkey 7387 showed slight to moderate dehydration and ptosis of the eyelids.

All monkeys from the 100 mg/kg/day dosage level died during weeks 2 through 5 of study. They showed the same symptoms of toxicity as the previous group, but they appeared sooner in the study (from week 1) and were more marked: anorexia, frothy emesis (sometimes brown in color) pale face and gums, swollen face and eyes, decreased activity from slight to severe, prostration and body trembling.

2. Body Weights (Tables 1-3):

Changes in body weight were similar for monkeys from the control and the 3 and 10 mg/kg/day dosage levels. Monkeys at the 30 and 100 mg/kg/day dosage levels lost body weight after the first week of study. There was statistically significant decreases in the body weight for the male monkeys at the 30 mg/kg/day dosage level in week 13 of the study. The female monkeys of the same dosage level and the monkeys from the 100 mg/kg/day dosage level were dead in this period.

3. Laboratory Test (Tables 4-15):

a. Hematology:

There were no noteworthy changes in monkeys from the 3 and 10 mg/kg/day dosage levels. In the first month of the study there was a slight increase (not statistically significant) of the A.P.T.T. values in the females at the 10 mg/kg/day dosage level and a statistically significant increase of the A.P.T.T. and prothrombin time values in monkeys at the 30 mg/kg/day dosage level. In the third month of the study there was a high increase in the above mentioned indices for the one surviving monkey from the 30 mg/kg/day dosage level. The same monkey (#7455) had pronounced anemia as well.

The statistically significant increase in the hematocrit in monkeys at the 10 mg/kg/day dosage level and in the platelet count in monkeys at the 3 mg/kg/day dosage level at 3 months of study, were within the normal physiological limits.

b. Biochemistry:

There were no noteworthy changes in monkeys from the control, 3 and 10 mg/kg/day dosage level. Only one monkey from the 3 mg/kg/day dosage level and one monkey from the 10 mg/kg/day dosage level showed trends toward decreases of alkaline phosphatase (432 and 474 units/l, respectively), without statistical significance.

In the first month of the study, decrease in serum alkaline phosphatase was noted in monkeys at the 30 mg/kg/day dosage level (statistically significant) and in one monkey in the same dosage level, the albumin in the serum was lower (3.22 g/100ml). The one surviving monkey (7455) from the 30 mg/kg/day dosage level showed decreasing of: blood sugar (66 mg/100ml), total protein (5.52 g/100ml) with albumin (2 g/100ml) and alkaline phosphatase (360 units/l) and slightly elevated cholesterol (240 mg/100ml).

c. Urinalysis:

No changes considered to be related to compound were seen in the urinalysis studies.

IV. PATHOLOGICAL STUDIES

A. METHODS:

1. Gross Pathology:

After completion of the compound administration period all surviving monkeys were anesthetized with Sernylan®*, exsanguinated and necropsied. At necropsy, the heart, liver, adrenals, spleen, pituitary, kidneys, testes/ovaries and brain were weighed and representative tissues were collected in buffered neutral 10% formalin. Eyes were fixed in Russell's fixative. The thyroid/parathyroid was weighed after fixation.

Monkeys which died during the study were necropsied as above.

2. Histopathology:

Microscopic examination of formalin fixed hematoxylin and eosin stained paraffin sections was performed for all monkeys in the control and treatment groups. The following tissues were examined:

adrenals	kidneys	lumbar spinal cord
aorta	liver	pituitary
bone	lung	stomach
brain	skin	testes/ovaries
esophagus	mesenteric lymph node	thyroid
eyes	retropharyngeal lymph node	parathyroid
gallbladder	mammary gland	thymus
heart (with coronary vessels)	nerve (with muscle)	trachea
duodenum	spleen	tonsil
ileum	pancreas	tongue
jejunum	prostate/uterus	urinary bladder
cecum	rib junction (bone marrow)	vagina
colon	salivary gland	tattoo
rectum		

and any other tissue(s) with lesions

*Phencyclidine HCl - Bio-Ceutic Laboratories, Inc., St. Joseph, Missouri.

B. RESULTS:

1. Gross Pathology (Table 16) and Organ Weights (Table 17):

No gross lesions considered compound related were seen in male and female rhesus monkeys which died on study or were sacrificed after 90 days of study.

Statistically significant variations in sex group mean weights of few organs occurred between the control and experimental groups. The following statistically significant organ weight variations occurred:

Organ	Dosage Level mg/kg/day	Sex	Weight	Change	P<
Heart	10	F	absolute,relative	decrease,decrease	0.05,0.01
Brain	10	F	absolute	decrease	0.01
Pituitary	3	M	relative	increase	0.05

The biological significance of these variations is unknown. These organ weight variations were not accompanied by morphologic changes which were considered compound related.

2. Histopathology (Table 18):

One male and two female rhesus monkeys at the 30 mg/kg/day dosage level and all male and female rhesus monkeys at the 100 mg/kg/day dosage level had marked diffuse lipid depletion in the adrenals. All male and female rhesus monkeys at the 30 and 100 mg/kg/day dosage levels had slight to moderate hypocellularity of the bone marrow. All male and female rhesus monkeys at the 30 and 100 mg/kg/day dosage levels had moderate atrophy of lymphoid follicles in the spleen. One female at the 30 mg/kg/day dosage level and all male and female rhesus monkeys at the 100 mg/kg/day dosage level had moderate atrophy of the lymphoid follicles in the lymph nodes.

No microscopic changes considered compound related were seen in the adrenals, bone marrow, spleen and lymph nodes of male and female rhesus monkeys at the 3 and 10 mg/kg/day dosage levels. No microscopic

lesions in tissues other than the adrenals, bone marrow, spleen and lymph nodes at the 30 and 100 mg/kg/day dosage levels were considered compound-related.

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FC-143: Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 1. Mean Body Weights of Monkeys Week 13 of Study.

Sex	Group I (Control)	Group II (3 mg/kg/day)	Group III (10 mg/kg/day)	Group IV (30 mg/kg/day)	Group V (100 mg/kg/day)
M	3.78	3.50	3.68	2.30*	dead
F	3.55	3.68	3.78	dead	dead

*Statistical significance.

FC-143: Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 2. Individual Body Weights, Kilograms.

Group, Monkey Number	Sex	Control 1	Control 2	Week of Study 1	2	3	4	5	6	7	8	9	10	11	12	13
Control:																
7362	M	3.15	3.30	3.15	3.30	3.35	3.10	3.20	3.20	3.00	3.15	3.20	3.05	3.20	3.40	3.50
7365	M	3.50	3.50	3.50	3.50	3.50	3.40	3.55	3.60	3.60	3.80	3.75	3.75	3.80	4.00	4.05
7336	F	3.05	3.20	3.25	3.25	3.35	3.15	3.00	3.15	3.20	3.30	3.45	3.30	3.35	3.35	3.60
7386	F	3.90	3.70	3.70	3.65	3.55	3.45	3.40	3.55	3.40	3.40	3.55	3.40	3.50	3.50	3.50
Mean		3.40	3.43	3.40	3.43	3.44	3.28	3.29	3.38	3.30	3.41	3.49	3.38	3.46	3.56	3.66
3 mg/kg/day:																
7364	M	3.70	3.90	3.85	3.95	3.85	3.85	3.80	3.80	3.85	4.10	4.10	4.05	4.05	4.20	4.30
7366	M	2.60	2.60	2.70	2.60	2.65	2.65	2.70	2.70	2.50	2.70	2.70	2.45	2.55	2.50	2.70
7384	F	3.55	3.60	3.70	3.80	3.80	3.80	3.70	3.70	3.60	3.55	3.80	3.55	3.70	3.90	3.75
7385	F	3.50	3.55	3.45	3.45	3.45	3.45	3.40	3.40	3.50	3.55	3.60	3.40	3.30	3.40	3.60
Mean		3.34	3.41	3.43	3.45	3.44	3.44	3.40	3.40	3.36	3.48	3.55	3.36	3.40	3.50	3.59
10 mg/kg/day:																
7363	M	3.55	3.70	3.70	3.65	3.65	3.65	3.65	3.60	3.60	3.70	3.65	3.75	3.85	3.90	3.90
7458	M	3.10	3.10	3.25	3.20	3.10	3.05	2.95	3.20	3.00	3.15	3.10	3.10	3.25	3.25	3.45
7328	F	3.30	3.30	3.45	3.40	3.40	3.30	3.20	3.30	3.25	3.45	3.60	3.50	3.40	3.60	3.75
7383	F	3.60	3.60	3.50	3.80	3.60	3.55	3.50	3.60	3.60	3.65	3.80	3.65	3.75	3.75	3.80
Mean		3.39	3.43	3.48	3.51	3.44	3.39	3.33	3.43	3.36	3.49	3.54	3.50	3.56	3.63	3.73

FC-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 2. Cont.

Individual Body Weights, Kilograms.

Group, Monkey Number	Sex	Control 1	Control 2	Week of Study 1	2	3	4	5	6	7	8	9	10	11	12	13
30 mg/kg/day:																
7367	M	3.40	3.40	3.25	3.25	3.10	2.95	2.65	2.30	2.10*	Died					
7455	M	3.50	3.30	3.20	3.05	2.85	2.65	2.45	2.50	2.55	2.60	2.70	2.70	2.65	2.50	2.30
7382	F	3.25	3.30	3.20	3.20	3.05	3.00	2.85	2.80	2.80	2.80	2.80	2.80	2.80	2.60	2.25* Die
7387	F	3.70	3.75	3.50	3.55	3.50	3.45	3.10	2.95	2.85	2.85	2.70	2.65	2.50	2.25*	Died
Mean		3.46	3.44	3.29	3.26	3.13	3.01	2.76	2.64	2.73	2.75	2.73	2.72	2.65	2.55	2.30
100 mg/kg/day:																
7361	M	3.50	3.85	3.50	3.30	3.00	2.55	2.40*	Died							
7456	M	3.10	3.10	2.60	2.70*	Died										
7335	F	2.80	2.95	2.70	2.45	2.05*	Died									
7381	F	3.85	3.80	3.55	3.20	2.80	2.60*	Died								
Mean		3.31	3.43	3.09	2.98	2.90	2.55									

*Terminal weight not included in mean.

FC-143: Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 3. T-Test Comparison of Body Weights.

Study Week	Sex	Control	3 mg/kg/day	10 mg/kg/day	30 mg/kg/day	100 mg/kg/day
13	M	3.78	3.50	3.68	2.30[a]	-
	F	3.55	3.68	3.78	-	-

*p<0.05
**p<0.01
[a]Not included in statistical analysis due to only one surviving animal.
- Line indicates animals had died prior to week 13.

FC-143: Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 4. Means and Significance of Hematological Values.

Hematology	Month of Study	Control	3 mg/kg/day	10 mg/kg/day	30 mg/kg/day
Erythrocytes, 10^6/cmm	1	4.46	4.26	4.71	4.53
	3	4.90	4.74	5.47	3.84[a]
Hemoglobin, g/100 ml	1	11.7	11.4	12.1	11.7
	3	12.9	12.7	13.3	9.7[a]
Hematocrit, %	1	38	37	39	36
	3	37	37	40**	30[a]
Platelets, 10^3/cmm	1	253	233	210	219
	3	210	285*	216	261[a]
Reticulocytes, %	1	0.2	0.5	0.5	0.2
	3	0.3	0.2	0.2	0.2[a]
Prothrombin Time, sec	1	12	12	13	15**
	3	11	11	11	30[a]
Activated P.T.T., sec	1	28	28	31	35**
	3	26	26	24	65[a]
Leucocytes, 10^3/cmm	1	9.49	9.78	9.93	8.44
	3	9.40	9.83	11.96	10.14[a]
Neutrophils, %	1	24	19	26	15
	3	16	19	25	36[a]
Lymphocytes, %	1	75	76	72	85
	3	80	76	67	54[a]
Eosinophils, %	1	1	5*	2	0
	3	3	3	6	3[a]
Monocytes, %	1	0	0	0	0
	3	1	2	2	7[a]
Basophils, %	1	0	0	0	0
	3	0	0	0	0[a]
MCV, μ^3	1	86	86	82	80
	3	75	78	73	78[a]
MCH, µµg	1	27	27	26	26
	3	26	27	24	25[a]
MCHC, g/100 ml	1	31	31	32	32*
	3	36	35	34	32[a]

*Significantly different from control group, $p<0.05$.
**Significantly different from control group, $p<0.01$.
[a]Value not used in statistical analysis due to only one animal surviving.

FC-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 5.

Individual Hematological Values - Control 1.

Group, Monkey Number	Sex	Erythrocytes 10^6/cmm	Hemoglobin g/100 ml	Hematocrit %	Platelets 10^3/cmm	Reticulocytes %	Prothrombin Time sec	Activated P.T.T. sec	Leucocytes 10^3/cmm	Neutrophils Seg. %	Neutrophils Non-Seg. %	Lymphocytes[a] %	Eosinophils[a] %	Monocytes[a] %	Basophils[a] %	MCV μ^3	MCH $\mu\mu g$	MCHC g/100 ml
Control:																		
7362	M	5.08	13.0	40	207	0.1	13	29	10.96	36	1	62	1	0	0	79	26	33
7365	M	4.72	11.9	38	319	0.3	13	30	14.79	27	0	72	1	0	0	81	25	31
7336	F	5.27	12.8	39	226	0.6	14	29	7.86	38	0	59	3	0	0	74	24	33
7386	F	4.20	11.1	34	227	0.5	14	21	12.09	59	0	39	1	1	0	81	26	33
Mean		4.82	12.2	38	245	0.4	14	27	11.43	40	0	58	2	0	0	79	25	33
3 mg/kg/day:																		
7364	M	4.50	11.5	37	155	0.4	13	25	8.98	42	0	57	0	1	0	82	26	31
7366	M	4.48	12.0	37	297	0.3	14	29	7.39	41	0	59	0	0	0	83	27	32
7384	F	4.55	11.7	38	160	0.2	13	30	14.72	31	0	64	5	0	0	84	26	31
7385	F	4.19	11.4	35	145	0.6	13	24	8.16	38	0	59	3	0	0	84	27	33
Mean		4.43	11.7	37	232	0.4	13	27	9.81	38	0	60	2	0	0	83	27	32
10 mg/kg/day:																		
7363	M	5.24	13.7	42	264	0.4	13	31	12.97	46	0	49	5	0	0	80	26	33
7458	M	5.29	12.2	36	263	0.2	13	29	17.34	16*	0	78	6	0	0	68	23	34
7328	F	5.32	12.5	39	192	0.8	13	31	7.89	35	0	65	0	0	0	73	23	32
7383	F	5.04	13.5	42	120	0.4	13	28	8.22	47	0	48	4	1	0	83	27	32
Mean		5.22	13.0	40	210	0.5	13	36	11.61	36	0	60	4	0	0	76	25	33
30 mg/kg/day:																		
7367	M	4.98	12.4	38	143	0.2	12	28	10.84	41	0	57	2	0	0	76	25	33
7455	M	5.16	13.6	40	133	0.5	12	24	8.65	21	0	76	3	0	0	78	26	34
7382	F	4.84	12.8	38	157	0.6	13	26	5.83	26	0	73	1	0	0	79	26	34
7387	F	4.67	12.2	35	113	0.6	14	27	5.10	29	0	68	1	2	0	75	26	35
Mean		4.91	12.8	38	137	0.5	13	26	7.61	29	0	68	2	1	0	77	26	34
100 mg/kg/day:																		
7361	M	4.75	12.4	36	282	0.3	12	27	10.77	30	0	67	3	0	0	76	26	34
7456	M	5.36	13.4	42	196	0.2	11	28	5.84	38	0	60	0	1	1	78	25	32
7335	F	5.46	12.8	40	185	0.2	14	28	12.8	38	0	57	5	0	0	73	23	32
7381	F	4.82	11.5	36	115	0.5	14	26	10.36	54	0	44	1	0	1	75	24	32
Mean		5.10	12.5	39	195	0.3	13	27	9.58	40	0	57	2	0	1	76	25	33

*Repeat determination

[a]The differential leucocyte means have been adjusted to equal 100%.

137-090

FC-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 6.

Individual Hematological Values - 1 Month.

Group, Monkey Number	Sex	Erythrocytes 10^6/cmm	Hemoglobin g/100 ml	Hematocrit %	Platelets 10^3/cmm	Reticulocytes %	Prothrombin Time sec	Activated P.T.T. sec	Leucocytes 10^3/cmm	Neutrophils Seg. %	Neutrophils Non-Seg. %	Lymphocytes[a] %	Eosinophils[a] %	Monocytes[a] %	Basophils[a] %	MCV μ^3	MCH µµg	MCHC g/100 ml
Control:																		
7362	M	4.80	11.9	38	224	0.2	12	30	6.91	28	0	69	3	0	0	79	25	31
7365	M	4.71	11.9	39	349	0.2	12	28	14.58	15	0	84	1	0	0	83	25	31
7336	F	4.20	11.2	37	246	0.2	13	28	7.46	11	0	89	0	0	0	88	27	30
7386	F	4.13	11.9	38	191	0.3	12	27	8.99	42	0	58	0	0	0	92	29	31
Mean		4.46	11.7	38	253	0.2	12	28	9.49	24	0	75	1	0	0	86	27	31
3 mg/kg/day:																		
7364	M	4.35	11.6	37	264	0.5	11	27	6.81	17	0	80	3	0	0	85	27	31
7366	M	3.96	10.7	35	188	0.4	12	28	5.83	16	0	78	6	0	0	88	27	31
7384	F	4.46	11.9	39	234	0.2	13	28	17.07	22	1	73	3	1	0	87	27	31
7385	F	4.25	11.2	35	247	0.9	12	29	9.41	18	0	73	9	0	0	82	26	32
Mean		4.26	11.4	37	233	0.5	12	28	9.78	19	0	76	5	0	0	86	27	31
10 mg/kg/day:																		
7363	M	4.42	12.3	38	168	1.0	13	27	8.08	42	0	57	1	0	0	86	28	32
7458	M	4.81	11.3	37	281	0.3	13	31	17.98	11	0	87	1	0	1	77	23	31
7328	F	4.70	12.0	39	181	0.5	13	33	7.01	35	0	63	2	0	0	83	26	31
7383	F	4.92	12.8	40	209	0.1	12	33	6.64	18	0	79	3	0	0	81	26	32
Mean		4.71	12.1	39	210	0t5	13	31	9.93	26	0	72	2	0	0	82	26	32
30 mg/kg/day:																		
7367	M	4.59	11.2	36	135	0.1	13	34	7.92	12	0	88	0	0	0	78	24	31
7455	M	4.44	11.8	37	237	0.2	14	33	11.11	27	0	73	0	0	0	83	27	32
7382	F	4.51	11.9	35	268	0.3	15	35	6.19	9	0	90	1	0	0	78	26	34
7387	F	4.56	12.0	37	237	0.2	16	38	8.54	13	0	87	0	0	0	81	26	32
Mean		4.53	11.7	36	219	0.2	15	35	8.44	15	0	85	0	0	0	80	26	32
100 mg/kg/day:																		
7361	M	Died, week 5																
7456	M	Died, week 2																
7335	F	Died, week 3																
7381	F	Died, week 4																

[a]The differential leucocyte means have been adjusted to equal 100%.

137-090

FC-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 7.

Individual Hematological Values - 3 Months.

Group, Monkey Number	Sex	Erythrocytes 10^6/cmm	Hemoglobin g/100 ml	Hematocrit %	Platelets 10^3/cmm	Reticulocytes %	Prothrombin Time sec	Activated P.T.T. sec	Leucocytes 10^3/cmm	Neutrophils Seg. %	Neutrophils Non-Seg. %	Lymphocytes[c] %	Eosinophils[c] %	Monocytes[c] %	Basophils[c] %	MCV μ^3	MCH uuu	MCHC g/100 ml
Control:																		
7362	M	4.89	12.9	37	217	0.2	11	32	7.82	20	0	74	4	2	0	76	26	35
7365	M	5.29	13.1	37	218	0.3	10	25	12.84	10	0	85	4	1	0	70	25	35
7336	F	4.72	12.9	36	170	0.4	11	25	8.41	16	0	79	4	1	0	76	27	36
7386	F	4.69	12.8	36	234	0.3	11	20	8.51	18	1	80	0	1	0	77	27	36
Mean		4.90	12.9	37	210	0.3	11	26	9.40	16	0	80	3	1	0	75	26	36
3 mg/kg/day:																		
7364	M	4.86	12.9	37	299	0.1	11	24	7.33	24	0	71	4	1	0	76	27	35
7366	M	4.46	12.0	34	278	0.2	11	26	5.44	25	0	74	0	0	1	76	27	35
7384	F	4.92	13.0	39	313	0.2	11	28	18.21	16	0	76	5	3	0	79	26	33
7385	F	4.71	13.0	37	248	0.2	11	24	8.35	10	0	82	5	3	0	79	28	35
Mean		4.74	12.7	37	285	0.2	11	26	9.83	19	0	76	3	2	0	78	27	35
10 mg/kg/day:																		
7363	M	5.04	13.6	40	214	0.2	11	24	8.41	34	0	60	4	2	0	79	27	34
7458	M	5.70	12.6	40	218	0.3	11	23	20.18	4	0	94	2	0	0	70	22	32
7328	F	5.47	13.4	40	219	0.3	11	23	10.72	33	0	51	11	5	0	73	24	34
7383	F	5.65	13.5	39	212	0.1	11	27	8.52	30	0	64	5	1	0	69	24	35
Mean		5.47	13.3	40	216	0.2	11	24	11.96	25	0	67	6	2	0	73	24	34
30 mg/kg/day:																		
7367	M	Died, week 7																
7455	M	3.84[a,b]	9.7	30	261	0.2	30	65	10.14	36	0	54	3	7	0	78	25	32
7382	F	Died, week 13																
7387	F	Died, week 12																
Mean		3.84	9.7	30	261	0.2	30	65	10.14	36	0	54	3	7	0	78	25	32
100 mg/kg/day:																		
7361	M	Died, week 5																
7456	M	Died, week 2																
7335	F	Died, week 3																
7381	F	Died, week 4																

[a] 2+ Poikilocytosis

[b] 2 Nucleated erythrocytes/100 leucocytes

[c] The differential leucocyte means have been adjusted to equal 100%.

FC-143: Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 8. Means and Significance of Biochemical Values.

Biochemistry	Month of Study	Control	3 mg/kg/day	10 mg/kg/day	30 mg/kg/day
Glucose, mg/100 ml	1	89	117*	104	122
	3	81	96	88	66[a]
B.U.N., mg/100 ml	1	23.0	21.2	22.5	26.1
	3	27.6	20.2	22.0	22.6[a]
Alk. Phos., int'l units/l	1	597	847	601	365*
	3	851	783	743	360[a]
S.G.O.T., int'l units/l	1	29	35	34	59**
	3	45	41	35	88[a]
S.G.P.T. int'l units/l	1[b]	15	21	34*	44
	3[c]	31	31	34	46[a]
Cholesterol, mg/100 ml	1	165	154	158	174
	3	165	141	154	240[a]
Total Protein, g/100 ml	1	7.94	8.23	8.66	8.36
	3	8.21	8.24	8.43	5.52[a]
Albumin, g/100 ml	1	4.78	5.05	4.66	4.28
	3	4.82	5.12	5.17	2.00[a]
Sodium, meq/liter	1	153	152	155	152
	3	151	154	159**	150[a]
Potassium, meq/liter	1	5.1	5.1	5.2	5.7
	3	5.5	5.6	6.0	5.9[a]
Chloride, meq/liter	1	112	110	113	112
	3	113	112	114	113[a]
γ-G.T.P., Sigma units/ml	1	61	49	47	33
	3	44	38	51	49[a]
C.P.K., Sigma units/ml	1	9	14	16	19*
	3	7	6	9	10[a]
Inorganic Phosphate, mg/100 ml	1	7.9	7.2	7.0	6.7
	3	6.9	6.3	7.3	5.0[a]

*Significantly different from control group, $p<0.05$.
**Significantly different from control group, $p<0.01$.
[a]Value not used in statistical analysis due to only one animal surviving.
[b]I.U./l
[c]Sigma units/ml

FC-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 9.

Individual Biochemical Values - Control 1.

Group, Monkey Number	Sex	Glucose mg/100 ml	B.U.N. mg/100 ml	Alk. Phos. int'l units/l	S.G.O.T. int'l units/l	S.G.P.T. int'l units/l	Cholesterol mg/100 ml	Total Protein g/100 ml	Albumin g/100 ml	Sodium meq/l	Potassium meq/l	Chloride meq/l	Inorganic Phosphate mg/100 ml	γ-G.T.P. Sigma u/ml	Creatinine Phosphokinase Sigma u/ml
Control:															
7362	M	94	41.0	780	40	99	219	8.68	5.40	160	5.0	111	6.5	67	15
7365	M	82	16.7	659	61	88	123	9.50	4.30	155	5.3	110	6.7	44	18
7336	F	79	24.0	915	30	80	185	9.52	5.30	156	4.3	110	6.5	41	85
7386	F	85	21.0	960	39	86	190	8.52	5.12	162	5.0	111	6.5	37	16
Mean		85	25.7	829	43	88	179	9.06	5.03	158	4.9	111	6.6	47	34
3 mg/kg/day:															
7364	M	111	19.0	880	42	94	197	9.08	5.28	155	4.3	108	5.0	50	12
7366	M	71	28.7	580	60	89	172	9.12	5.80	157	4.9	108	7.1	30	26
7384	F	96	22.0	570	38	106	133	10.12	5.19	162	6.0	113	6.1	32	16
7385	F	107	22.0	1320	60	76	154	8.72	4.80	158	5.2	116	5.4	41	29
Mean		96	22.9	838	50	91	164	9.26	5.27	158	5.1	111	5.9	38	21
10 mg/kg/day:															
7363	M	89	27.2	1167	46	118	237	9.84	5.10	167	6.2	117	6.7	78	16
7458	M	180	24.2	806	63	136	107	10.08	3.99	150	4.9	107	7.7	55	14
7328	F	98	20.0	776	26	75	189	8.48	5.14	157	4.4	109	6.3	51	34
7383	F	98	27.3	581	31	91	168	8.32	5.25	159	5.1	112	6.0	59	64
Mean		116	24.7	833	42	105	175	9.18	4.87	158	5.2	111	6.7	61	32
30 mg/kg/day:															
7367	M	108	26.9	970	47	114	150	9.38	5.60	170	6.2	116	6.9	65	15
7455	M	110	24.0	687	37	86	205	9.50	5.31	163	5.3	111	6.6	59	9
7382	F	132	27.9	641	40	79	176	11.10	5.72	165	5.5	112	6.8	43	18
7387	F	117	23.8	978	45	138	194	9.44	5.60	155	3.9	113	5.4	39	16
Mean		117	25.7	819	42	104	181	9.86	5.56	163	5.2	113	6.4	52	15
100 mg/kg/day:															
7361	M	93	29.0	598	43	80	155	8.60	5.00	159	5.9	116	6.9	64	17
7456	M	100	23.0	799	40	104	202	9.00	5.69	157	4.5	109	5.7	44	22
7335	F	75	28.0	570	40	96	151	8.98	5.19	157	5.2	111	5.6	58	20
7381	F	119	22.1	1233	40	103	124	9.60	4.89	159	5.2	112	6.7	47	10
Mean		97	25.5	800	41	96	158	9.05	5.19	158	5.2	112	6.2	53	17

001746

137-090

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 10.

Individual Biochemical Values - 1 Month.

Group, Monkey Number	Sex	Glucose mg/100 ml	B.U.N. mg/100 ml	Alk. Phos. int'l units/l	S.G.O.T. int'l units/l	S.G.P.T. int'l units/l	Cholesterol mg/100 ml	Total Protein g/100 ml	Albumin g/100 ml	Sodium meq/l	Potassium meq/l	Chloride meq/l	Inorganic Phosphate mg/100 ml	γ-G.T.P. Sigma u/ml	Creatinine Phosphokinase Sigma u/ml
Control:															
7362	M	87	33.9	611	27	18	191	7.30	4.82	153	5.4	117	6.6	81	8
7365	M	84	14.2	626	33	17	121	8.40	4.11	153	5.4	111	8.4	50	11
7336	F	87	23.9	672	25	15	142	7.90	4.89	148	4.2	109	8.4	68	7
7386	F	96	14.9	480	31	10	206	8.15	5.30	158	5.4	112	8.1	44	11
Mean		89	23.0	597	29	15	165	7.94	4.78	153	5.1	112	7.9	61	9
3 mg/kg/day:															
7364	M	112	18.0	970	30	36	173	8.15	5.20	150	4.3	106	6.9	77	4
7366	M	131	23.3	693	39	19	148	8.05	5.42	154	4.9	110	6.6	26	7
7384	F	105	24.2	539	30	15	141	8.70	4.85	152	5.8	111	7.5	47	39
7385	F	120	19.1	1185	40	13	153	8.00	4.72	152	5.2	114	7.8	47	7
Mean		117	21.2	847	35	21	154	8.23	5.05	152	5.1	110	7.2	49	14
10 mg/kg/day:															
7363	M	98	24.9	552	40	35	219	9.40	4.62	161	6.3	118	6.9	65	7
7458	M	97	22.5	732	40	43	134	9.05	4.32	151	4.9	109	8.4	44	20
7328	F	98	22.7	640	23	19	145	8.20	4.50	152	4.3	111	5.4	37	24
7383	F	124	20.0	480	31	37	132	8.00	5.19	154	5.2	113	7.2	43	14
Mean		104	22.5	601	34	34	158	8.66	4.66	155	5.2	113	7.0	47	16
30 mg/kg/day:															
7367	M	112	35.2	376	48	30	180	8.20	4.70	157	6.0	110	6.6	40	25
7455	M	86	21.0	322	61	80	177	8.55	3.22	148	5.2	112	6.9	40	16
7382	F	104	25.2	400	83	43	161	8.15	4.21	149	5.9	111	6.0	28	17
7387	F	185	22.8	360	45	23	179	8.55	5.00	153	5.6	114	7.2	24	18
Mean		122	26.1	365	59	44	174	8.36	4.28	152	5.7	112	6.7	33	19
100 mg/kg/day:															
7361	M	Died, week 5													
7456	M	Died, week 2													
7335	F	Died, week 3													
7381	F	Died, week 4													

FC-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 11. Individual Biochemical Values - 3 Months.

Group, Monkey Number	Sex	Glucose mg/100 ml	B.U.N. mg/100 ml	Alk. Phos. int'l units/l	S.G.O.T. int'l units/l	S.G.P.T. Sigma units/ml	Cholesterol mg/100 ml	Total Protein g/100 ml	Albumin g/100 ml	Sodium meq/l	Potassium meq/l	Chloride meq/l	Inorganic Phosphate mg/100 ml	γ-G.T.P. Sigma u/ml	Creatinine Phosphokinase Sigma u/ml
Control:															
7362	M	95	41.9	804	55	44	197	7.59	4.99	150	5.5	114	5.6	37	7
7365	M	77	17.4	744	47	30	135	9.18	4.40	151	6.1	113	8.0	53	8
7336	F	67	33.1	786	39	24	150	8.31	4.98	151	5.1	114	7.3	42	7
7386	F	86	18.1	1068	39	27	177	7.76	4.90	153	5.1	109	6.7	45	6
Mean		81	27.6	851	45	31	165	8.21	4.82	151	5.5	113	6.9	44	7
3 mg/kg/day:															
7364	M	106	17.1	1092	41	28	164	7.72	5.09	153	5.8	112	7.0	45	7
7366	M	111	18.1	594	39	33	126	8.09	5.52	153	5.5	109	5.3	51	6
7384	F	94	23.4	432	39	33	132	8.93	4.91	153	5.2	112	6.5	27	6
7385	F	74	22.0	1014	43	29	142	8.21	4.97	155	6.0	114	6.4	29	6
Mean		96	20.2	783	41	31	141	8.24	5.12	154	5.6	112	6.3	38	6
10 mg/kg/day:															
7363	M	87	24.9	936	42	42	194	8.44	5.61	164	7.0	119	8.0	43	7
7458	M	88	21.1	936	38	31	139	9.71	4.69	159	6.2	112	9.0	52	12
7328	F	75	21.8	624	30	25	155	7.93	5.27	156	4.8	110	5.6	60	7
7383	F	100	20.0	474	30	37	128	7.62	5.11	158	5.8	113	6.5	48	9
Mean		88	22.0	743	35	34	154	8.43	5.17	159	6.0	114	7.3	51	9
30 mg/kg/day:															
7367	M	Died, week 7													
7455	M	66	22.6	360	88	46	240	5.52	2.00	150	5.9	113	5.0	49	10
7382	F	Died, week 13													
7387	F	Died, week 12													
Mean		66	22.6	360	88	46	240	5.52	2.00	150	5.9	113	5.0	49	10
100 mg/kg/day:															
7361	M	Died, week 5													
7456	M	Died, week 2													
7335	F	Died, week 3													
7381	F	Died, week 4													

TABLE 12. Means and Significance of Urinalysis Values.

Urinalysis	Month of Study	Control	3 mg/kg/day	10 mg/kg/day	30 mg/kg/day
Volume, ml	1	35	33	51	41
	3	71	94	51	40[a]
pH	1	8.5	8.5	8.1	8.1
	3	8.3	7.6	8.2	6.6[a]
Specific Gravity	1	1.028	1.026	1.026	1.026
	3	1.018	1.015	1.024	1.031[a]

[a]Value not used in statistical analysis due to only one animal surviving.

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 13.

Individual Urinalysis Values - Control 1.

Group, Monkey Number	Sex	Volume ml	Color and Appear.	pH	Spec. Grav.	Protein	Glucose	Occult Blood	Ketones	Leuco-cytes	Erythro-cytes	Epi. Cells	Urates	Triple Phos.	Cal. Oxal.	Uric Acid Crystals	Bacteria	Casts
Control:																		
7362	M	100	LS-cl	7.6	1.010	N	N	tr	N	-	occ	occ	F	occ	-	-	M	-
7365	M	28	LS-cl	7.2	1.037	N	N	N	N	-	1-3	occ	F	occ	-	-	N	-
7336	F	27	LS-C	7.0	1.036	N	N	N	1+	-	-	-	occ	occ	occ	-	F	-
7386	F	70	LS-cl	8.4	1.023	N	N	4+	N	-	-	occ	occ	occ	M	-	M	-
Mean		56		7.6	1.027													
3 mg/kg/day:																		
7364	M	25	LS-cl	7.8	1.032	N	N	tr	N	-	-	occ	F	F	F	-	M	-
7366	M	25	LS-cl	7.2	1.035	N	N	tr	N	-	-	occ	F	occ	occ	-	M	-
7384	F	215	LS-C	8.3	1.026	N	N	N	N	-	-	occ	occ	occ	-	-	M	-
7385	F	35	LS-cl	8.3	1.020	N	N	N	N	-	-	occ	F	occ	-	-	M	-
Mean		75		7.9	1.028													
10 mg/kg/day:																		
7363	M	20	LS-cl	7.7	1.020	N	N	tr	N	-	-	occ	F	F	-	-	M	-
7458	M	50	LS-cl	7.5	1.036	N	N	tr	N	-	-	occ	F	occ	F	-	M	-
7328	F	35	LS-cl	7.8	1.036	N	N	tr	N	-	-	1-3	F	occ	M	-	F	-
7383	F	35	LS-cl	8.2	1.020	N	N	3+	N	-	-	occ	occ	occ	-	-	F	-
Mean		35		7.8	1.028													
30 mg/kg/day:																		
7367	M	20	LS-cl	7.1	1.050	N	N	tr	N	-	1-3	1-3	occ	occ	occ	-	M	-
7455	M	35	LS-cl	6.8	1.030	N	N	tr	N	-	1-3	1-3	occ	F	-	-	M	-
7382	F	20	LS-cl	7.0	1.055	N	N	N	N	-	-	1-3	F	occ	-	-	F	-
7387	F	48	LS-cl	8.2	1.030	N	N	N	N	-	-	occ	F	occ	occ	-	M	-
Mean		31		7.3	1.041													
100 mg/kg/day:																		
7361	M	21	LS-cl	7.6	1.035	N	N	tr	N	-	occ	-	F	occ	-	-	M	-
7456	M	25	LS-cl	7.1	1.042	N	N	tr	3+	-	-	occ	F	occ	F	-	M	-
7335	F	25	LS-cl	7.2	1.041	N	N	tr	1+	-	1-3	-	occ	occ	F	-	F	-
7381	F	40	LS-cl	8.1	1.042	N	N	1+	1+	-	-	1-3	occ	occ	M	-	F	-
Mean		28		7.5	1.040													

Code:

tr - Trace
1+ - Trace to slight
2+ - Slight to moderate
3+ - Moderate
4+ - Marked

S - Straw
LS - Light Straw
DS - Dark Straw
LAm - Light Amber
DAm - Dark Amber
cl - Cloudy
C - Clear

N - Negative
F - Few
L - Loaded
M - Many
R - Rare
occ - Occasional

QNS - Quantity not sufficient
norm - Normal
- None seen

FC-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 14.

Individual Urinalysis Values - 1 Month.

Group, Monkey Number	Sex	Volume ml	Color and Appear.	pH	Spec. Grav.	Protein	Glucose	Occult Blood	Ketones	Leuco-cytes	Erythro-cytes	Epi. Cells	Urates	Triple Phos.	Cal. Oxal.	Uric Acid Crystals	Bacteria	Casts
Control:																		
7362	M	55	LS-C	8.5	1.021	N	N	N	N	-	occ	-	occ	occ	M	-	M	-
7365	M	35	LS-C	8.5	1.028	N	N	N	N	-	-	-	occ	F	occ	-	M	-
7336	F	20	LS-C	8.5	1.033	N	N	3+	N	-	-	1-3	F	F	F	-	M	-
7386	F	30	LS-C	8.5	1.030	N	N	tr	N	-	-	occ	M	F	M	-	M	-
Mean		35		8.5	1.028													
3 mg/kg/day:																		
7364	M	20	LS-C	8.8	1.019	N	N	N	N	-	-	occ	F	M	occ	-	M	-
7366	M	20	LS-C	8.5	1.036	N	N	N	N	-	-	occ	F	F	F	-	M	-
7384	F	40	DS-cl	8.0	1.021	1+	N	4+	2+	-	8-12	-	F	occ	F	-	M	-
7385	F	50	LS-cl	8.5	1.027	N	N	N	N	-	-	occ	F	occ	M	-	M	-
Mean		33		8.5	1.026													
10 mg/kg/day:																		
7363	M	65	LS-cl	7.5	1.023	N	N	N	N	-	occ	-	F	occ	M	-	M	-
7458	M	35	LS-C	8.0	1.028	N	N	N	N	-	-	-	occ	occ	M	-	M	-
7328	F	55	LS-cl	8.5	1.026	N	N	N	N	-	-	1-3	occ	occ	M	-	M	-
7383	F	50	LS-cl	8.5	1.028	N	N	tr	N	-	occ	occ	F	occ	M	-	M	-
Mean		51		8.1	1.026													
30 mg/kg/day:																		
7367	M	30	LS-C	7.5	1.024	N	N	N	N	-	-	occ	occ	occ	-	-	L	-
7455	M	30	LS-cl	8.0	1.026	N	N	N	N	-	occ	occ	M	F	-	-	M	-
7382	F	60	LS-cl	8.3	1.022	N	N	N	N	-	occ	-	F	F	-	-	M	-
7387	F	45	LS-cl	8.5	1.032	N	N	N	N	-	-	occ	F	occ	occ	-	M	-
Mean		41		8.1	1.026													
100 mg/kg/day:																		
7361	M	Died, week 5																
7456	M	Died, week 2																
7335	F	Died, week 3																
7381	F	Died, week 4																

Code:
tr - Trace
1+ - Trace to slight
2+ - Slight to moderate
3+ - Moderate
4+ - Marked

S - Straw
LS - Light Straw
DS - Dark Straw
LAm - Light Amber
DAm - Dark Amber
cl - Cloudy
C - Clear

N - Negative
F - Few
L - Loaded
M - Many
R - Rare
occ - Occasional

QNS - Quantity not sufficient
norm - Normal
- None seen

FC-143:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 15.

Individual Urinalysis Values - 3 Months.

Group, Monkey Number	Sex	Volume ml	Color and Appear.	pH	Spec. Grav.	Protein	Glucose	Occult Blood	Ketones	Leuco-cytes	Erythro-cytes	Epi. Cells	Urates	Triple Phos.	Cal. Oxal.	Uric Acid Crystals	Bacteria	Casts
Control:																		
7362	M	110	LS-C	8.2	1.012	N	N	N	N	-	-	occ	F	occ	-	-	M	-
7365	M	40	LS-cl	8.1	1.029	N	N	N	1+	-	occ	1-3	F	F	-	-	M	-
7336	F	85	LS-C	8.2	1.015	N	N	N	tr	-	-	occ	F	occ	F	-	M	-
7386	F	50	LS-C	8.8	1.016	N	N	3+	N	occ	-	occ	F	F	F	-	M	-
Mean		71		8.3	1.018													
3 mg/kg/day:																		
7364	M	50	LS-C	6.0	1.020	N	N	N	tr	-	-	-	F	occ	-	-	M	-
7366	M	150	LS-C	7.9	1.007	N	N	N	N	-	-	occ	F	occ	-	-	M	-
7384	F	125	LS-C	8.1	1.010	N	N	N	N	-	-	occ	F	F	F	-	M	-
7385	F	50	LS-C	8.5	1.021	N	N	tr	N	-	occ	1-3	M	F	M	-	M	-
Mean		94		7.6	1.015													
10 mg/kg/day:																		
7363	M	40	LS-C	8.0	1.027	N	N	N	N	-	-	occ	F	occ	occ	-	M	-
7458	M	35	LS-cl	8.7	1.022	N	N	N	N	-	-	-	F	occ	-	-	M	-
7328	F	50	LS-C	9.0	1.029	N	N	N	N	-	occ	occ	F	occ	-	-	M	-
7383	F	80	LS-cl	7.0	1.019	N	N	N	N	-	occ	occ	F	F	-	-	M	-
Mean		51		8.2	1.024													
30 mg/kg/day:																		
7367	M	Died, week 7																
7455	M	40	S-C	6.6	1.031	N	N	1+	N	1-3	occ	-	F	M	occ	-	M	-
7382	F	Died, week 13																
7387	F	Died, week 12																
Mean		40		6.6	1.031													
100 mg/kg/day:																		
7361	M	Died, week 5																
7456	M	Died, week 2																
7335	F	Died, week 3																
7381	F	Died, week 4																

Code: tr - Trace
1+ - Trace to slight
2+ - Slight to moderate
3+ - Moderate
4+ - Marked

S - Straw
LS - Light Straw
DS - Dark Straw
LAm - Light Amber
DAm - Dark Amber
cl - Cloudy
C - Clear

N - Negative
F - Few
L - Loaded
M - Many
R - Rare
occ - Occasional

QNS - Quantity not sufficient
norm - Normal
- None seen

FC-143: Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 16. Summary of Gross Necropsy Observations, Terminal Sacrifice.

Site Lesion	Group, Monkey Number	0 mg/kg/day				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day				100 mg/kg/day			
		M	M	F	F	M	M	F	F	M	M	F	F	M*	M	F*	F*	M*	M*	F*	F*
		7362	7365	7136	7386	7364	7366	7384	7385	7363	7458	7328	7183	7367	7455	7382	7387	7361	7436	7335	7381
No Gross Lesions				x			x														
External																					
swelling, eye area															x						
alopecia																	x				
denydrated																	x				
emaciated																	x				
red vaginal discharge																	x				
scab, facial area																	x				
Lung																					
mite lesion		x	x		x		x		x		x	x	x	x		x	x				
adhesions			x						x		x		x		x						
dark red foci/reddish purple area							x					x							x		x
yellow, white foci														x					x		
nodules																		x			
Heart																					
hemorrhage, subendocardial																			x	x	
gelatinized fat, endocardial																				x	
atrophy																					x
Lymph Nodes																					
enlarged			x																		
reddish black in color																			x		
Thymus																					
atrophy															x						
Abdominal Cavity																					
depletion of fat																					x
Stomach																					
dark red foci											x				x		x				
erosion, mucosa, pyloric portion													x								
mucosal hyperemia														x							
yellowish gelatinous material, fundic portion															x						
hemorrhage, fundic mucosa																	x				
ulcers																			x		
Small Intestine																					x
greenish-gray mucoid material																					
dark red/brown mucoid material															x						
liquid, blood tinged fluid																	x				
reddish brown in color																		x			
congestion, mucosa																		x			
hemorrhage, mucosa																			x		
Large Intestine																					x
congestion, mucosa														x							
hemorrhage, mucosa																	x				
dark reddish black foci																	x		x		
semi solid, blood stained contents																		x			
																			x		

*Died on Study

137-090

FC-143: Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 16. Cont. Summary of Gross Necropsy Observations.

Site Lesion	Group, Monkey Number	0 mg/kg/day				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day				100 mg/kg/day			
		M	M	F	F	M	M	F	F	M	M	F	F	M*	M	F*	F*	M*	M*	F*	F*
		7362	7365	7336	7386	7364	7366	7384	7385	7363	7458	7328	7383	7167	7455	7382	7387	7361	7456	7335	7381
Pancreas																					
accessory spleen									x												
Liver																					
cyst																					
brownish color												x									
accentuated lobulations															x						
granular surface															x				x		
yellowish mottling															x						
reddish yellow color																x					
																			x		
Kidneys																					
brownish discoloration															x						
Skin																					
subcutaneous edema, abdomen																x					
subcutaneous hemorrhage, abdomen																			x		

*Died on Study

137-090

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 17. Absolute (Grams) and Relative (% Body Weight) Organ Weights, Terminal Sacrifice and Deaths.

Group, Monkey Number	Sex	Body Wt. kg	Spleen g	Spleen %	Liver g	Liver %	Adrenals g	Adrenals %x10	Kidneys g	Kidneys %	Testes/ Ovaries g	Testes/ Ovaries %x10^2
Terminal Sacrifice:												
Control:												
7362	M	3.25	2.35	0.07	70.73	2.18	0.65	0.20	11.82	0.36	0.85	0.03
7365	M	3.85	7.87	0.20	79.15	2.06	0.71	0.18	17.06	0.44	3.23	0.08
Mean		3.55	5.11	0.14	74.94	2.12	0.68	0.19	14.44	0.40	2.04	0.06
7336	F	3.40	5.03	0.15	84.79	2.49	-	-	13.80	0.41	0.28	0.82
7386	F	3.50	3.87	0.11	77.77	2.22	0.62	0.18	19.58	0.56	0.27	0.77
Mean		3.45	4.45	0.13	81.28	2.36	0.62[a]	0.18[a]	16.69	0.48	0.28	0.80
3 mg/kg/day:												
7364	M	4.10	4.67	0.11	91.40	2.23	0.77	0.19	19.76	0.48	3.66	0.09
7366	M	2.65	1.87	0.07	63.17	2.38	0.82	0.31	12.40	0.47	0.85	0.03
Mean		3.38	3.27	0.09	77.29	2.31	0.80	0.25	16.08	0.47	2.26	0.06
7384	F	3.70	6.82	0.18	102.64	2.77	0.78	0.21	17.60	0.48	0.18	0.49
7385	F	3.45	2.94	0.09	67.25	1.95	0.55	0.16	14.44	0.42	0.16	0.46
Mean		3.58	4.88	0.13	84.95	2.36	0.67	0.19	16.02	0.45	0.17	0.48
10 mg/kg/day:												
7363	M	3.80	2.39	0.06	87.25	2.30	0.74	0.19	16.84	0.44	1.75	0.05
7458	M	3.25	4.91	0.15	82.30	2.53	0.67	0.21	16.54	0.51	1.99	0.06
Mean		3.53	3.65	0.11	84.78	2.41	0.71	0.20	16.69	0.48	1.87	0.05
7328	F	3.55	4.06	0.11	83.00	2.34	0.66	0.19	15.32	0.43	0.29	0.82
7383	F	3.70	3.99	0.11	85.35	2.31	0.86	0.23	13.56	0.37	0.39	1.05
Mean		3.63	4.03	0.11	84.18	2.32	0.76	0.21	14.44	0.40	0.34	0.94
30 mg/kg/day[a]:												
7455	M	2.40	3.50	0.15	70.76	2.95	0.84	0.35	16.85	0.70	1.16	0.05
Deaths:												
30 mg/kg/day:												
7367	M	2.10	1.45	0.07	75.33	3.59	1.63	0.78	16.34	0.78	1.94	0.09
7382	F	2.25	3.01	0.13	112.87	5.02	1.74	0.77	19.03	0.85	0.21	0.93
7387	F	2.25	1.97	0.09	85.17	3.79	1.20	0.53	15.96	0.71	0.32	1.42
100 mg/kg/day:												
7361	M	2.40	1.65	0.07	79.02	3.29	1.59	0.66	21.88	0.91	1.37	0.06
7456	M	2.70	1.76	0.07	85.08	3.15	1.45	0.54	14.77	0.55	0.71	0.03
7335	F	2.05	2.49	0.12	74.28	3.62	1.03	0.50	15.40	0.75	0.10	0.51
7381	F	2.60	3.05	0.12	82.58	3.18	1.16	0.45	18.28	0.70	0.13	0.50

Group mean relative organ weights shown in this table were calculated by averaging the individually calculated relative organ weights.

*Significantly different from Control group mean, $p<0.05$.

**Significantly different from Control group mean, $p<0.01$.

[a]Not included in analysis.

- = Not available

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 17. Cont. Absolute (Grams) and Relative (% Body Weight) Organ Weights, Terminal Sacrifice and Deaths.

Group, Monkey Number	Sex	Body Wt. kg	Heart g	Heart %	Thyroid/ Parathyroid g	Thyroid/ Parathyroid %x10	Brain g	Brain %	Pituitary g	Pituitary %x10²
Terminal Sacrifice:										
Control:										
7362	M	3.25	11.69	0.36	1.050	0.32	87.04	2.68	0.053	0.16
7365	M	3.85	18.17	0.47	0.296	0.08	90.39	2.35	0.063	0.16
Mean		3.55	14.93	0.42	0.673	0.20	88.72	2.51	0.058	0.16
7336	F	3.40	15.30	0.45	-	-	82.64	2.43	0.050	0.15
7386	F	3.50	14.75	0.42	0.839	0.24	81.55	2.33	0.073	0.21
Mean		3.45	15.03	0.44	0.839[a]	0.24[a]	82.10	2.38	0.062	0.18
3 mg/kg/day:										
7364	M	4.10	18.90	0.46	0.893	0.22	96.01	2.34	0.080	0.20
7366	M	2.65	12.70	0.48	0.378	0.14	83.50	3.15	0.051	0.19
Mean		3.38	15.80	0.47	0.636	0.18	89.76	2.75	0.066	0.19*
7384	F	3.70	16.87	0.46	0.694	0.19	78.66	2.13	0.086	0.23
7385	F	3.45	15.19	0.44	0.543	0.16	80.21	2.32	0.053	0.15
Mean		3.58	16.03	0.45	0.619	0.17	79.44	2.23	0.070	0.19
10 mg/kg/day:										
7363	M	3.80	15.10	0.40	1.211	0.32	77.73	2.05	0.063	0.17
7458	M	3.25	14.14	0.44	0.488	0.15	83.38	2.57	0.047	0.14
Mean		3.53	14.62	0.42	0.850	0.23	80.56	2.31	0.055	0.16
7328	F	3.55	11.85	0.33	0.461	0.13	77.19	2.17	-	-
7383	F	3.70	11.69	0.32	0.537	0.15	75.88	2.05	0.071	0.19
Mean		3.63	11.77*	0.32**	0.499	0.14	76.54**	2.11	0.071[a]	0.19[a]
30 mg/kg/day[a]:										
7455	M	2.40	10.50	0.44	0.292	0.12	75.01	3.13	0.049	0.20
Deaths:										
30 mg/kg/day:										
7367	M	2.10	10.39	0.49	0.532	0.25	82.27	3.92	0.068	0.32
7382	F	2.25	11.93	0.53	0.543	0.24	83.22	3.70	0.070	0.31
7387	F	2.25	10.21	0.45	0.845	0.38	91.45	4.06	0.057	0.25
100 mg/kg/day:										
7361	M	2.40	14.54	0.61	0.791	0.33	92.43	3.85	0.072	0.30
7456	M	2.70	15.55	0.58	0.718	0.27	95.42	3.53	0.046	0.17
7335	F	2.05	11.44	0.56	0.479	0.23	74.28	3.62	0.056	0.27
7381	F	2.60	12.95	0.50	0.417	0.16	86.20	3.32	0.082	0.32

Group mean relative organ weights shown in this table were calculated by averaging the individually calculated relative organ weights.

*Significantly different from Control group mean, p 0.05.

**Significantly different from Control group mean, p<0.01.

[a]Not included in analysis.

- = Not available

FC-143: Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 18. Microscopic Observations.

Tissue Lesion	Group, Sex Monkey Number	Control M 7362	Control M 7365	Control F 7336	Control F 7386	3 mg/kg/day M 7364	3 mg/kg/day M 7366	3 mg/kg/day F 7384	3 mg/kg/day F 7385	10 mg/kg/day M 7363	10 mg/kg/day M 7458	10 mg/kg/day F 7328	10 mg/kg/day F 7383	30 mg/kg/day M 7455	30 mg/kg/day M 7367*	30 mg/kg/day F 7382*	30 mg/kg/day F 7387*	100 mg/kg/day M 7456*	100 mg/kg/day M 7361*	100 mg/kg/day F 7335*	100 mg/kg/day F 7381*
Brain		1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1	1	1	1
focal perivascular lymphoid infiltrates											3										
Spinal cord		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Peripheral nerve		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Eye		1		1	1	1	1						1		1	1	1	1	1		1
Sarcocystis sp. in ocular muscle			x					x												x	
focal lymphoid infiltrates in sclera												3									
focal lymphoid infiltrates in lacrimal gland									3					3							
focal lymphoid infiltrate in palpebral conjunctiva										3	3										
cystic tarsal gland											3										
Pituitary		1	1	1	1	1	1	1	1	1		1	1	1		1			1		
diffuse congestion															3		3	3		3	3
small parenchymal cyst											x										
Thyroid		1	1	1		1		1	1	1	1	1	1	1	1				1	1	
foci of interstitial lymphoid infiltrates					3		2										2				
focal interstitial fibrosis					3												2				
diffuse congestion															3			3			3
Parathyroid		1	1	1	1	1	1	-	-	-	-	-	-	-	1	-	-		-	-	1
diffuse congestion																		3			
Tongue		1								1			1			1	1	1	1		
foci of inflammatory cell infiltrates in lamina propria and mucosal epithelium			3	3	4	2	3	2	3		3	3		2	2					2	2
foci of inflammatory cell infiltrates in muscle			2					3			3	2		2						2	
Sarcocystis sp.								x				x									

Code: x - condition present; a - autolyzed; 1 - not remarkable; 2 - very slight; 3 - slight; 4 - moderate; 5 - marked; 6 - extreme; - = not available; *Died or sacrificed in extremis

FC-143: Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 15. Cont. Microscopic Observations.

Tissue Lesion	Group, Sex, Monkey Number	Control				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day				100 mg/kg/day			
		M 7362	M 7365	F 7336	F 7386	M 7364	M 7366	F 7384	F 7385	M 7363	M 7458	F 7328	F 7383	M 7455	M 7367*	F 7382*	F 7387*	M 7456*	M 7361*	F 7335*	F 7381*
Tonsil						1								-		1		-	-	-	
foci of inflammatory cell infiltrates in mucosal epithelium and tonsillar crypt		3	4	2	3		4	3	3	3	3	4	4		2		3				4
Sarcocystis sp. in muscle			x																		
Gongylonema sp. in mucosal epithelium					x												4				4
atrophy of lymphoid follicles																					
Adrenal							1														
foci of dystrophic mineralization		3	3	2	2	3		2			3	2	2					2			
diffuse congestion															3	4	3	3		4	3
diffuse lipid depletion															5	5	5	5	5	5	5
foci of lymphoid infiltrates in sinusoids				3		2		2	3	3	3		2								
acidophilic degeneration of individual to small groups of cells														2			3				
Trachea			1												1		1	1	1		
foci of inflammatory cell infiltrates in lamina propria		3		3	3	3	2	2	3	3	3	3	2	2		3				3	3
Salivary gland				1		1				1									1	1	
focal interstitial lymphoid infiltrates		2	3		2		3	4	3		2	2	3	3		2	3				
diffuse congestion															3	3		3			3
decreased cell size, loss of cytoplasmic granules															4			4			
Lung																					
acarian pigment (peribronchial, peribronchiolar, perivascular)		3	2	2	2	3	2	2	2	2	2	3	2	3	2	2	4	2		2	2
focal perivascular lymphoid infiltrates						3					3	3									
focal peribronchial/peribronchiolar lymphoid aggregates		4	4	3	4	3	3	4	3	3	4	4	3	3		2	2			3	3
lung mite in bronchiolar lumen		x			x																
interstitial pneumonia		3	4		4	3		3	4	3			3	4		4			3		
diffuse congestion															3	3	3	4			
foreign body pneumonia			5						5												
focal hemorrhage			3														5				
acute focal bronchopneumonia		4				3					4							3			
numerous aggregates of pigment laden alveolar macrophages																					

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137-090

FC-143: Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 18. Cont. Microscopic Observations.

Tissue Lesion	Group, Sex, Monkey Number	Control				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day				100 mg/kg/day			
		M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
		7362	7365	7336	7386	7364	7366	7384	7385	7363	7458	7328	7383	7455	7367*	7382*	7387*	7456*	7361*	7335*	7381*
Heart			1			1				1	1		1	1		1			1		
focal interstitial lymphoid infiltrates		3		3	3		2	3	3						3			2		2	
focus of lymphoid infiltrate in endocardium												3						3			
focal subendocardial hemorrhage																	4			4	4
atrophy of epicardial fat																					
Aorta		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Spleen		1	1	1	1	1	1	1	1	1	1										
atrophy of lymphoid follicles												3	3	4	4	4	4	4	4	4	4
diffuse congestion														3	3	4	3	4	4	3	4
focal amyloidosis in lymphoid follicles																				3	
increased amount of hemosiderin pigment																	3				
Lymph node		1		1	1	1	1	1	1	1	1	1	1	1	1						
atrophy of lymphoid follicles																	4	4	4	4	4
increased amount of hemosiderin pigment			3															3			
neutrophil infiltrate in sinuses																3			3	5	
diffuse congestion																3					3
lymphoid hyperplasia			3																		
Esophagus		1			1		1									1		1		1	1
foci of inflammatory cell infiltrates in lamina propria			3	2		2		3	2		3	2	2	3	2		2		2		
foci of interstitial lymphoid infiltrates in muscularis			2					2			2	2	2								
Gongylonema sp. in mucosal epithelium										x											
Stomach																					
foci of inflammatory cell infiltrate in lamina propria		3	4	3	3	3	3	4	4	4	3	4	3	3				3	3	2	4	3
diffuse congestion												2			3	3					3	
foci of inflammatory cell infiltrates in submucosa						4				4		4	3								
foci of inflammatory cell infiltrates in muscularis								3			3										
foci of inflammatory cell infiltrates in serosa											3										
parasitic granuloma in omentum											x										
focal mucosal hemorrhage												2		2						2	
focal coagulation necrosis in mucosa																				3	

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137-090

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TABLE 18. Cont. Microscopic Observations.

Tissue Lesion	Group, Sex Monkey Number	Control M 7362	Control M 7365	Control F 7336	Control F 7386	3 mg/kg/day M 7364	3 mg/kg/day M 7366	3 mg/kg/day F 7384	3 mg/kg/day F 7385	10 mg/kg/day M 7363	10 mg/kg/day M 7458	10 mg/kg/day F 7328	10 mg/kg/day F 7383	30 mg/kg/day M 7455	30 mg/kg/day M 7367*	30 mg/kg/day F 7382*	30 mg/kg/day F 7387*	100 mg/kg/day M 7456*	100 mg/kg/day M 7361*	100 mg/kg/day F 7335*	100 mg/kg/day F 7381*
Small intestine		1	1	1	1	1	1	1	1	1	1	1	1	1							
diffuse villous atrophy																		5	5		
focal hemorrhage															3				3	3	
diffuse congestion															3	3	3			3	x
focal aggregate of brown pigment-laden foamy macrophages in mesentery																					
inflammatory cell infiltrates in serosa																		4			
atrophy of lymph nodule															4			4		4	
Cecum		1	1	-	1	1	1	1	1		1	1	1					1			1
transmural inflammatory cell infiltrates																			4		
diffuse congestion															3	3	3		3	3	
focal mucosal hemorrhage															2				2	4	
inflammatory cell infiltrates in serosa										2											
parasitic granuloma in muscularis														x							
atrophy of lymph nodule																	4			4	
Colon		1	1	1	1	1	1	1	1	1	1	1	1	1							1
diffuse congestion															3	3	3		3	3	
parasitic granuloma in submucosa																		x			
transmural inflammatory cell infiltrates																		4			
focal mucosal hemorrhage															3						
atrophy of lymph nodule																	4			4	
Rectum		1	1	1	1	1	1	1	1	1	1	1	1	1				-	1		1
diffuse congestion															3	3	3			3	
inflammatory cell infiltrates in muscularis																				3	
atrophy of lymphoid nodule																	4			4	
Pancreas		1	1				1			1		1	1					a	1	1	a
focal periductal lymphoid infiltrates				3	2	3		3			3			2							
focal interstitial lymphoid infiltrates								3	2												
diffuse congestion														3	3	3					
Thymus		1	1	1	1	1	1	1	1	1	1	1	1	-	-	-	-	-	-	-	-

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TABLE 18. Cont. Microscopic Observations.

Tissue Lesion	Group, Sex Monkey Number	Control M 7362	Control M 7365	Control F 7336	Control F 7386	3 mg/kg/day M 7364	3 mg/kg/day M 7366	3 mg/kg/day F 7384	3 mg/kg/day F 7385	10 mg/kg/day M 7363	10 mg/kg/day M 7458	10 mg/kg/day F 7328	10 mg/kg/day F 7383	30 mg/kg/day M 7455	30 mg/kg/day M 7367*	30 mg/kg/day F 7382*	30 mg/kg/day F 7387*	100 mg/kg/day M 7456*	100 mg/kg/day M 7361*	100 mg/kg/day F 7335*	100 mg/kg/day F 7381*
Liver																					
portal inflammatory cell infiltrates		3	3	3	3			3	2	3	3	2	2		2				1		
parenchymal inflammatory cell infiltrates		2	2	2	3	3	3	3	3	3	3	2			4	3	3	3		3	2
diffuse congestion																				3	3
acidophilic degeneration of individual to small groups of hepatocytes									3								3				
diffuse hepatocellular hypertrophy with cytoplasmic vacuolation														3		3					
neutrophil infiltrates in sinusoids														3							
Gallbladder																					
foci of inflammatory cell infiltrates in lamina propria		3	3	4	3	3	2	2	3	2	3	3	3	1	a	a	a	a	a	1	a
Kidney																					
focal interstitial lymphoid infiltrates		2	2		2	3	3	4	2	2	3	2	3	2		2	2		2	2	
multinucleated lining epithelium in papillary ducts			x	x				x					x								
cyst in medulla			x																		
chronic interstitial nephritis				3																	
diffuse congestion															4	3	3	3	3	3	3
microlith in renal tubules																		x			
small foci of dystrophic mineralization				2										2			2		2	2	
Urinary bladder																					
foci of inflammatory cell infiltrates in lamina propria		3	2	3	2	2	3	2	3	3	3	1	1	1	1		1		1		
diffuse congestion																3		3		3	3
Testes																					
prepuberal development		x	x			x	x			x	x			x	x			x	x		
chronic focal vasculitis			4																		
focal perivascular lymphoid infiltrate											2										
Ovaries																					
small foci of dystrophic mineralization				1			1	1			1	1				1			1	1	
diffuse congestion			2												2						
															3						

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TABLE 18. Cont. Microscopic Observations.

Tissue Lesion	Group, Sex	Control				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day				100 mg/kg/day			
	Monkey Number	M 7362	M 7365	F 7336	F 7386	M 7364	M 7366	F 7384	F 7385	M 7363	M 7458	F 7328	F 7383	M 7455	M 7367*	F 7382*	F 7387*	M 7456*	M 7361*	F 7335*	F 7381*
Prostate																					
focal interstitial lymphoid infiltrates		3	3			2	3			2	3			2	1			1	-		
focal lymphoid infiltrate in corpus cavernosum			3				2			2				3							
Uterus																					
diffuse congestion												1	1				1				
blood in uterine glands				2	2			2								3				3	3
small foci of hemorrhage in endometrium				2	2			3								2				2	
brown pigment-laden macrophages in endometrium									3												
inflammatory cell infiltrates in endometrium				3	2			4	2												
proteinaceous fluid and inflammatory cells in uterine lumen																				3	
Vagina																					
foci of lymphoid infiltrates in lamina propria and mucosal epithelium				3	4			3	3			4	4			2	3			2	5
foci of lymphoid infiltrates in muscularis					2				2				3								3
Sarcocystis sp.							x														
focal lymphoid infiltrate in tunica adventitia							3														
diffuse congestion																3					
focal neutrophil infiltrate in mucosa												3									
Skeletal muscle		1		1	1	1	1			1		1									
Sarcocystis sp.			x					x	x						x				1		
focal interstitial inflammatory cell infiltrates			3				4	2		3		2								x	
interstitial fibrosis															4		4				3
focal/multifocal atrophy of muscle														4		4		4			4
increased sarcolemmal nuclei															3						
Skin																					
brown/black pigment in dermis		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
dermal inflammatory cell infiltrates			2				3	3													
diffuse acanthosis		3		3																	
diffuse congestion																					
hyperkeratosis					3	3		3		3	3			3	3	3		3			
few large areas of hemorrhage in subcutis							3											5		3	3

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TABLE 18. Cont. Microscopic Observations.

	Control				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day				100 mg/kg/day			
	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
Tissue / Lesion	7362	7365	7336	7386	7364	7366	7384	7385	7363	7458	7328	7383	7455	7367*	7382*	7387*	7456*	7361*	7335*	7381*
Mammary gland																				
brown pigment in dermis	x	x		x	x			1												
hyperkeratosis	3		3	3	3	3	3		x	x 3	x		x 3	x 3	 3	x	x	x	x	x
dermal inflammatory cell infiltrates			3	3	2		3		3		3	3	2							
inflammatory exudate in acinar lumen/ducts		2		2												2				
inflammatory cell infiltrates in intralobular connective tissue		3							2									3		
diffuse congestion													x							
intraepidermal microabscess																				
Femur	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	1	1	1	1	1
Bone marrow (Rib junction)	1	1	1	1	1	1	1	1	1	1	1	1								
hypocellular marrow													3	4 3	4 3	3 4	4 3	4 3	4 4	4 3
congestion																				
Miscellaneous																				
acute focal cheilitis, lip																4				

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