

International Research and Development Corporation

OT-28

VIII

SPONSOR: 3M Company
COMPOUND: Fluorad® Fluorochemical Surfactant FC-95
SUBJECT: Ninety-Day Subacute Rhesus Monkey
Toxicity Study.



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137-092

**Exhibit
1191**

State of Minnesota v. 3M Co.,
Court File No. 27-CV-10-28862

3MA10065004

1191.0001

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I. SYNOPSIS

Fluorad® Fluorochemical Surfactant FC-95 was administered by gavage to rhesus monkeys at dosage levels of 0, (distilled water only) 0.5, 1.5 and 4.5 mg/kg/day for 90 days. Two male and two female monkeys were initiated at each dosage level and also in the control group. The monkeys were observed twice daily for general physical appearance, behavior and pharmacotoxic signs. Body weights were recorded weekly. Hematological and biochemical studies and urinalysis were conducted once in the control period and at the end of the first and third month of the study.

The monkeys treated at the 4.5-mg/kg/day dosage level died or were sacrificed in extremis between week 5 and 7 of the study. These monkeys exhibited signs of toxicity in the gastrointestinal tract (anorexia, emesis, black stool and dehydration) from the first or second day of study. All the high-dose monkeys had decreased activity and before death showed marked to severe rigidity, convulsions, generalized body trembling, prostration and loss of body weight. The mean body weight decreased from 3.44 kg at the beginning of the study to 2.70 kg at week 5 of study. At 1 month of study all monkeys at the 4.5-mg/kg/day dosage level had decreased serum cholesterol values and serum alkaline phosphatase activity.

All monkeys at the 1.5-mg/kg/day dosage level survived to the end of the study. The monkeys exhibited slightly decreased activity from the first week of the study which occasionally became moderate to marked. Monkeys at the 1.5-mg/kg/day dosage level occasionally had black stools, diarrhea, mucous in the stool and bloody stool and exhibited dehydration or general body trembling at the end of study. The monkeys from this group had a slight decrease in mean body weight.

In the laboratory tests, there was a decrease in the alkaline phosphatase activity and the concentration of inorganic phosphate in the serum at 3 months of study.

All monkeys at the 0.5-mg/kg/day dosage level survived to the end of the study. Monkeys at this dosage level exhibited an occasional soft stool, diarrhea, anorexia and emesis. Slightly decreased activity was noted in three monkeys at this dosage level. At 3 months of study a slight decrease in the serum alkaline phosphatase activity was noted.

No gross or microscopic pathological lesions which were considered compound-related were seen in tissues other than the adrenals, pancreas, and submandibular salivary glands of male and female rhesus monkeys at the 4.5-mg/kg/day dosage level. Microscopically, the adrenals from male and female monkeys at the 4.5-mg/kg/day dosage level had compound-related marked diffuse lipid depletion; the pancreas from male and female monkeys at the 4.5-mg/kg/day dosage level had compound-related moderate diffuse atrophy of exocrine cells; the submandibular salivary glands from male and female monkeys had compound-related moderate diffuse atrophy of the serous alveolar cells.

No statistically significant variations in sex group mean weights of organs occurred between the control and experimental groups.

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II. COMPOUND

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

<u>Label</u>	<u>Description</u>
Fluorad® Fluorochemical Surfactant FC-95 3-M Stock No. 98-0207-0103-7 Lot 640 Net wt. 5 lbs. 2,2 kg.	white powder

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III. CLINICAL STUDIES

A. METHOD:

1. General Procedure:

Eight male (weighing from 2.55 to 3.55 kg) and eight female (weighing from 2.70 to 3.75 kg) rhesus monkeys were initiated in this study. The monkeys were purchased from Primate Imports, Port Washington, New York. The monkeys were housed individually in hanging wire mesh "squeeze-type" cages and maintained in a temperature-, humidity- and light-controlled environment. 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 also were conducted twice during the treatment period. Complete physical examinations were conducted by the staff veterinarian prior to initiation of compound administration. Only monkeys in good health were selected.

This study was initiated on February 16, 1978. Terminal sacrifices were conducted on May 17, 1978.

2. Compound Administration:

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

<u>Dosage Level</u> <u>(mg/kg/day)</u>	<u>Number of Monkeys</u>	
	<u>Male</u>	<u>Female</u>
0 (Control)	2	2
0.5	2	2
1.5	2	2
4.5	2	2

The monkeys in the control group were previously employed as the control group in an aborted 90 day study in monkeys on FC-95 (study 137-087). The test compound suspended in distilled water, was administered 7 days a week by gavage. All doses were given in the same volume of water. This volume of distilled water was given to the 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, behavior and pharmacotoxic signs. Individual body weights were recorded weekly. General physical examinations were conducted in the control period and monthly during the study. Food consumption was estimated.

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: hemoglobin¹, hematocrit², erythrocyte count³, total³ and differential leucocyte counts, reticulocyte count⁴, platelet count⁵, prothrombin time⁶ and activated partial thromboplastin time⁷ (APTT). Mean corpuscular hemoglobin, mean corpuscular volume and mean corpuscular hemoglobin concentration were calculated.

b. Biochemistry:

Biochemical studies included: the determinations of fasting blood glucose⁸, blood urea nitrogen⁸, the activities of serum alkaline phosphatase⁸, serum glutamic oxalacetic

transaminase⁸, and serum glutamic pyruvic transaminase⁸, and the concentrations of cholesterol⁹, total protein⁹, albumin⁸, sodium¹⁰, potassium¹⁰, chloride⁹, inorganic phosphate⁹, as well as the activities of γ -glutamyl transpeptidase¹¹ and creatinine phosphokinase¹².

c. Urinalysis:

Urinalysis included: measurement of volume, pH¹³ and specific gravity; description of color and appearance; qualitative tests for protein¹³, glucose¹³, ketones¹³, occult blood¹³ and microscopic examination of the sediment.

d. Statistical Analysis:

All statistical analyses compared the treatment groups with the control group, by sex.

Body weights (week 13), percent change in body weights between control period and 1, 2 and 3 months (sexes combined), hematological, biochemical and urinalysis parameters (months 1 and 3) and absolute and relative organ weights (terminal sacrifice) were compared by analysis of variance (one-way classification), Bartlett's test for homogeneity of variances and the appropriate t-test (for equal or unequal variances) as described by Steel and Torrie¹⁴ using Dunnett's¹⁵ multiple comparison tables to judge significance of differences.

B. RESULTS:

1. General Behavior, Appearance and Survival:

There was no mortality in the control, 0.5- and 1.5-mg/kg/day dosage levels. Three monkeys at the 4.5-mg/kg/day dosage level died between week 5 and 6 of the study. The fourth monkey from this group was sacrificed in extremis in week 7 of the study.

a. Control:

The monkeys from this group showed an occasional soft stool or diarrhea (slight to severe). For one day Monkey 7358 had

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bloody diarrhea, anorexia and slight ataxia and for 3 days Monkey 7368 had anorexia. Emesis was noted rarely.

b. 0.5 mg/kg/day:

Monkeys 7466 and 7504 exhibited occasional diarrhea or soft stools. For Monkeys 7463 and 7483 the soft stools and diarrhea were frequent with occasional appearance of mucus in the stools. On one occasion bloody mucus in the stool and in the refuse pan was observed for Monkey 7483. Occasional anorexia and emesis were noted for Monkeys 7463, 7466 and 7504. Similarly, a slight intermittent decrease in activity was noted for Monkeys 7463, 7483 and 7504.

c. 1.5 mg/kg/day:

All monkeys at this dosage level exhibited a slight decrease in activity during the first week of study. For Monkey 7501 the decreased activity frequently was noted throughout the study and by week 13 had become moderate. Although no emesis, soft stools and diarrhea were noted for this monkey, slight general body trembling and mucus in the stool was observed in week 12, as well as slight dehydration in weeks 12 and 13. For Monkey 7501 and 7500 anorexia became persistent during weeks 12 and 13. For Monkey 7500 diarrhea and soft stool appeared along with mucus in the stool at week 2, black stool at week 8 and slight dehydration in week 12. This monkey exhibited "bruising" around the right eye followed by "bruising" around both eyes at week 12.

For Monkey 7486 occasional soft stool and diarrhea were observed along with anorexia which became persistent in week 10. During weeks 10 and 11 slight dehydration was also noted. Monkey 7462 had occasional soft stool, emesis for 1 day each in weeks 1 and 3 and the decreased activity was observed in week 1 only.

d. 4.5 mg/kg/day:

At 4.5 mg/kg/day the monkeys showed apparent signs of toxicity in the gastrointestinal tract from the first to the second day of the study (anorexia and partial anorexia, emesis, black stool and/or dehydration from slight to moderate). All had decreased activity from slight to severe. Before death they showed marked to severe rigidity, convulsions, moderate generalized body trembling and finally prostration. Monkey 7485 had petechial hemorrhages on the skin of the inguinal area, thorax and face and Monkey 7484 had pale gums after week 3 of the study.

2. Body Weights (Table 1):

Changes in the body weights were similar for monkeys in the control and at the 0.5-mg/kg/day dosage level. The male monkeys in the 1.5-mg/kg/day dosage level had a decrease in their body weight from 3.15 kg at the beginning of the study to 2.93 kg at the end of the study and from 3.22 kg to 2.75 kg for the female monkeys. The change in body weight for this group of monkeys was not statistically significant from the control group.

The monkeys at the 4.5-mg/kg/day dosage level showed a loss of the body weight after 2 weeks of the study. Their average body weight decreased from 3.44 kg at the beginning of the study to 3.23 kg (week 2) - 3.13 kg (week 3) - 2.97 kg (week 4) - 2.70 kg (week 5) for both sexes. At week 6 and 7 of the study they died. There was no statistical evaluation of the body weights for monkeys at the 4.5-mg/kg/day dosage level, because they were not alive at week 13, when the statistics were done.

3. Laboratory Tests (Tables 2-13):

a. One Month of the Study:

At 1 month of study there were no pathological changes in values for monkeys from the control and 0.5-mg/kg/day dosage level.

At the 1.5-mg/kg/day dosage level only Monkey 7501 had a slight decrease in the erythrocytes which was recovered in the third month of study.

Both the male and female monkeys at the 4.5-mg/kg/day dosage level had low values for serum cholesterol which were statistically significance.

Monkey 7484 had a decreased alkaline phosphatase activity (312 unit/l), serum potassium (3.6 meq/liter) and chloride concentration (102 meq/liter) and Monkey 7503 also had low serum chloride concentration (102 meq/liter).

Although the S.G.O.T. activity of male Monkeys 7484 and 7485 was in the highest expected normal range (115 units) the differences between these values and that of the control were not statistically significant.

The only unusual changes in the urinalysis were the appearance of glucose from Monkey 7500 (1.5 mg/kg/day) and from Monkeys 7485 and 7503 (4.5 mg/kg/day). However, these monkeys had no pathological increase of the blood glucose.

b. Three Months of the Study:

There was a statistically significant decrease in the serum alkaline phosphatase activity for the male monkeys at the 0.5-mg/kg/day dosage level and for two Monkeys, 7500 and 7501, at the 1.5-mg/kg/day dosage level. These latter monkeys also had a decreased values of serum potassium concentrations. Monkey 7501 at 1.5-mg/kg/day had very low serum cholesterol and Monkey 7500 at 1.5-mg/kg/day had a slight decrease in the inorganic phosphate (4.2 mg/100 ml) concentration.

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 animals in the control and treatment groups. The following tissues were examined:

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

and any other tissue(s) with lesions

*Phencyclidine HCl - BioCaotic Laboratories, Inc.,
St. Joseph, Missouri.

B. RESULTS:

1. Gross Pathology (Table 14) and Organ Weights (Table 15):

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

No statistically significant variations in sex group mean weights of organs occurred between the control and experimental groups.

2. Histopathology (Table 16):

All male and female monkeys at the 4.5 mg/kg/day dosage level had marked diffuse lipid depletion in the adrenals. One male and two females at the 4.5 mg/kg/day dosage level had moderate diffuse atrophy of the pancreatic exocrine cells. The lesion consisted of decreased cell size and loss of zymogen granules. Two male and one female monkeys at the 4.5 mg/kg/day dosage level had moderate diffuse atrophy of the serous alveolar cells characterized by decreased cell size and loss of cytoplasmic granules. These microscopic findings were considered compound-related.

No microscopic changes which were considered compound-related were seen in the adrenals, pancreas or submandibular salivary glands in male and female monkeys at the 0.5 and 1.5 mg/kg/day dosage levels. No microscopic lesions in tissues other than the adrenals, pancreas and submandibular salivary glands of male and female monkeys at the 4.5 mg/kg/day dosage level were considered compound-related.

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PC-95: Ninety-Day Subacute Rheum Monkey Toxicity Study.

TABLE 1. Individual Body Weights, Kilograms.

Group, Monkey Number	Sex	Control		Study Weeks												
		-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Control:																
73755	M	3.20	3.20	3.25	3.15	3.25	3.25	3.15	3.10	3.20	3.30	3.40	3.40	3.45	3.35	3.55
73758	M	3.65	3.55	3.65	3.30	3.30	3.45	3.50	3.70	3.70	3.60	3.90	3.90	4.10	3.90	3.75
73768	F	3.10	3.10	3.15	3.10	3.20	3.20	3.10	3.20	3.15	3.05	3.25	3.30	3.45	3.25	3.15
73772	F	3.55	3.65	3.60	3.35	3.80	3.85	3.80	3.90	4.10	4.10	4.35	4.40	4.70	4.30	4.20
Mean		3.38	3.38	3.41	3.23	3.39	3.44	3.39	3.53	3.54	3.51	3.73	3.75	3.93	3.70	3.66
0.5 mg/kg/day:																
7463	M	2.40	2.55	2.55	2.40	2.50	2.60	2.40	2.50	2.55	2.55	2.70	2.65	2.55	2.60	2.65
7483	M	3.50	3.55	3.45	3.40	3.50	3.60	3.55	3.55	3.65	3.55	3.65	3.65	3.75	3.70	3.55
7466	F	3.20	3.40	3.25	3.35	3.35	3.50	3.50	3.70	3.70	3.60	3.70	3.80	3.65	3.65	3.55
7504	F	3.25	3.15	3.10	3.10	3.20	3.30	3.15	3.20	3.30	3.20	3.40	3.40	3.35	3.35	3.35
Mean		3.09	3.16	3.09	3.06	3.14	3.25	3.15	3.24	3.30	3.23	3.36	3.38	3.33	3.33	3.28
1.5 mg/kg/day:																
7462	M	2.70	2.90	2.70	2.60	2.70	2.75	2.70	2.70	2.80	2.80	2.90	3.05	3.00	2.95	2.80
7486	M	3.40	3.40	3.15	3.30	3.15	3.30	3.10	3.20	3.20	3.30	3.35	3.40	3.30	3.25	3.05
7500	F	3.85	3.75	3.75	3.45	3.45	3.40	3.30	3.35	3.40	3.30	3.45	3.40	3.50	3.35	3.20
7501	F	2.75	2.70	2.55	2.45	2.50	2.55	2.50	2.55	2.55	2.50	2.55	2.50	2.50	2.45	2.30
Mean		3.18	3.19	3.04	2.95	2.95	3.00	2.90	2.95	2.99	2.98	3.06	3.09	3.08	3.00	2.84
4.5 mg/kg/day:																
7484	M	3.45	3.30	3.15	3.25	2.90	2.55	2.20	2.15*	Died						
7485	M	3.25	3.20	3.30	3.00	3.00	2.75	2.50*	Died							
7502	F	3.50	3.50	3.55	3.20	3.25	3.25	3.10	3.10	2.70	2.65*	Died				
7503	F	3.80	3.75	3.80	3.45	3.35	3.35	2.80	2.55*	Died						
Mean		3.50	3.44	3.45	3.23	3.13	2.98	2.70	3.10	2.70	Died					

*Terminal weight not included in mean.

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FC-95:

Ninety-Day Subacute Rhesus Monkey Toxicity Study.

TABLE 2.

MALES: Means and Significance of Hematological Values.

Hematology	Study Month	Control	0.5 mg/kg/day	1.5 mg/kg/day	4.5 mg/kg/day
Erythrocytes, 10 ⁶ /cmm	Control	4.93	5.36	5.04	5.47
	1	4.67	4.81	4.66	4.71
	3	4.63	4.84	4.45	-
Hemoglobin, g/100 ml	Control	12.3	12.7	12.3	13.7
	1	12.4	13.8	13.2	12.8
	3	12.3	12.4	11.6	-
Hematocrit, %	Control	35	38	37	39
	1	37	37	37	37
	3	39	39	36	-
Platelets, 10 ³ /cmm	Control	129	140	114	180
	1	181	226	161	177
	3	205	226	223	-
Reticulocytes, %	Control	0.5	0.9	0.6	1.0
	1	0.3	0.3	0.2	0.2
	3	0.2	0.3	0.1	-
Prothrombin Time, sec	Control	11	11	11	11
	1	11	12	11	12
	3	12	11	11	-
Activated P.T.T., sec	Control	29	28	29	26
	1	24	25	24	29
	3	25	22	28	-
Leucocytes, 10 ³ /cmm	Control	7.03	10.29	8.22	6.39
	1	10.59	10.41	8.39	11.37
	3	8.67	7.06	9.04	-
MCV, μ ³	Control	71	70	73	71
	1	79	77	80	78
	3	84	80	81	-
MCH, μg	Control	25	24	25	25
	1	27	29	28	27
	3	27	26	26	-
MCHC, g/100 ml	Control	36	34	34	36
	1	34	37	36	35
	3	32	33	32	-

- = Not available

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FC-95:

Ninety-Day Subacute Rhesus Monkey Toxicity Study.

TABLE 2. Cont.

FEMALES: Means and Significance of Hematological Values.

Hematology	Study Month	Control	0.5 mg/kg/day	1.5 mg/kg/day	4.5 mg/kg/day
Erythrocytes, $10^6/\text{cmm}$	Control	5.66	5.56	5.11	5.08
	1	5.02	4.56	3.95	5.00
	3	4.71	4.79	4.37	-
Hemoglobin, g/100 ml	Control	13.1	12.6	12.5	11.3
	1	14.1	13.4	12.0	12.9
	3	12.0	12.2	11.7	-
Hematocrit, %	Control	39	38	34	35
	1	40	38	35	37
	3	38	39	37	-
Platelets, $10^3/\text{cmm}$	Control	176	164	164	182
	1	151	177	158	194
	3	232	236	229	-
Reticulocytes, %	Control	0.4	0.8	0.3	0.8
	1	0.2	0.1	0.2	0.1
	3	0.1	0.1	0.1	-
Prothrombin Time, sec	Control	11	10	11	11
	1	11	11	11	12
	3	12	11	11	-
Activated P.T.T., sec	Control	27	27	26	27
	1	27	27	25	28
	3	25	29	27	-
Leucocytes, $10^3/\text{cmm}$	Control	7.39	10.31	8.81	12.71
	1	8.77	7.82	9.14	11.28
	3	4.62	9.09**	6.84*	-
MCV, μ^3	Control	68	69	67	68
	1	79	82	88	75
	3	81	81	85	-
MCH, μg	Control	23	23	25	23
	1	28	30	31	26
	3	26	26	27	-
MCHC, g/100 ml	Control	34	33	37	34
	1	36	36	35	35
	3	32	31	32	-

*Significantly different from Control group mean, $p < 0.05$.**Significantly different from Control group mean, $p < 0.01$.

- = Not available

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3MA10065021

1191.0018

FC-95: Ninety-Day Subacute Rheus Monkey Toxicity Study.

TABLE 1. Individual Hematological Values - Control.

Group, Monkey Number	Sex	Erythro- cytes $10^6/\text{cmm}$	Hemo- globin g/100 ml	Hemato- crit %	Plate- lets $10^3/\text{cmm}$	Reticu- locytes %	Pro- thrombin Time sec	Activated P.T.T. sec	Leuco- cytes $10^3/\text{cmm}$	Seg. Seg.	Lympho- cytes %	Eosino- phils %	Mono- cytes %	Baso- phils %	MCV μ	MCH ng	MCHC g/100 ml
Control:																	
0.5 mg/kg/day:																	
7355	M	4.65	11.4	32	110	0.7	10	31	5.39	19	0	0	0	0	69	25	36
7358	M	5.20	13.2	38	147	0.2	11	27	8.66	13	0	0	0	0	71	25	35
7368	F	5.78	13.4	41	180	0.5	11	25	7.61	24	1	0	0	0	71	23	33
7372	F	5.53	12.7	36	172	0.3	11	28	7.17	12	0	0	0	0	65	23	35
Mean		5.29	12.7	37	152	0.4	11	28	7.21	17	0	0	0	0	70	24	35
1.5 mg/kg/day:																	
7463	M	5.38	12.7	37	131	0.5	10	27	9.73	58	0	0	0	0	69	24	34
7483	M	5.34	12.7	38	148	1.2	11	28	10.84	47	0	0	0	0	71	24	33
7466	F	5.64	13.2	39	157	1.2	10	29	9.61	20	0	0	0	0	69	21	34
7504	F	5.47	11.9	37	170	0.3	10	25	11.00	28	0	0	0	0	68	22	32
Mean		5.46	12.6	38	152	0.8	10	27	10.30	38	0	0	0	0	69	23	33
4.5 mg/kg/day:																	
7462	M	5.03	12.2	37	101	0.2	11	28	7.28	16	0	0	0	0	74	24	33
7486	M	5.04	12.4	36	126	0.9	11	29	9.15	22	0	0	0	0	71	25	34
7500	F	4.96	12.4	32	142	0.2	11	26	10.07	53	0	0	0	0	65	25	39
7501	F	5.25	12.5	36	186	0.3	11	26	7.54	34	0	0	0	0	69	24	35
Mean		5.07	12.4	35	139	0.4	11	27	8.51	31	0	0	0	0	70	25	35
4.5 mg/kg/day:																	
7484	M	5.40	12.9	36	197	0.8	11	27	6.72	20	0	0	0	1	67	24	36
7485	M	5.54	14.5	41	162	1.2	11	25	6.05	33	0	0	0	0	74	26	35
7502	F	5.27	12.7	35	191	0.5	10	25	13.89	34	0	0	0	1	66	24	36
7503	F	4.88	10.9	34	173	1.0	11	29	11.53	35	0	0	0	0	70	22	32
Mean		5.27	12.8	37	181	0.9	11	27	9.55	31	0	0	0	1	69	24	35

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FC-95: Ninety-Day Subacute Rhesus Monkey Toxicity Study.

TABLE 4.		Individual Hematological Values - 1 Month.															
Group, Monkey Number	Sex	Erythrocytes 10 ⁶ /mm	Hemoglobin g/100 ml	Hematocrit %	Platelets 10 ³ /mm	Reticulocytes %	Prothrombin Time sec	Activated P.T.T. sec	Leucocytes 10 ³ /mm	Seg. Non-Seg. %	Lymphocytes %	Eosinophils %	Monoocytes %	Basophils %	MCV μ l	MCH pg	MCHC g/100 ml
Control:																	
0.5 mg/kg/day:																	
7355	M	4.74	12.5	38	166	0.0	12	26	5.22	48	0	0	0	0	80	26	33
7358	M	4.60	12.3	36	196	0.5	10	21	15.95	61	0	0	0	0	78	27	34
7368	F	5.43	14.7	42	134	0.1	11	25	11.05	64	0	0	1	0	77	27	35
7372	F	4.60	13.4	37	168	0.2	11	28	6.48	23	0	0	0	0	80	29	36
Mean		4.84	13.2	38	166	0.2	11	25	9.68	49	0	0	0	0	79	27	35
1.5 mg/kg/day:																	
7463	M	4.92	14.0	37	220	0.2	11	26	10.52	65	0	0	0	0	75	28	38
7483	M	4.69	13.5	37	232	0.3	12	24	10.29	53	0	0	0	0	79	29	36
7466	F	4.74	14.0	39	222	0.0	11	24	7.42	37	0	0	0	0	82	30	36
7504	F	4.38	12.7	36	131	0.1	11	29	8.22	40	0	0	0	0	82	29	35
Mean		4.68	13.6	37	201	0.2	11	26	9.11	49	0	0	0	0	80	29	36
4.5 mg/kg/day:																	
7462	M	4.67	13.3	37	160	0.2	11	24	8.54	59	0	0	0	0	79	28	36
7486	M	4.64	13.1	37	161	0.2	11	24	8.23	47	0	0	1	0	80	28	35
7500	F	4.01	12.0	32	155	0.2	11	26	11.06	50	0	0	0	0	80	30	38
7501	F	3.89	12.0	37	160	0.1	11	23	7.21	48	0	0	0	0	95	31	32
Mean		4.30	12.6	36	159	0.2	11	24	8.76	51	0	0	0	0	84	29	35
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7484	M	4.66*	12.0	34	204	0.0	12	32	11.83	82	0	0	1	0	73	26	35
7485	M	4.76	13.5	39	149	0.4	11	26	10.90	66	0	0	1	0	82	28	35
7502	F	4.20	12.7	35	202	0.1	11	27	12.90	60	0	0	0	0	83	30	36
7503	F	5.80	13.0	38	186	0.1	12	29	9.66	62	0	0	0	0	66	22	34
Mean		4.86	12.8	37	185	0.2	12	29	11.32	68	0	0	1	0	76	27	35

At Anulocytosis

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EC-95: Ninety-Day Subacute Rheus Monkey Toxicity Study.

TABLE 5. Individual Hematological Values - 3 Months.

Group, Monkey Number	Sex	Erythro- cytes 10 ⁶ /cmm	Hema- globin g/100 ml	Hemato- crit %	Plate- lets 10 ³ /cmm	Reticu- locytes %	Pro- thrombin Time sec	Activated P.T.T. sec	Lenco- cytes 10 ³ /cmm	Neutrophils		Eosino- phils		Mono- cytes		Baso- phils		MCV μ ³	MCH mg	MCHC g/100 ml	
										Seg.	Non-Seg.	Seg.	Non-Seg.	Seg.	Non-Seg.	Seg.	Non-Seg.				
Control:																					
0.5 mg/kg/day:																					
7355	M	4.59	12.1	37	187	0.3	12	26	6.63	49	0	0	0	0	0	0	0	81	26	33	
7358	M	4.67	12.5	40	222	0.0	11	23	10.70	20	0	3	76	1	0	0	0	86	27	31	
7368	F	5.05	12.5	40	235	0.2	12	24	4.33	38	0	1	61	0	0	0	0	79	25	31	
7372	F	4.36	11.5	36	228	0.0	11	25	4.91	27	0	7	66	0	0	0	0	83	26	32	
Mean		4.67	12.2	38	218	0.1	12	25	6.64	34	0	3	63	0	0	0	0	82	26	32	
1.5 mg/kg/day:																					
7463	M	5.01	12.8	39	230	0.3	10	20	7.15	46	0	1	53	0	0	0	0	78	26	33	
7483	M	4.66	12.0	38	222	0.2	11	24	6.96	42	0	4	54	0	0	0	0	82	26	32	
7466	F	4.86	12.9	41	229	0.0	11	27	9.30	15	0	2	83	0	0	0	0	84	27	31	
7504	F	4.72	11.5	37	242	0.1	11	31	8.82	33	0	1	66	0	0	0	0	78	24	31	
Mean		4.81	12.3	39	231	0.2	11	26	8.06	34	0	2	64	0	0	0	0	81	26	32	
4.5 mg/kg/day:																					
7462	M	4.30	11.3	35	230	0.1	11	29	7.71	18	0	1	81	0	0	0	0	81	26	32	
7486	M	4.60	11.9	37	216	0.1	11	26	10.37	18	0	1	81	0	0	0	0	80	26	32	
7500	F	4.12	11.1	35	234	0.1	11	26	7.22	34	0	2	64	0	0	0	0	85	27	32	
7501	F	4.61	12.2	39	224	0.0	11	27	6.45	47	0	3	50	0	0	0	0	85	26	31	
Mean		4.41	11.6	37	226	0.1	11	27	7.94	29	0	2	69	0	0	0	0	83	26	32	
4.5 mg/kg/day:																					
7484	M	Died																			
7485	M	Died																			
7502	F	Died																			
7503	F	Died																			
Mean																					

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Ninety-Day Subacute Rhesus Monkey Toxicity Study.

TABLE 6.

MALES: Summary of Mean Biochemical Values.

Biochemistry	Study Month	Control	0.5 mg/kg/day	1.5 mg/kg/day	4.5 mg/kg/day
Glucose, mg/100 ml	Control	118	106	102	116
	1	96	92	115	99
	3	77	80	107	-
B.U.N., mg/100 ml	Control	23.7	29.8	31.4	19.6
	1	23.3	33.3	32.8	29.1
	3	28.2	26.5	19.6	-
Alkaline Phosphatase, int'l units/l	Control	1070	680	1035	1300
	1	1113	897	1110	564
	3	1095	747*	891	-
S.G.O.T., int'l units/l	Control	22	23	18	25
	1	56	49	54	115
	3	56	49	53	-
S.G.P.T., int'l units/l	Control	40	32	29	35
	1	42	27	38	27
	3	35	28	28	-
Cholesterol, mg/100 ml	Control	183	172	185	190
	1	198	200	213	87**
	3	162	152	122	-
Total Protein, g/100 ml	Control	8.38	8.74	8.68	8.90
	1	8.46	8.59	8.74	8.90
	3	7.85	8.07	8.38	-
Albumin, g/100 ml	Control	4.96	5.22	5.36	5.50
	1	4.75	5.17	5.22	5.31
	3	4.70	4.69	4.98	-
Sodium, meq/l	Control	150	156	156	160
	1	161	160	160	153
	3	153	151	150	-
Potassium, meq/l	Control	4.9	5.6	5.4	4.6
	1	4.9	4.6	4.7	4.7
	3	4.2	4.2	4.8	-
Chloride, meq/l	Control	112	114	116	113
	1	117	118	121	105
	3	112	110	111	-
Inorganic Phosphate, mg/100 ml	Control	6.8	6.4	6.0	6.4
	1	8.1	6.4	8.5	4.9*
	3	7.4	6.5	6.0	-
γ - Glutamyl Transpeptidase Sigma units/ml	Control	56	36	50	46
	1	42	45	55	26
	3	56	29	45	-
Creatinine Phosphokinase, Sigma units/ml	Control	25	44	11	13
	1	62	34	67	55
	3	20	40	40	-

*Significantly different from Control group mean, $p < 0.05$.**Significantly different from Control group mean, $p < 0.01$.

- = Not available

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3MA10065025

1191.0022

FC-95:

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TABLE 6. Cont.

FEMALES: Summary of Mean Biochemical Values.

Biochemistry	Study Month	Control	0.5 mg/kg/day	1.5 mg/kg/day	4.5 mg/kg/day
Glucose, mg/100 ml	Control	107	139	113	144
	1	163	98	119	154
	3	88	97	108	-
B.U.N., mg/100 ml	Control	23.6	22.0	20.7	22.4
	1	25.2	25.5	26.4	31.6
	3	28.7	21.5	22.6	-
Alkaline Phosphatase, int'l units/l	Control	1173	1013	770	875
	1	1092	942	753	615
	3	831	861	618	-
S.G.O.T., int'l units/l	Control	16	39	20	37
	1	46	55	45	75*
	3	36	36	27	-
S.G.P.T., int'l units/l	Control	23	42	32	37
	1	23	37	35	45
	3	29	27	34	-
Cholesterol, mg/100 ml	Control	180	208	204	176
	1	198	221	169	112*
	3	165	169	100	-
Total Protein, g/100 ml	Control	7.70	8.77	8.67	8.88
	1	7.66	8.47	8.63	8.82*
	3	7.49	8.02	8.47	-
Albumin, g/100 ml	Control	4.71	5.27	5.20	5.16
	1	4.86	5.41	5.42	5.39
	3	4.77	4.82	5.21	-
Sodium, meq/l	Control	156	158	157	159
	1	155	162	157	156
	3	152	151	149	-
Potassium, meq/l	Control	4.8	5.3	5.2	5.3
	1	4.7	5.1	3.8	4.3
	3	4.6	5.1	3.7	-
Chloride, meq/l	Control	111	112	115	116
	1	111	116	113	110
	3	113	111	109	-
Inorganic Phosphate, mg/100 ml	Control	6.4	7.5	5.4	6.4
	1	6.5	8.2	5.7	5.6
	3	6.5	7.3	4.7	-
γ - Glutamyl Transpeptidase Sigma units/ml	Control	38	50	43	34
	1	41	47	28	30
	3	32	40	30	-
Creatinine Phosphokinase, Sigma units/ml	Control	10	20	24	27
	1	50	39	31*	49
	3	5	10	7	-

*Significantly different from Control group mean, $p < 0.05$.**Significantly different from Control group mean, $p < 0.01$.

- = Not available

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1191.0023

PC-95; Ninety-day Subacute Rhesus Monkey Toxicity Study.

TABLE 7. Individual Biochemical Values - Control.

Group, Monkey Number	Sex	Glucose mg/100 ml	R.O.N. mg/100 ml	Alkaline Phosphatase int'l u/l	S.G.O.T. int'l u/l	S.G.P.T. int'l u/l	Choles- terol mg/100 ml	Total Protein g/100 ml	Albumin g/100 ml	Sodium meq/l	Potas- sium meq/l	Chlo- ride meq/l	Inorganic Phosphate mg/100 ml	γ - Glutamyl Transpeptidase Sigma u/ml	Creatinine Phos. Sigma u/ml
Control:															
<u>0.5 mg/kg/day:</u>															
7355	M	119	20.2	1050	46	24	192	8.65	4.92	153	5.4	115	7.1	51	38
7358	M	117	27.2	1090	33	21	174	8.11	5.00	148	4.4	110	6.6	61	12
7368	F	117	24.9	1170	23	18	155	8.09	4.93	158	5.4	111	6.6	39	18
7372	F	97	22.2	1175	23	14	204	7.30	4.49	153	4.2	111	6.2	37	2
Mean		113	23.6	1121	31	19	181	8.04	4.84	153	4.9	112	6.6	47	18
<u>1.5 mg/kg/day:</u>															
7463	M	123	26.5	635	33	29	182	7.94	4.96	149	4.4	111	5.2	35	81
7483	M	90	33.2	725	31	17	161	9.53	5.49	164	6.7	117	7.5	38	6
7466	F	121	19.1	1250	33	31	208	8.61	5.07	161	5.6	114	8.5	55	13
7504	F	156	24.9	775	51	46	208	8.93	5.46	155	5.0	109	6.4	44	27
Mean		123	25.9	846	37	31	190	8.75	5.25	157	5.4	113	6.9	43	32
<u>4.5 mg/kg/day:</u>															
7462	M	96	29.9	800	36	17	196	8.26	5.00	150	4.6	111	5.9	46	9
7486	M	109	32.9	1270	22	20	174	9.10	5.71	162	6.2	120	6.2	55	13
7500	F	116	18.4	1080	29	19	172	8.82	5.18	162	5.4	118	5.4	51	33
7501	F	109	22.9	460	34	21	236	8.52	5.22	151	4.9	112	5.3	34	14
Mean		108	26.0	903	30	19	195	8.68	5.28	156	5.3	115	5.7	47	17
<u>4.5 mg/kg/day:</u>															
7484	M	120	19.0	985	30	18	186	9.25	5.69	163	4.7	114	6.5	34	8
7485	M	112	20.2	1615	40	32	194	8.54	5.30	156	4.5	112	6.3	58	18
7502	F	137	23.6	965	36	22	182	8.90	5.17	160	5.0	116	6.7	33	36
7503	F	150	21.1	785	38	51	170	8.86	5.14	157	5.6	116	6.1	34	17
Mean		130	21.0	1088	36	31	183	8.89	5.33	159	5.0	115	6.4	40	20

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TABLE B.		Individual Biochemical Values - 1 Month.											
Group, Monkey Number	Sex	Glucose mg/100 ml	B.U.N. mg/100 ml	Alkaline Phosphatase Int'l u/l	S.G.O.T. S.G.P.T. Sigma u/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	Y - Glutamyl Transpeptidase Sigma u/ml
<u>Control:</u>													
<u>0.5 mg/kg/day:</u>													
7355	M	103	23.3	1146	40	39	212	8.36	5.19	164	5.0	119	8.9
7358	M	89	23.2	1080	72	45	184	8.55	4.30	157	4.7	114	7.3
7368	F	196	30.0	1158	51	25	188	8.13	5.16	157	5.0	109	6.7
7372	F	129	20.3	1026	41	20	208	7.19	4.55	152	4.3	113	6.2
Mean		129	24.2	1103	51	32	198	8.06	4.80	158	4.8	114	7.3
<u>1.5 mg/kg/day:</u>													
7463	M	82	30.8	924	58	31	208	8.06	5.36	159	4.5	121	5.8
7483	M	101	35.8	870	40	22	192	9.12	4.97	161	4.6	115	7.0
7486	F	100	24.1	1164	48	38	230	8.45	5.30	165	5.7	118	8.7
7504	F	96	26.9	720	61	36	211	8.48	5.51	158	4.5	113	7.7
Mean		95	29.4	920	52	32	210	8.53	5.29	161	4.8	117	7.3
<u>4.5 mg/kg/day:</u>													
7462	M	131	29.8	870	50	37	222	8.60	5.30	161	4.1	123	8.5
7486	M	98	35.8	1350	58	38	204	8.87	5.14	159	5.3	119	8.4
7500	F	125	23.9	816	40	39	154	8.55	5.15	159	3.9	113	6.1
7501	F	112	28.9	690	50	31	184	8.70	5.69	155	3.7	112	5.3
Mean		117	29.6	932	50	36	191	8.68	5.32	159	4.3	117	7.1
<u>4.5 mg/kg/day:</u>													
7484	M	97	35.0	312	115	21	76	8.11	5.02	154	3.6	102	4.6
7485	M	100	23.2	816	115	32	97	9.68	5.59	152	5.7	107	5.1
7502	F	172	26.2	564	80	54	128	8.90	5.69	163	4.2	118	6.3
7503	F	155	37.0	666	69	36	96	8.74	5.08	149	4.3	102	4.8
Mean		131	30.4	590	95	36	99	8.86	5.35	155	4.5	107	5.2

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PC-95; Ninety-Day Subacute Rhesus Monkey Toxicity Study.

TABLE 9.														
Individual Biochemical Values -- 3 Months.														
Group, Monkey Number	Sex	Glucose mg/100 ml	B.U.N. mg/100 ml	Alkaline Phosphatase Int'l u/l	S.G.O.T. Int'l u/l	S.G.P.T. Sigma u/ml	Choles- terol mg/100 ml	Total Protein g/100 ml	Albumin g/100 ml	Sodium meq/l	Potas- sium meq/l	Chlor- ide meq/l	Inorganic Phosphate mg/100 ml	Y - (Glutamy) Creatinine Phos. Sigma u/ml
Control:														
7355	M	83	34.1	1110	59	40	179	7.69	4.78	154	4.0	115	8.0	43
7358	M	70	22.3	1080	52	29	144	8.00	4.61	152	4.3	109	6.7	68
7368	F	112	26.9	876	33	29	144	7.68	5.01	152	4.4	110	5.8	36
7372	F	63	30.4	786	39	29	185	7.30	4.53	151	4.8	115	7.1	27
Mean		82	28.4	963	46	32	163	7.67	4.71	152	4.4	112	6.9	44
0.5 mg/kg/day:														
7463	M	83	22.8	690	42	26	160	7.62	4.97	152	4.2	111	5.8	40
7483	M	76	30.1	804	56	29	143	8.52	4.41	150	4.1	108	7.2	18
7466	F	106	18.1	978	32	27	178	8.11	4.80	153	5.5	110	8.4	38
7504	F	87	24.8	744	40	27	160	7.92	4.81	148	4.7	111	6.1	42
Mean		88	24.0	804	43	27	160	8.04	4.75	151	4.6	110	6.9	35
1.5 mg/kg/day:														
7462	M	92	15.2	816	82	35	132	8.51	4.85	149	5.0	112	6.8	46
7486	M	121	23.9	966	23	20	112	8.24	5.11	151	4.5	109	5.1	43
7500	F	106	17.7	690	22	33	113	8.81	4.98	150	3.4	109	4.2	35
7501	F	110	27.5	546	32	34	87	8.12	5.44	148	3.9	109	5.1	24
Mean		107	21.1	755	40	31	111	8.42	5.10	150	4.2	110	5.3	37
4.5 mg/kg/day:														
7484	M	Died												
7485	M	Died												
7502	F	Died												
7503	F	Died												
Mean														

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TABLE 10.

MALES: Summary of Mean Urinalysis Values.

Urinalysis	Study Month	Control	0.5 mg/kg/day	1.5 mg/kg/day	4.5 mg/kg/day
Volume, ml	Control	22	22	28	58
	1	30	25	40	38
	3	10	33	75	-
pH	Control	7.2	8.3	8.5	8.4
	1	6.4	5.5	5.9	6.4
	3	7.0 ^a	7.2 ^a	8.0 ^a	-
Specific Gravity	Control	1.032	1.027	1.030	1.034
	1	1.028	1.027	1.021	1.033
	3	1.034 ^a	1.033 ^a	1.024	-

^aSignificance not determined due to only one value in the Control group.

- = Not available

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3MA10065030

1191.0027

FC-95: Ninety-Day Subacute Rhesus Monkey Toxicity Study.

TABLE 10. Cont. FEMALES: Summary of Mean Urinalysis Values.

Urinalysis	Study Month	Control	0.5 mg/kg/day	1.5 mg/kg/day	4.5 mg/kg/day
Volume, ml	Control	32	53	20	30
	1	25	13	28	23
	3	80	30	40	-
pH	Control	8.1	7.9	8.3	8.8
	1	5.8	5.5	6.4	6.5
	3	8.0	9.0	8.0	-
Specific Gravity	Control	1.031	1.027	1.031	1.027
	1	1.032	1.032	1.028	1.036
	3	1.021	1.021	1.025	-

- = Not available

137-092

3MA10065031

1191.0028

PC-95: Ninety-Day Subacute Rheus Monkey Toxicity Study.

TABLE 11. Individual Urinalysis Values - Control.

Group, Monkey Number	Sex	Volume ml	Color and Appear.	Spec. Grav.	Protein	Glucose	Occult Blood	Re-tones	Leuco-cytes	Erythro-cytes	Epi. Cells	Urates	Triple Phos.	Cal. Ox. Crystals	Bac-teria	Casts
<u>Control:</u>																
<u>0.5 mg/kg/day:</u>																
7355	M	25	LS-cl	7.7	1.029	N	N	N	-	-	occ	F	F	-	M	-
7358	M	20	LS-cl	6.7	1.035	N	N	N	-	-	occ	occ	occ	-	F	-
7368	F	8	DS-cl	9.0	1.034	2+	3+	N	-	30+	1-3	F	occ	-	M	-
7372	F	55	LS-cl	7.2	1.028	N	N	N	-	1-3	occ	F	occ	-	M	-
<u>1.5 mg/kg/day:</u>																
7463	M	30	LS-cl	9.0	1.020	N	tr	N	-	-	-	F	occ	occ	M	-
7483	M	15	DS-cl	7.6	1.034	N	N	N	-	-	-	F	occ	-	M	-
7466	F	80	LS-cl	6.8	1.023	N	N	N	-	occ	occ	F	occ	-	M	-
7504	F	25	S-C	9.0	1.031	N	N	N	-	-	occ	occ	occ	-	F	-
<u>4.5 mg/kg/day:</u>																
7462	M	25	LS-cl	8.0	1.033	N	N	N	-	-	-	F	occ	-	M	-
7486	M	30	S-C	9.0	1.027	N	N	N	-	occ	-	F	occ	-	M	-
7500	F	30	S-C	7.7	1.024	N	tr	1+	-	occ	occ	F	occ	-	F	-
7501	F	10	S-C	8.8	1.037	N	N	N	-	-	occ	F	occ	-	F	-
<u>4.5 mg/kg/day:</u>																
7484	M	105	LS-cl	7.7	1.034	N	N	N	-	occ	occ	F	occ	-	F	-
7485	M	12	S-C	9.0	1.033	N	N	N	-	-	occ	F	occ	-	M	-
7502	F	30	LS-C	8.8	1.028	N	tr	1+	-	-	occ	F	occ	-	F	-
7503	F	30	LS-C	8.8	1.025	N	tr	N	-	-	occ	F	occ	-	M	-

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
 - - None seen

3MA10065032

1191.0029

FC-95: Ninety-Day Subacute Rheumatoid Monkey Toxicity Study.

TABLE 12. Individual Urinalysis Values - 1 Month.

Group, Monkey Number	Sex	Volume ml	Color and Appear.	pH	Spec. Grav.	Protein	Glucose	Blood	Occult	Ke- tones	Leuco- cytes	Rythro- cytes	Ep- cells	Urates	Triple Phos.	Cal. Ox.	Crystals	Uric Acid	Bac- teria	Casts
<u>Control:</u>																				
7355	M	25	LS-C	6.8	1.030	N	N	N	N	3+	1-3	occ	1-3	F	F	-	-	-	M	-
7358	M	35	LS-C1	6.0	1.025	N	N	N	N	3+	-	occ	1-3	F	occ	-	-	-	M	-
7368	F	15	S-C1	6.0	1.032	N	N	N	N	3+	3-5	-	occ	F	F	M	-	-	M	-
7372	F	35	S-C1	5.5	1.032	N	N	N	N	N	-	occ	-	M	F	occ	-	-	F	-
<u>0.5 mg/kg/day:</u>																				
7463	M	25	LS-C1	5.5	1.024	N	N	N	N	3+	-	-	occ	F	F	F	-	-	F	-
7463	M	25	LS-C1	5.5	1.029	N	N	N	N	3+	-	-	occ	F	occ	-	-	-	M	-
7466	F	6	LS-C1	5.5	1.028	N	N	N	N	3+	-	occ	1-3	F	F	M	-	-	M	-
7504	F	20	LS-C1	5.5	1.035	N	N	N	N	3+	-	-	occ	F	occ	M	-	-	F	-
<u>1.5 mg/kg/day:</u>																				
7462	M	30	LS-C	6.2	1.025	N	N	N	N	3+	-	1-3	-	F	F	-	-	-	F	-
7486	M	50	LS-C1	5.5	1.017	N	N	N	N	3+	-	-	occ	F	occ	-	-	-	F	-
7500	F	40	LS-C1	6.8	1.020	N	1+	N	N	N	occ	-	occ	F	occ	occ	-	-	M	-
7501	F	15	LS-C1	6.0	1.036	N	N	N	N	3+	occ	1-3	occ	P	occ	occ	-	-	M	-
<u>4.5 mg/kg/day:</u>																				
7484	M	40	LS-C1	6.5	1.030	N	N	N	N	N	-	occ	occ	F	F	-	-	-	F	-
7485	M	35	LS-C1	6.2	1.035	tr	1+	tr	tr	N	-	occ	-	M	F	-	-	-	M	-
7502	F	5	LS-C1	7.0	1.037	N	N	N	N	2+	-	-	1-3	F	F	-	-	-	M	-
7503	F	40	LS-C1	6.0	1.035	N	1+	3+	3+	2+	-	-	occ	F	occ	-	-	-	M	-

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 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
 - - None seen

FC-95: Ninety-day Subacute Rheus Monkey Toxicity Study.

TABLE 11. Individual Urinalysis Values - 3 Months.

Group, Monkey Number	Sex	Volume ml	Color and Appear.	pH	Spec. Grav.	Protein	Glucose	Blood	Occult	Ketones	Leuco-cytes	Erythro-cytes	Epi. Cells	Urates	Triple Phos.	Gal. Ox.	Uric Acid Crystals	Bacteria	Casts
<u>Control:</u>																			
7355	M	20	S-cl	7.0	1.034	N	N	N	N	4+	-	occ	8-10	F	occ	-	-	M	-
7358	M	0																	
7368	F	30	S-cl	7.5	1.026	N	N	N	N	4+	-	-	1-3	M	occ	F	-	M	-
7372	F	130	S-cl	8.5	1.016	2+	N	4+	4+	1+	1-3	occ	5-8	M	M	-	-	M	-
<u>0.5 mg/kg/day:</u>																			
7463	M	35	S-cl	7.3	1.028	N	N	N	N	1+	occ	occ	-	M	occ	M	-	M	-
7483	M	30	S-cl	7.0	1.038	N	N	N	N	4+	-	-	occ	M	M	occ	-	M	-
7466	F	25	S-cl	9.0	1.021	N	N	N	N	N	-	-	5-8	M	M	F	-	M	-
7504	F	35	S-cl	9.0	1.020	N	N	1+	1+	N	occ	-	1-3	F	F	F	-	M	-
<u>1.5 mg/kg/day:</u>																			
7462	M	50	S-cl	8.0	1.025	N	N	N	N	N	-	-	1-3	M	F	F	-	M	-
7486	M	100	S-cl	8.0	1.023	N	N	N	N	N	-	-	-	F	F	F	-	N	-
7500	F	55	S-cl	8.0	1.016	N	N	4+	4+	3+	-	-	occ	F	occ	occ	-	M	-
7501	F	25	S-cl	8.0	1.033	N	N	4+	4+	3+	-	-	occ	F	F	occ	-	M	-
<u>4.5 mg/kg/day:</u>																			
7484	M	Died																	
7485	M	Died																	
7502	F	Died																	
7503	F	Died																	

137-092	cc - Trace	S - Straw	N - Negative	occ - Occasional
1+	Trace to slight	LS - Light Straw	F - Few	occ - Quantity not sufficient
2+	Slight to moderate	DS - Dark Straw	L - Loaded	occ - None seen
3+	Moderate	LAm - Light Amber	M - Many	
4+	Marked	DAm - Dark Amber	R - Rare	
		cl - Cloudy		
		C - Clear		

FC-95: Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 14. Necropsy Observations, Terminal Sacrifice and Deaths.

Site Lesion	Group, S Monkey Number	Control				0.5 mg/kg/day				1.5 mg/kg/day				4.5 mg/kg/day			
		M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
Adrenals enlarged brown in color		7355	7358	7368	7372	7463	7483	7466	7504	7462	7486	7500	7501	7484*	7485*	7502*	7503*
Lung yellowish mite lesions dark red area yellowish foci pleural adhesions dark red raised focus		x	x		x	x	x			x		x		x	x		x
Mesentery nodule accessory splenic tissue					x											x	
Thymus atrophied															x		x
Stomach raised nodules edema, glandular mucosa					x											x	
Small intestine dark yellow thick fluid, lumen														x			
Large intestine esophagostomum nodule void of contents							x			x	x	x	x	x	x	x	x
Ileocolic orifice congestion													x				
Liver accentuated lobulations yellowish focus/area brown in color mottled		x	x		x				x		x	x	x				x
Miscellaneous intramuscular subcutaneous hemorrhage, hindlimbs abscess, right hand								x							x		

*Died or sacrificed in extremis.

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3MA10065035

1191.0032

NC-95; Ninety Day Subacute Rheus Monkey Toxicity Study.

TABLE 15. Absolute (grams) and Relative (% Body Weight) Organ Weights, Terminal Sacrifice.

Group, Monkey Number	Sex	Body Wt. kg	Spleen		Liver		Adrenals		Kidneys		Ovaries		Heart		Thyroid/ Parathyroid		Brain		Pituitary	
			g	%	g	%	g	%x10	g	%	g	%x10 ²	g	%	g	%x10	g	%	g	%x10 ²
Control:																				
7355	M	3.55	3.70	0.10	87.49	2.46	0.77	0.22	15.47	0.44	1.04	0.03	14.69	0.41	0.557	0.16	85.21	2.40	0.049	0.14
7358	M	3.75	4.01	0.11	68.48	1.83	0.79	0.21	16.60	0.44	1.40	0.04	14.83	0.40	0.885	0.24	91.83	2.45	0.068	0.18
Mean		3.65	3.86	0.11	77.99	2.15	0.78	0.21	16.04	0.44	1.22	0.03	14.76	0.40	0.721	0.20	88.52	2.42	0.059	0.16
7368	F	3.15	2.81	0.09	59.58	1.89	0.85	0.27	15.06	0.48	0.35	1.11	13.39	0.43	0.485	0.15	71.29	2.26	0.061	0.19
7372	F	4.20	4.03	0.10	95.60	2.28	0.80	0.19	16.25	0.39	0.30	0.71	16.94	0.40	0.857	0.20	88.03	2.10	0.071	0.17
Mean		3.68	3.42	0.09	77.59	2.08	0.83	0.23	15.66	0.43	0.33	0.91	15.17	0.41	0.671	0.18	79.66	2.18	0.066	0.18
0.5 mg/kg/day:																				
7463	M	2.65	2.68	0.10	81.09	3.06	0.61	0.23	11.64	0.44	0.45	0.02	9.35	0.35	0.444	0.17	83.26	3.14	0.042	0.16
7483	M	3.55	2.19	0.06	86.79	2.44	0.58	0.16	15.32	0.43	0.95	0.03	15.01	0.42	0.580	0.16	86.83	2.45	0.070	0.20
Mean		3.10	2.44	0.08	83.94	2.75	0.60	0.20	13.48	0.44	0.70	0.02	12.18	0.39	0.512	0.17	85.05	2.79	0.056	0.18
7466	F	3.55	4.07	0.11	92.19	2.60	0.81	0.23	16.14	0.45	0.67	1.89	14.11	0.40	0.693	0.20	89.28	2.51	0.065	0.18
7504	F	3.35	4.85	0.14	87.28	2.61	0.59	0.18	12.75	0.38	0.11	0.33	13.00	0.39	0.747	0.22	76.26	2.28	0.062	0.19
Mean		3.45	4.46	0.13	89.74	2.60	0.70	0.20	14.45	0.42	0.39	1.11	13.56	0.39	0.720	0.21	82.77	2.40	0.064	0.18
1.5 mg/kg/day:																				
7462	M	2.80	3.39	0.12	80.63	2.88	0.65	0.23	11.82	0.42	0.59	0.02	11.70	0.42	0.627	0.22	87.56	3.13	0.056	0.20
7486	M	3.05	2.44	0.08	85.38	2.80	0.80	0.26	13.79	0.45	1.77	0.06	14.85	0.49	0.902	0.30	87.53	2.87	0.086	0.28
Mean		2.93	2.92	0.10	83.01	2.84	0.73	0.25	12.81	0.44	1.18	0.04	13.28	0.45	0.765	0.26	87.55	3.00	0.071	0.24
7500	F	3.20	3.51	0.11	84.15	2.63	0.91	0.28	16.76	0.52	0.32	1.00	15.48	0.48	0.772	0.24	77.43	2.42	0.055	0.17
7501	F	2.30	1.55	0.07	16.03	0.70	0.79	0.34	10.77	0.47	0.11	0.48	9.66	0.42	0.814	0.35	74.35	3.23	0.056	0.24
Mean		2.75	2.53	0.09	50.09	1.66	0.85	0.31	13.77	0.50	0.22	0.74	12.57	0.45	0.793	0.30	75.89	2.83	0.056	0.21
Died on Study:																				
4.5 mg/kg/day:																				
7484	M	2.15	1.22	0.06	80.55	3.75	1.45	0.67	15.73	0.73	0.54	0.03	11.13	0.52	0.805	0.37	81.29	3.78	0.060	0.28
7485	M	2.50	2.06	0.08	79.73	3.19	1.82	0.73	18.17	0.73	0.62	0.03	12.33	0.49	0.824 ^a	0.33 ^a	77.60	3.10	0.040	0.16
7502	F	2.65	2.21	0.08	86.20	3.25	1.14	0.43	15.08	0.57	0.15	0.57	15.20	0.57	0.709	0.27	77.11	2.91	0.060	1.89
7503	F	2.55	1.25	0.05	78.44	3.08	1.70	0.67	14.97	0.59	0.08	0.31	11.45	0.45	0.668	0.26	81.33	3.19	0.070	0.27

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

^a - Weight of thyroids only.

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FC-95:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 16. Microscopic Observations.

Tissue Lesion	Group, Monkey Number	Control				0.5 mg/kg/day				1.5 mg/kg/day				4.5 mg/kg/day			
		M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
Brain		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Spinal Cord		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
Eye		1				1	1			1	1	1	1		1	1	
foci of inflammatory cell infiltrates in palpebral/ocular conjunctiva			2	2	2	2			2								2
foci of lymphoid infiltrates in lacrimal gland			3														
cystic tarsal glands														x			
Pituitary		1		1	1	1	1	-	1	1	1	1	1	1	1	1	1
large focus of lymphoid infiltrate in pars nervosa			3														
Adrenals							1	1			1						
foci of dystrophic mineralization			3		3					2			2	2	3	3	2
focus of lymphoid infiltrate in medulla				2													
diffuse congestion															4	4	4
acidophilic degeneration of individual to small groups of cells			3	3	3	2				2	2			2	3	3	2
multifocal lipid depletion								3				3					
diffuse lipid depletion														5	5	5	5
Thyroid		1	1		1	1	1	1	1	1	1	1	1	1	1	1	1
focus of interstitial lymphoid infiltrates					2												
Parathyroid		-	1	1	1	1	-	1	-	-	-	-	1	1	-	1	1
Tongue					1	1			1		1		1		1	1	1
focal hyalin degeneration of muscle		3					3			3				4			
foci of inflammatory cell infiltrates in mucosal epithelium and lamina propria		3	2	2				2				2					
foci of inflammatory cell infiltrate in muscle							2			2				3			
Gongylonema sp. in mucosal epithelium							x										
Trachea														1	1	1	
foci of inflammatory cell infiltrates in lamina propria			4	3	2	2	2	3	2	2	2	2	3				2
foci of inflammatory cell infiltrates in lamina propria and trachealis muscle			3														
Esophagus		1	1										1	1	1	1	1
foci of inflammatory cell infiltrates in lamina propria				3	2	3	3	2	2	4	3	2					
Heart		1				1				1		1			1	1	
foci of interstitial lymphoid infiltrates			2	3	3		3	2	3	3		2		2			2
small focus of myocardial necrosis							2										

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

137-092

3MA10065037

1191.0034

FC-95:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 16. Cont.

Microscopic Observations.

Tissue Lesion	Group, Monkey Number	Control				0.5 mg/kg/day				1.5 mg/kg/day				4.5 mg/kg/day			
		M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
Aorta		7355	7358	7368	7372	7463	7483	7486	7504	7462	7486	7500	7501	7484*	7485*	7502*	7501*
		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Salivary Gland						1		1		1		1				1	
foci of interstitial lymphoid infiltrates		2	2	3	2		3		2	2		2					
decreased cell size, loss of cytoplasmic granules															4	4	
dilated ducts					3												
Lung																	
acute focal bronchitis								3									
focal perivascular neutrophil infiltrates							4										
focal aggregates of alveolar macrophages						3											
acarian pigment (peribronchiolar, peribronchial, perivascular)		2	2	2	2	3	2	2	2	2	2	2	2	2	2	2	2
foci of perivascular lymphoid infiltrates									3	3							
foci of peribronchial/peribronchiolar lymphoid aggregates		3	3	3	3	3	3	2	3	3	3	3	3	3	2	2	2
lung mite in bronchiolar lumen						x									x		
acute focal bronchopneumonia			3				3										
chronic focal pleuritis							3										
interstitial pneumonia															3	3	
focal accumulation of blood and neutrophils in alveoli										3							
focal hemorrhage, focal interstitial fibrosis																	3
Tonsil					-	-	-	-	x	-	-	1		-	1	-	
keratin-filled cyst																	
foci of inflammatory cell infiltrates in mucosal epithelium and lamina propria			4	3													
foci of inflammatory cell infiltrates in surface epithelium and tonsillar crypts		3	4			3				3				3			
Thymus		1	1	1	1	1	1	1	1	1	1	1	1	-	-	-	-
Lymph Nodes		-	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
diffuse reticuloendothelial cell hyperplasia																	3
Stomach		1												1		1	
foci of inflammatory cell infiltrates in lamina propria			4	3		2	3		2	4		2					
foci of inflammatory cell infiltrates in lamina propria and submucosa					5			4				3		2		3	
foci of inflammatory cell infiltrates in lamina propria and serosa												3					
Small Intestine		1	1	1	1	1	1	1	1	1	1	1	1	1	a	1	
multifocal cystic dilatation of duodenal glands																	4

Code: x - condition present
1 - not remarkable
2 - very slight

3 - slight
4 - moderate
5 - marked

6 - extreme
- = not available
* - died or sacrificed in extremis

137-092

3MA10065038

1191.0035

FC-95:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 16. Cont. Microscopic Observations.

Tissue Lesion	Group, Monkey Number	Control				0.5 mg/kg/day				1.5 mg/kg/day				4.5 mg/kg/day			
		M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
Cecum		7355	7358	7368	7372	7463	7483	7466	7504	7462	7486	7500	7501	7484*	7485*	7502*	7503*
parasitic granuloma in mesentery															x		
parasitic granuloma in submucosa							x									x	
parasitic granuloma in muscularis																	x
foci of inflammatory cell infiltrates in submucosa, serosa and mesentery						3											
Colon		1	1	1		1	1	1		1	1						
focal mucosal hemorrhage			3														
parasitic granuloma in muscularis and submucosa							x									x	
parasitic granuloma in serosa and mesentery												x					
foci of inflammatory cell infiltrates in muscularis and serosa							3										
foci of inflammatory cell infiltrates in submucosa, muscularis and serosa												3					
foci of inflammatory cell infiltrates in muscularis, serosa and mesentery												3					
parasitic granuloma in mesentery														x	x	x	
parasitic granuloma in muscularis																	x
chronic focal serositis																	3
Rectum		1	1	1	1	1	1	1		1	1	1	1	1	1	1	1
foci of inflammatory cell infiltrates in muscularis							2										
Liver		1															
portal inflammatory cell infiltrates			3	2	2	2	2	3		3					2		3
multifocal bile duct proliferation			2				2			2	2	2					
acidophilic degeneration of individual to small groups of hepatocytes			3										3				3
parenchymal inflammatory cell infiltrates			3		3		2	2	2	3		3					
diffuse congestion															4	4	4
neutrophilic infiltrate in sinusoids															3		
brown pigment in Kupffer cells																3	
focal/multifocal cytoplasmic vacuolation of hepatocytes			2									4					
small focus of hepatocellular necrosis											2						
Gallbladder														a	a		
foci of inflammatory cell infiltrates in lamina propria			3	3	3	2		2	3	3		3	2	2			
foci of inflammatory cell infiltrates in lamina propria and muscularis							3					2				3	3
foci of hemorrhage in lamina propria and muscularis																	4
Pancreas		1	1	1		1	1			1	1				1		
focal lymphoid infiltrates in peripancreatic fat tissue					3												
decreased cell size, loss of zymogen granules																4	4
focal interstitial lymphoid infiltrates							2	3				3	2			4	4

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

137-092

3MA10065039

1191.0036

FC-95:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 16. Cont.

Microscopic Observations.

Tissue Lesion	Group, Monkey Number	Control				0.5 mg/kg/day				1.5 mg/kg/day				4.5 mg/kg/day			
		M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Spleen		7355	7358	7368	7372	7463	7483	7466	7504	7462	7486	7500	7501	7484*	7485*	7502*	7503*
diffuse atrophy of lymphoid follicles		1	1	1	1	1	1	1	1	1	1	1	1		1	1	3
Kidney																	
multinucleated lining epithelium in papillary ducts		x				x	x	x		x							
focal interstitial lymphoid infiltrates		2	2	3	2	2	2	3	3		3	2	2	2	2	2	2
focus of glomerular fibrosis				x													
diffuse congestion										3				4	3	3	3
microolith in renal tubules												x		x			x
cystic glomeruli						x											
Urinary Bladder		1				-								1	1		
foci of inflammatory cell infiltrates in lamina propria			3	3		2	2	3		2	3	2	2			3	
foci of inflammatory cell infiltrates in lamina propria and muscularis					3												
foci of inflammatory cell infiltrates in lamina propria and serosa																	4
Prostate		-	-							1				-	1		
foci of interstitial lymphoid infiltrates						3	3										
lymphoid nodules/infiltrates in corpus cavernosum						3	2										
Sarcocystis sp. in muscle										x							
Uterus			1				1				1				1		
inflammatory exudate in lumen of uterine glands												2					
small foci of hemorrhage in endometrium				2								2					
inflammatory cell infiltrates in endometrium				3				2									
focus of lymphoid infiltrates in serosa																	2
Testes																	
prepuberal development		x	x			x	x			x	x			x	x		
Ovaries				1					1							1	1
small foci of dystrophic mineralization				3			2				2	2					
Vagina																	
foci of lymphoid infiltrates in mucosal epithelium and lamina propria			4	3		4	3			3	2			3	4		
foci of lymphoid infiltrates in muscularis			2	2		2	2			2							
focus of mucosal epithelium necrosis			2														
Skeletal muscle		1	1			1	1	1		1	1	1		1	1	1	
Sarcocystis sp.										x							
foci of interstitial inflammatory cell infiltrates				3	2			2									
small foci of necrosis				3												2	

Code: x - condition present 3 - slight 6 - extreme
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 2 - very slight 5 - marked * - died or sacrificed in extremis

137-092

3MA10065040

1191.0037

FC-95:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 16. Cont.

Microscopic Observations.

Tissue Lesion	Group, Monkey Number	Control				0.5 mg/kg/day				1.5 mg/kg/day				4.5 mg/kg/day			
		M 7355	M 7358	F 7368	F 7372	M 7463	M 7483	F 7466	F 7504	M 7462	M 7486	F 7500	F 7501	M 7484*	M 7485*	F 7502*	F 7503*
Skin																	
brown/black pigment in dermis		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
dermal inflammatory cell infiltrates						2		2							2		
focus of subcutaneous hemorrhage					4												
hyperkeratosis											3			3			3
focal hemorrhage in dermis								3									
multifocal foreign body granulomas								x									
Mammary Gland																	
dermal inflammatory cell infiltrates		2		3	2		3	2	3			2	2				2
inflammatory exudate in ducts						2		2									
intraepidermal microabscess			x														
dilated ducts						x				x							
brown pigment in dermis		x	x	x	x	x	x	x	x	x	x		x	x	x	x	x
hyperkeratosis		3	3		3		3		3	3	4	3		3			
Bone/Bone marrow (Rib junction)																	
hypocellular marrow		1	1	1	1	1	1	1	1	1	1	1	1		1		3
diffuse congestion																3	

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

137-092

3MA10065041

1191.0038