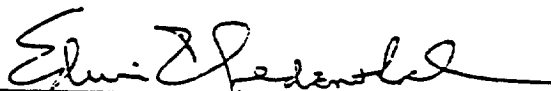


International Research and Development Corporation

T-2999

SPONSOR: 3M Company
COMPOUND: FM-3422
SUBJECT: Ninety Day Subacute Rhesus Monkey
Toxicity Study.



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I. SYNOPSIS

FM-3422 was administered to rhesus monkeys by gavage at dosage levels of 1, 3, 10 or 30 mg/kg/day. A control group received the vehicle, propylene glycol. 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, biochemical and urinalysis studies were conducted once in the control period and at 1 and 3 months of study.

One monkey treated with 30 mg/kg/day died during the last week of the study.

On and after the second day of study, all the monkeys, including the control group showed anorexia, slight to marked decrease in activity and ataxia. The ataxia disappeared from all the monkeys directly after the amount of propylene glycol used was reduced from 5 to 2 ml/kg on study day 3. Occasional emesis and diarrhea (sometimes severe) were observed. Several weeks after the initiation of the study black stool, mucus and bloody mucus in the stool were observed in most of the monkeys from each group. For two monkeys receiving 30 mg/kg/day the above mentioned signs of toxicity persisted for almost all the treatment period. One monkey at the 30 mg/kg/day dosage level died during the last week of the study.

Most of the monkeys, including those in the control group lost body weight early in the study. At 12 weeks of study all the monkeys were at or near the original body weight except for the groups receiving 10 and 30 mg/kg/day. At the end of the study the differences in the mean body weights of the treated and control groups were not statistically significant.

Microscopically, the adrenals from one male and two female rhesus monkeys at the 30 mg/kg/day dosage level had compound-related slight to severe lipid depletion. The pancreas from the two female monkeys at the 30 mg/kg/day dosage level had compound-related moderate atrophy of exocrine cells. None of the tissues from the other monkeys had lesions that would be considered compound-related.

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

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II. COMPOUND

The compound was received from 3M Company, Saint Paul, Minnesota on October 28, 1977 as indicated below:

<u>Label</u>	<u>Description</u>
FM-3422 41-2700-3422-0 Lot 784/Net-35 DR-1	off-white to tan waxy substance

III. CLINICAL STUDIES

A. METHOD:

1. General Procedure:

Ten male (weighing from 3.00 to 4.35 kg) and 10 female (weighing from 3.05 to 4.20 kg) rhesus monkeys were initiated into this study. The monkeys were purchased from Primate Imports Corporation, Port Washington, New York on October 25, 1977. 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 (14 weeks), the monkeys were tattooed on the inner surface of the thigh and intrapalpebral tuberculin tests were conducted. Tuberculin tests also were conducted at bimonthly intervals during the treatment period. Complete physical examinations were conducted by the staff veterinarian prior to initiation of the compound administration and only monkeys in good health were selected for use.

This study was initiated on February 9, 1978. Terminal sacrifices were conducted on May 10, 1978.

2. Compound Administration:

At the end of the conditioning period the monkeys were divided into 5 groups on a random basis, so that the average body weights were similar:

<u>Group</u>	<u>Number of Monkeys</u>		<u>Dosage Level</u>
	<u>Male</u>	<u>Female</u>	
I	2	2	Control
II	2	2	1 mg/kg/day
III	2	2	3 mg/kg/day
IV	2	2	10 mg/kg/day
V	2	2	30 mg/kg/day

The test compound was dissolved in propylene glycol by heating to approximately 30° C. The solution was administered by gavage. For study day 1 and 2 all of the treated monkeys received 5 ml/kg of the solution. On and after study day 3 the amount of propylene glycol was reduced to 2 ml/kg. The control group received 5- and then 2-ml/kg of propylene glycol on the same regimen as the treated groups.

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. 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, activated partial thromboplastin time (APTT)⁷. Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) were calculated.

b. Biochemistry:

Biochemical studies included: blood glucose⁸, blood urea nitrogen⁸, serum alkaline phosphatase⁸, serum glutamic oxaloacetic transaminase (SGOT)⁸, serum glutamic pyruvic transaminase (SGPT)⁸,

cholesterol⁹, total protein⁹, albumin⁸, sodium¹⁰, potassium¹⁰, chloride⁹, inorganic phosphate⁹, γ -glutamyl transpeptidase¹¹, creatinine phosphokinase¹². Sorbitol dehydrogenase was not determined because reliable data could not be obtained with the present instrumentation.

c. Urinalyses:

Urinalyses 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:

Analysis of terminal body weights and organ weights (absolute and relative) and clinical laboratory tests were performed using analysis of variance (one-way classification), Bartlett's test for homogeneity of variances and the appropriate t-test (for equal and unequal variances) as described by Steel and Torrie using Dunnett's multiple comparison table to judge significance of differences.

B. RESULTS:

1. General Behavior, Appearance and Survival:

Monkey 7490 receiving 30 mg/kg/day died during the last week of the study. The death was preceded by a marked loss of body weight (1.25 kg) with a marked decrease in activity and ataxia.

Except for one monkey receiving 3 mg/kg/day, ataxia was observed for all the monkeys in the control and treated groups beginning at day 2. For most of the monkeys the ataxia was slight but for a few the ataxia was moderate or marked. With the reduction in the amount of propylene glycol use the ataxia disappeared usually before the end of the first week.

In addition to the ataxia the monkeys in the control and treated groups had anorexia, slight to moderate decreased activity appearing on study day 2. Occasional emesis also was observed.

For the monkeys in the control group, diarrhea was occasionally observed but for Monkey 7470, the diarrhea was chronic at the end of the study. After the second week of study, bloody mucus in the stool and black stool were noted. Except for the chronic diarrhea, the observations for the monkeys receiving 1 mg/kg/day were the same as that of the controls.

At the 3 mg/kg/day dosage level Monkey 7487 was observed to have black stool and mucus in the stool during weeks 11 and 13. Frequently, severe diarrhea was noted for Monkey 7474 during week 12. For the monkeys at the 10 mg/kg/day dosage level, occasional diarrhea was observed.

Of the monkeys receiving 30 mg/kg/day, 7499 had bloody mucus in the stool, emesis and severe diarrhea from the third day of the study. Severe diarrhea was observed for Monkeys 7472 and 7490. In addition for Monkey 7490 mucus in the stool, bloody mucus and blood in the stool also was noted. For Monkeys 7499 and 7490 the signs of toxicity persisted for most of the treatment period. Monkey 7490 that died in the last week of the study showed marked decrease in activity and marked ataxia on the day prior to death.

2. Body Weights (Table 1):

During the first month of study, all the monkeys lost weight including those in the control group. The percentage change in mean body weight, at monthly intervals were:

Study Weeks	Group, dose in mg/kg/day				
	0	1	3	10	30
0- 4	-3.94	-0.29	-0.29	-7.04	-7.32
4- 8	+1.16	+3.25	+4.57	+1.82	-3.04
8-12	+3.76	+2.87	+1.09	+0.60	-3.98

For the group receiving 30 mg/kg/day the low mean body weight resulted mainly from the 1.25 kg loss in body weight for Monkey 7490,

which died. However, there were no statistically significant differences between the body weights of the treated and control monkeys.

3. Laboratory Tests (Tables 2-10):

After the first month of treatment no unusual changes were observed for the blood and urine analyses. For Monkey 7491, receiving 10 mg/kg/day, there was a slight decrease in hematocrit, hemoglobin concentration and erythrocyte count at 1 month of study as compared to the pretreatment period. This decrease was not found at 3 months of study.

For most of the monkeys at 3 months of study, the blood glucose values were in the lower range of expected values. Also at 3 months of study, low cholesterol values (56 and 67 mg/100 ml) were found for two monkeys receiving 30 mg/kg/day, and for one monkey receiving 10 mg/kg/day (84 mg/100 ml). For Monkey 7477 which had a cholesterol value of 67 mg/100 ml, a low potassium value (3.5 meq/liter) was found also.

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.

The monkey which died during the study was 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		thymus
heart (with coronary vessels)	mammary gland	trachea
duodenum	nerve (with muscle)	tonsil
ileum	spleen	tongue
jejunum	pancreas	urinary bladder
cecum	prostate/uterus	vagina
colon	rib junction (bone marrow)	tattoo
rectum	salivary gland	

and any other tissue(s) with lesions.

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

B. RESULTS:

1. Gross Pathology (Table 11) and Organ Weights (Table 12):

No gross lesions considered compound-related were seen in monkeys sacrificed after 90 days of study.

Statistically significant variations in sex group mean weights of liver and brain occurred at the 10 and 30 mg/kg/day dosage levels as follows:

<u>Organ</u>	<u>Dosage Level (mg/kg/day)</u>	<u>Sex</u>	<u>Weight</u>	<u>Change</u>	<u>p<</u>
Liver	10	M	relative	increase	0.05
	30	M	absolute, relative	increase, increase	0.05, 0.01
Brain	10	M	absolute	decrease	0.01
	30	M	absolute	decrease	0.05

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

2. Histopathology (Table 13):

One male and two female monkeys at the 30 mg/kg/day dosage level, sacrificed after 90 days of study, had slight to severe lipid depletion in the adrenal glands. The two female monkeys at the 30 mg/kg/day dosage level had moderate atrophy of pancreatic exocrine cells. The lesion was characterized by decreased cell size with loss of zymogen granules. One of the two pancreas also had several eosinophilic intranuclear inclusions in exocrine cells. These microscopic findings were considered compound-related.

No microscopic changes which were considered compound-related were seen in the adrenal glands of male or female monkeys at the 1, 3 or 10 mg/kg/day levels. No microscopic changes which were considered compound-related were seen in the pancreas of male monkeys at the 30 mg/kg/day level or in male or female monkeys at the 1, 3 or 10 mg/kg/day levels. No microscopic lesions in tissues other than the adrenal glands and pancreas of monkeys at the 30 mg/kg/day levels were considered compound-related.

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7479	M	3.10	3.00	3.25	3.15	3.15	3.05	3.15	3.20	3.25	3.30	3.20	3.20	3.25	3.35	3.10*
7493	F	3.75	3.80	3.70	3.70	3.60	3.55	3.60	3.60	3.70	3.70	3.60	3.80	3.60	3.85	3.55*
7495	F	3.00	3.05	3.00	3.00	2.85	2.85	2.90	3.00	3.05	3.00	2.90	2.95	3.00	3.05	2.75*
Mean		3.56	3.55	3.59	3.55	3.48	3.41	3.41	3.43	3.45	3.45	3.38	3.43	3.41	3.58	3.24
<u>1 mg/kg/day:</u>																
7467	M	3.85	4.00	3.75	3.95	3.75	3.85	3.85	3.95	3.95	4.00	3.95	4.00	4.05	4.10	3.85*
7473	M	3.25	3.20	3.30	3.25	3.10	3.10	3.10	3.25	3.20	3.15	3.10	3.10	3.25	3.60	2.90*
7489	F	3.05	3.05	2.95	3.00	2.90	3.00	3.05	3.10	3.20	3.15	3.15	3.25	3.20	3.15	3.10*
7492	F	4.15	4.00	3.85	3.75	3.60	3.55	3.55	3.55	3.65	3.65	3.60	3.50	3.60	3.50	3.45*
Mean		3.58	3.56	3.46	3.49	3.34	3.38	3.39	3.46	3.50	3.49	3.45	3.46	3.53	3.59	3.33
<u>3 mg/kg/day:</u>																
7469	M	4.10	4.00	4.05	4.00	3.95	4.00	4.05	4.00	4.10	4.10	4.00	4.15	4.15	4.20	4.10*
7474	M	3.45	3.20	3.45	3.55	3.55	3.55	3.60	3.75	3.75	3.75	3.70	3.80	4.00	3.70	3.55*
7487	F	3.60	3.75	3.45	3.45	3.30	3.30	3.40	3.50	3.55	3.50	3.45	3.55	3.55	3.60	3.10*
7497	F	3.05	3.10	3.20	3.30	3.30	3.15	3.20	3.20	3.30	3.30	3.10	3.20	3.10	3.30	3.05*
Mean		3.55	3.51	3.54	3.58	3.53	3.50	3.56	3.61	3.68	3.66	3.56	3.68	3.70	3.70	3.45

*Terminal weight.

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TABLE 1. Cont.

Individual and Group Mean Body Weights, Kilograms.

Group, Monkey Number	Sex	Control		Week of Study												
		-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13
10 mg/kg/day:																
7475	M	3.80	3.60	3.60	3.50	3.30	3.50	3.45	3.45	3.60	3.55	3.40	3.50	3.50	3.55	3.45*
7480	M	3.45	3.30	3.40	3.55	3.40	3.25	3.35	3.40	3.45	3.45	3.40	3.50	3.60	3.75	3.55*
7491	F	4.20	4.15	3.60	3.60	3.50	3.50	3.50	3.45	3.40	3.45	3.35	3.45	3.35	3.20	3.05*
7498	F	3.10	3.15	2.90	3.05	2.95	2.95	3.00	2.95	3.10	3.00	2.90	3.05	3.00	3.00	2.95*
Mean		3.64	3.55	3.38	3.43	3.29	3.30	3.33	3.31	3.39	3.36	3.26	3.38	3.36	3.38	3.25
30 mg/kg/day:																
7472	M	3.45	3.40	3.10	3.20	3.15	3.15	3.25	3.25	3.30	3.30	3.25	3.30	3.20	3.25	3.05*
7477	M	3.50	3.55	3.25	3.50	3.50	3.60	3.65	3.65	3.75	3.75	3.75	3.90	3.95	4.00	3.75*
7490	F	4.00	4.20	3.65	3.65	3.55	3.50	3.65	3.55	3.65	3.60	3.50	3.45	3.15	2.95	2.85**
7499	F	3.00	3.05	2.75	2.95	2.80	2.90	2.95	2.85	3.00	2.90	2.85	2.90	2.80	2.85	2.65*
Mean		3.49	3.55	3.19	3.33	3.25	3.29	3.38	3.33	3.43	3.39	3.34	3.39	3.28	3.26	3.15

*Terminal weight.

**Terminal weight not included in mean.

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Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 2.

Individual Hematological Values - Control.

Group, Monkey Number	Sex	Erythro- cytes 10 ⁶ /cmm	Hemo- globin g/100 ml	Hemato- crit %	Lenco- cytes 10 ³ /cmm	Platelet Count 10 ³ /cmm	Reticulo- cytes %	Pro- thrombin Time, Sec	P.T.T. Sec	Neutrophils		Lympho- cytes %	Eosino- phils %	Mono- cytes %	Baso- phils %	PCV %	HCT μg	MCBC g/100 ml
										Seg. %	Non-Seg. %							
Control:																		
7470	M	5.07	11.8	37	14.51	142	1.3	12	28	56	0	43	1	0	0	73	23	32
7479	M	5.73	13.2	37	9.06	119	0.2	11	24	15	0	83	1	1	0	65	23	36
7493	F	4.91	12.0	36	12.20	109	0.9	13	23	18	0	80	0	2	0	71	24	33
7495	F	5.48	11.6	36	8.20	103	0.6	12	24	38	0	59	3	0	0	66	21	32
Mean		5.30	12.2	37	10.99	118	0.8	12	25	32	0	66	1	1	0	69	23	33
1 mg/kg/day:																		
7467	M	5.54	14.0	39	8.55	185	0.2	12	26	35	0	62	3	0	0	70	25	36
7473	M	5.05	12.3	37	9.13	116	1.3	11	24	12	0	86	0	2	0	73	24	33
7489	F	4.67	11.0	35	11.69	236	0.6	12	23	27	0	71	2	0	0	75	24	31
7492	F	5.24	11.7	36	7.26	102	0.4	11	30	12	0	87	0	1	0	69	22	33
Mean		5.13	12.3	37	9.16	160	0.6	12	26	22	0	76	1	1	0	72	24	33
3 mg/kg/day:																		
7469	M	5.14	12.7	38	13.51	130	0.4	11	23	15	0	82	3	0	0	74	25	33
7474	M	4.98	12.2	36	9.32	182	1.2	12	22	31	0	66	1	2	0	72	24	34
7487	F	5.23	12.6	39	7.00	169	0.7	12	24	44	0	56	0	0	0	75	24	32
7497	F	4.24	10.2	30	5.82	246	0.5	12	29	31	0	67	1	1	0	71	24	34
Mean		4.90	11.9	36	8.91	182	0.7	12	25	30	0	68	1	1	0	73	24	33
10 mg/kg/day:																		
7475	M	5.25	12.1	37	13.03	234	1.5	11	24	35	0	60	5	0	0	70	23	33
7480	M	4.78	10.5	33	8.93	168	0.3	12	25	33	1	63	3	0	0	69	22	32
7491	F	5.08	12.0	36	14.81	174	0.5	11	29	57	0	41	2	0	0	71	24	33
7498	F	4.78	10.7	33	8.97	107	0.9	11	25	40	0	60	0	0	0	69	22	32
Mean		4.97	11.3	35	11.44	171	0.8	11	26	41	0	56	3	0	0	70	23	33
30 mg/kg/day:																		
7472	M	5.30	11.8	32	8.49	248	1.1	12	25	32	0	64	4	0	0	60	22	37
7477	M	4.98	12.2	39	12.21	252	0.7	12	23	22	0	76	2	0	0	78	24	31
7490	F	5.69	13.2	41	10.61	144	0.6	13	29	34	0	66	0	0	0	72	23	32
7499	F	5.64	13.0	33	9.12	241	0.7	12	26	27	0	71	2	0	0	59	23	39
Mean		5.40	12.6	36	10.11	221	0.8	12	26	29	0	69	2	0	0	67	23	35

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TABLE 1.

Individual Hematological Values - 1 Month.

Group, Monkey Number	Sex	Erythro- cytes 10 ⁶ /cmm	Hemo- globin g/100 ml	Hemato- crit %	Leuco- cytes 10 ³ /cmm	Platelet Count 10 ³ /cmm	Reticulo- cytes %	Pro- thrombin Time, Sec	P.T.T. Sec	Neutrophils		Lympho- cytes %	Eosino- phils %	Mono- cytes %	Baso- phils %	MCV μ	MCH μg	MCHC g/100 ml
										Seg.	Non-Seg.							
Control:																		
7470	M	4.82	11.8	35	14.44	158	0.7	10	30	45	0	49	4	2	0	73	24	34
7479	M	5.48	13.0	39	10.61	157	0.4	12	28	25	0	75	0	0	0	71	24	33
7493	F	4.88	12.5	38	14.59	137	0.6	12	29	53	0	46	1	0	0	78	26	33
7495	F	5.27	13.6	41	8.60	129	0.4	11	26	26	0	73	1	0	0	78	26	33
Mean		5.11	12.7	38	12.06	145	0.5	11	28	37	0	60	2	1	0	75	25	33
1 mg/kg/day:																		
7467	M	4.82	12.6	39	8.10	113	0.2	11	31	45	0	54	1	0	0	81	26	32
7473	M	5.05	12.7	35	7.86	117	0.3	12	30	6	0	94	0	0	0	69	25	16
7489	F	4.66	12.0	36	14.53	127	0.3	12	30	33	0	67	0	0	0	77	26	33
7492	F	5.30	13.4	38	12.53	132	0.4	12	31	49	0	50	1	0	0	72	25	35
Mean		4.96	12.7	37	10.76	122	0.3	12	31	33	0	66	1	0	0	75	26	34
3 mg/kg/day:																		
7469	M	4.89	12.8	37	12.39	140	0.3	12	31	23	0	77	0	0	0	76	26	35
7474	M	4.55	12.4	35	8.39	127	0.4	13	32	39	0	61	0	0	0	77	27	35
7487	F	5.55	13.8	40	8.44	128	0.2	12	26	45	0	55	0	0	0	72	25	35
7497	F	5.14	13.9	39	8.24	120	0.2	12	29	58	0	42	0	0	0	76	27	36
Mean		5.03	13.2	38	9.37	129	0.3	12	30	41	0	59	0	0	0	75	26	35
10 mg/kg/day:																		
7475	M	4.89	12.6	38	15.44	129	0.5	12	29	45	0	55	0	0	0	78	26	33
7480	M	4.48	11.1	33	7.22	139	0.2	12	29	43	0	57	0	0	0	74	25	34
7491	F	4.48	10.9	30	18.53	134	0.4	13	32	68	0	32	0	0	0	67	24	36
7498	F	5.38	12.3	37	8.50	155	0.3	11	26	57	0	43	0	0	0	69	23	33
Mean		4.81	11.7	35	12.42	139	0.4	12	29	53	0	47	0	0	0	72	25	34
30 mg/kg/day:																		
7472	M	4.94	12.3	35	9.29	121	0.2	13	28	27	0	71	2	0	0	71	25	35
7477	M	4.87	13.1	38	9.46	128	0.2	12	29	24	0	76	0	0	0	78	27	35
7490	F	5.36	13.2	40	11.04	127	0.2	12	30	29	0	71	0	0	0	75	25	33
7499	F	4.94	11.9	35	11.61	134	0.4	12	32	51	0	49	0	0	0	71	24	34
Mean		5.03	12.7	37	10.35	128	0.3	12	30	33	0	66	1	0	0	74	25	34

TABLE 4.

Individual Hematological Values - 3 Months.

Group, Monkey Number	Sex	Erythrocytes 10 ⁶ /cmm	Hemoglobin g/100 ml	Hematocrit %	Leucocytes 10 ³ /cmm	Platelet Count 10 ³ /cmm	Reticulocytes %	Prothrombin Time, Sec	P.T.T. Sec	Neutrophils		Lymphocytes %	Eosinophils %	Monocytes %	Basophils %	MCV μ	MCH μg	MCHC g/100 ml
										Seg.	Non-Seg.							
<u>Control:</u>																		
7470	H	5.16	13.3	37	12.63	156	0.1	11	29	27	0	69	3	1	0	72	26	36
7479	H	5.61	13.8	38	7.24	154	0.4	11	25	30	0	69	1	0	0	68	25	36
7493	F	5.04	13.6	36	11.04	174	0.4	11	26	38	0	59	3	0	0	71	27	38
7454	F	4.70	14.1	39	6.41	194	0.2	11	24	54	0	44	1	0	1	83	30	36
Mean		5.13	13.7	38	9.33	170	0.3	11	26	37	0	61	2	0	0	74	27	37
<u>1 mg/kg/day:</u>																		
7467	H	5.42	14.2	41	6.50	195	0.0	11	24	49	0	49	2	0	0	76	27	35
7473	H	5.30	12.8	35	5.55	165	0.0	11	25	41	0	56	2	0	1	66	25	37
7489	F	5.01	12.3	36	14.31	138	0.2	11	24	46	2	49	2	1	0	72	25	34
7492	F	5.12	12.7	35	8.47	113	0.3	10	24	54	0	45	1	0	0	68	25	36
Mean		5.21	13.0	37	8.71	153	0.1	11	24	48	1	49	2	0	0	71	26	36
<u>3 mg/kg/day:</u>																		
7469	H	5.48	13.2	40	12.55	158	0.0	10	25	52	1	41	3	3	0	73	25	33
7474	H	5.94	13.3	36	7.38	133	0.5	12	25	51	0	47	1	1	0	61	22	37
7487	F	6.09	14.8	42	6.05	137	0.4	11	27	54	0	43	1	2	0	70	24	35
7497	F	5.70	14.0	38	9.91	157	0.3	11	23	70	1	29	0	0	0	67	25	37
Mean		5.80	13.8	39	8.97	146	0.3	11	25	57	1	39	1	2	0	68	24	36
<u>10 mg/kg/day:</u>																		
7475	H	5.16	13.9	40	20.36	127	0.4	11	22	57	0	39	3	1	0	78	27	35
7480	H	5.91	12.4	37	8.63	129	0.3	11	24	52	0	47	0	1	0	63	21	34
7491	F	4.57	13.6	39	12.33	114	0.1	12	24	70	0	29	1	0	0	85	30	35
7498	F	4.91	12.1	36	8.64	109	0.6	11	22	51	0	47	1	1	0	73	25	34
Mean		5.14	13.0	38	12.49	120	0.4	11	23	58	0	40	1	1	0	75	26	35
<u>30 mg/kg/day:</u>																		
7472	H	4.76	11.4	33	11.43	139	0.5	11	22	71	0	28	1	0	0	70	24	35
7477	H	5.16	11.0	39	9.01	145	0.1	11	23	38	0	59	2	1	0	76	25	33
7490	F	Noted																
7499	F	5.40	12.2	37	7.82	137	0.3	11	21	51	0	47	1	1	0	69	23	33
Mean		5.11	12.2	36	9.42	140	0.3	11	22	53	0	45	1	1	0	72	24	34

TABLE 5.

Individual Biochemical Values - Control.

Group, Monkey Number	Sex	Glu- cose mg/100 ml	B.U.N. mg/100 ml	Alk. Phos. Int'l units/l	S.G.O.T. Int'l units	S.G.P.T. Int'l units	Choles- terol mg/100 ml	Total Protein mg/100 ml	Albumin mg/100 ml	Sodium meq/ liter	Potass- ium meq/ liter	Chloride meq/ liter	Inorganic Phosphate mg/100 ml	Glutaryl Transpeptidase Sigma units/ml	Creatinine Phosphokinase Sigma units/ml
Control:															
7470	H	107	20.5	510	69	35	159	8.67	4.39	154	5.1	112	4.7	41	29
7478	H	129	26.0	546	79	27	160	8.54	4.70	159	5.9	118	6.4	28	57
7493	F	123	27.9	1050	71	31	163	9.23	5.80	170	6.7	121	5.2	46	52
7495	F	146	28.1	498	43	35	192	8.81	5.67	165	5.4	117	3.7	30	44
Mean		126	25.6	651	66	32	169	8.81	5.14	162	5.8	117	5.0	36	46
1 mg/kg/day:															
7467	H	99	20.1	801	55	33	241	8.59	5.24	157	6.5	118	5.7	37	5
7473	H	107	22.3	837	88	42	174	8.10	5.23	158	5.8	118	6.0	32	28
7489	F	193	28.1	564	48	7	168	8.75	5.12	160	5.2	114	6.1	35	50
7492	F	125	18.2	969	88	30	166	8.77	4.70	166	6.1	127	6.2	36	80
Mean		131	22.2	793	40	28	187	8.55	5.07	160	5.9	119	6.0	35	41
3 mg/kg/day:															
7469	H	142	26.3	1236	102	26	158	8.47	5.38	162	5.9	119	7.0	57	36
7474	H	114	19.5	471	49	30	188	8.16	5.39	156	4.7	112	4.2	16	35
7487	F	134	21.9	765	64	32	196	8.10	5.20	159	5.1	111	4.1	35	43
7497	F	118	26.0	570	88	54	196	8.55	5.16	152	4.8	111	5.0	31	20
Mean		127	23.4	761	76	36	184	8.32	5.28	157	5.1	113	5.1	35	34
10 mg/kg/day:															
7475	H	142	31.3	792	58	22	210	8.55	4.99	166	4.8	118	5.5	51	100
7480	H	118	14.7	648	71	32	130	8.45	5.07	158	6.5	117	6.6	48	23
7491	F	153	22.1	768	100	23	148	8.67	4.80	157	5.3	116	5.1	31	104
7498	F	123	19.1	451	48	21	208	8.57	5.30	157	6.9	117	4.2	22	26
Mean		134	21.8	665	59	25	174	8.56	5.04	158	5.9	117	5.4	38	63
30 mg/kg/day:															
7472	H	101	25.1	291	48	23	168	8.49	5.51	153	3.9	109	5.0	35	22
7477	H	122	30.0	1065	71	37	196	8.75	5.50	168	5.8	121	5.4	76	49
7490	F	150	21.9	483	50	23	171	9.18	4.92	162	5.3	119	6.7	28	114
7499	F	124	25.1	627	59	46	160	9.54	4.52	160	6.2	111	5.7	17	24
Mean		124	25.5	617	57	32	174	8.99	5.11	161	5.3	115	5.7	49	52

TABLE 6.

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.P.T. Int'l units	S.G.O.T. Int'l units	Cholesterol mg/100 ml	Total Protein mg/100 ml	Albumin mg/100 ml	Sodium meq/ liter	Potassium meq/ liter	Chloride meq/ liter	Inorganic Phosphate mg/100 ml	Glutamyl Transpeptidase Sigma units/ml	Creatinine Phosphokinase Sigma units/ml
Control:															
7470	H	86	19.0	882	19	48	174	8.79	4.39	153	5.5	113	7.6	52	48
7479	H	105	24.0	864	20	30	156	8.53	4.81	153	4.6	107	8.4	36	16
7491	F	106	20.0	906	22	29	154	9.29	5.20	154	5.2	108	9.1	39	8
7495	F	105	21.2	540	25	33	178	9.18	5.72	159	5.9	111	7.3	48	5
Mean		101	21.1	798	22	35	166	8.95	5.03	155	5.3	110	8.1	44	19
1 mg/kg/day:															
7467	H	119	17.0	750	20	33	226	8.17	4.92	152	4.9	105	7.2	34	4
7473	H	107	29.0	852	18	33	182	7.99	5.23	151	4.1	111	7.6	29	4
7489	F	121	21.8	516	44	29	154	8.74	5.05	156	4.5	109	7.4	32	2
7492	F	100	19.1	858	17	21	150	9.45	4.52	157	4.7	113	7.9	27	6
Mean		112	21.7	744	25	29	178	8.59	4.93	154	4.6	110	7.5	31	4
3 mg/kg/day:															
7469	H	111	27.2	1290	21	42	154	8.60	5.58	158	5.1	112	7.3	51	6
7474	H	96	17.8	540	17	31	148	7.91	5.17	152	5.0	110	5.6	14	2
7487	F	126	20.9	612	27	35	172	7.64	5.10	152	4.2	107	6.2	25	16
7497	F	120	26.0	672	15	35	186	8.90	5.49	151	4.8	113	6.8	31	4
Mean		113	23.0	779	20	36	165	8.26	5.34	153	4.8	111	6.5	30	7
10 mg/kg/day:															
7475	H	151	22.4	690	22	46	181	9.09	5.00	157	5.0	114	6.4	34	10
7480	H	131	21.2	528	15	29	110	8.84	5.01	152	5.1	113	7.8	42	5
7491	F	119	13.0	744	10	30	110	8.22	4.82	150	4.5	111	5.1	29	5
7498	F	122	20.1	486	14	31	168	8.25	5.43	150	4.8	113	5.7	39	2
Mean		131	19.2	612	15	34	142	8.60	5.07	152	4.9	113	6.3	36	6
30 mg/kg/day:															
7472	H	90	24.9	276	12	28	132	8.83	5.74	151	3.7	106	6.3	40	3
7477	H	98	22.5	996	19	40	137	8.60	5.39	115	5.6	118	7.4	68	7
7490	F	89	15.4	384	15	28	110	9.21	5.60	154	4.3	110	5.5	30	2
7499	F	114	21.0	630	14	38	106	9.01	4.90	154	4.4	111	6.3	38	3
Mean		98	21.0	572	15	34	121	8.91	5.41	154	4.5	111	6.4	44	4

FM-3422:

Ninety Day Subacute Rheus Monkey Toxicity Study.

TABLE 7.

Individual Biochemical Values - 3 Months.

Group, Monkey Number	Sex	Glucose mg/100 ml	B.U.N. mg/100 ml	Alk. Phos. Sigma units	S.G.P.T. Sigma units	S.G.O.T. Sigma units	Cholesterol mg/100 ml	Total Protein mg/100 ml	Albumin g/100 ml	Sodium meq/ liter	Potassium meq/ liter	Chloride meq/ liter	Inorganic Phosphate mg/100 ml	Glutaryl Transpeptidase Sigma units/ml	Creatinine Phosphokinase Sigma units/ml
Control:															
7470	H	96	2.08	972	15	38	9.00	4.42	163	150	4.5	122	5.8	53	11
7479	H	126	22.2	930	19	29	8.40	4.72	162	151	4.4	113	6.7	46	9
7493	F	96	19.0	750	19	34	8.95	4.92	160	151	5.5	114	6.9	43	7
7495	F	117	24.2	504	25	31	8.68	5.49	179	156	4.7	113	6.3	51	6
Mean		103	21.6	789	20	33	8.76	4.89	166	152	4.8	113	6.4	48	8
1 mg/kg/day:															
7467	H	98	21.0	840	17	30	225	8.20	5.10	151	4.2	108	6.0	49	5
7473	H	71	15.4	852	17	38	175	7.92	5.20	152	4.5	115	7.1	32	7
7489	F	96	22.4	420	14	20	160	8.90	4.70	153	4.2	111	6.1	23	9
7492	F	70	19.8	756	12	28	125	8.90	4.21	154	4.7	117	6.1	27	5
Mean		84	24.7	717	15	29	171	8.48	4.80	153	4.4	113	6.3	33	7
3 mg/kg/day:															
7469	H	107	25.0	1110	19	41	131	8.90	5.34	160	4.8	113	6.4	47	6
7474	H	82	24.9	480	15	38	161	8.28	5.12	154	5.0	115	4.9	16	6
7487	F	93	29.0	570	17	27	155	7.70	4.96	150	4.3	113	5.0	24	7
7497	F	83	27.8	780	22	31	165	8.95	5.32	155	4.8	117	6.3	32	5
Mean		91	26.7	735	18	34	153	8.46	5.19	155	4.7	115	5.7	30	6
10 mg/kg/day:															
7475	H	105	22.2	720	22	32	172	9.80	5.09	158	4.3	111	5.8	38	6
7480	H	125	15.3	708	19	33	104	8.70	5.12	150	5.0	114	6.3	41	8
7491	F	88	30.2	1032	15	42	84	9.38	5.14	151	4.5	115	5.5	23	6
7498	F	85	21.2	528	20	38	184	8.60	5.48	115	4.5	113	5.0	32	7
Mean		101	22.2	747	19	36	134	9.12	5.21	154	4.6	113	5.7	34	7
30 mg/kg/day:															
7472	H	92	18.4	1014	23	43	108	8.60	5.12	153	4.2	113	5.6	26	9
7477	H	77	27.6	378	14	32	67	9.55	6.09	155	3.5	110	6.7	49	6
7499	F	109	15.8	612	23	47	56	9.42	4.92	155	5.0	109	5.7	30	5
7490	F	Died													
Mean		93	20.6	668	20	41	77	9.19	5.38	154	4.2	111	6.0	38	7

FH-3422:

Ninety Day Subacute Rheuma Monkey Toxicity Study.

TABLE 8.

Individual Urinalysis Values - Control.

Group, Monkey Number	Sex	Volume ml	Color and Appear.	pH	Spec. Grav.	Protein	Glucose	Occult Blood	Ke- tones	Leuco- cytes	Erythro- cytes	Epi. Cells	Urites	Triple Phos.	Calc. Ox.	Bac- teria
Controls:																
7470	M	45	S-cl	7.8	1.024	N	N	N	N	-	-	occ	F	occ	-	N
7479	M	18	S-cl	7.4	1.042	N	N	N	N	-	-	occ	F	F	-	F
7493	F	30	S-cl	6.2	1.037	N	N	N	N	-	-	occ	occ	occ	-	F
7495	F	23	DS-cl	7.6	1.040	N	N	2+	N	-	-	occ	F	F	-	N
1 mg/kg/day:																
7467	M	15	S-cl	7.8	1.042	N	N	N	N	-	occ	occ	F	F	-	N
7473	M	65	LS-cl	7.8	1.030	N	N	N	N	-	occ	-	F	occ	-	F
7489	F	25	S-cl	6.3	1.033	N	N	tr	N	-	-	-	F	F	-	F
7492	F	14	S-cl	8.0	1.040	N	N	N	N	-	occ	-	F	F	-	F
3 mg/kg/day:																
7469	M	25	S-cl	7.8	1.024	N	N	N	N	-	1-3	-	occ	F	-	F
7474	M	20	S-cl	8.2	1.032	N	N	N	N	-	-	-	occ	F	-	F
7487	F	45	S-cl	9.0	1.032	N	N	N	N	-	-	occ	F	occ	-	F
7497	F	25	S-cl	7.3	1.035	N	N	N	N	-	occ	occ	F	F	-	N
10 mg/kg/day:																
7475	M	25	S-cl	8.0	1.040	N	N	N	N	-	-	occ	F	occ	-	N
7480	M	30	S-cl	6.8	1.019	N	N	tr	N	-	-	-	F	H	-	F
7491	F	20	S-cl	7.4	1.038	N	N	N	N	-	-	-	F	occ	-	F
7498	F	35	LS-cl	8.0	1.030	N	N	tr	N	-	occ	occ	F	F	-	F
30 mg/kg/day:																
7472	M	9	DS-cl	7.8	1.033	N	N	N	N	-	-	-	F	F	-	F
7477	M	30	S-cl	7.7	1.043	N	N	N	N	-	-	-	F	occ	-	F
7490	F	155	LS-cl	8.5	1.013	N	N	N	N	-	occ	-	occ	F	-	F
7499	F	23	S-cl	7.6	1.041	N	N	2+	N	-	occ	1-3	F	F	-	N

137-088

Code: tr - Trace S - Straw N - Negative LAm - Light Amber
 1+ - Trace to slight LS - Light straw F - Few DAm - Dark Amber
 2+ - Slight to moderate DS - Dark straw M - Many occ - Occasional
 3+ - Moderate cl - Cloudy L - Loaded - None seen
 4+ - Marked C - Clear R - Rare

FH-1422:

Ninety Day Subacute Rheus Monkey Toxicity Study.

TABLE 9.

Individual Urinalysis Values - 1 Month.

Group, Monkey Number	Sex	Volume ml	Color and Appear.	pH	Spec. Grav.	Protein	Glucose	Occult Blood	Ketones	Leucocytes	Erythrocytes	Epi. Cells	Urate	Triple Phos.	Calc. Ox.	Bacterin
<u>Control:</u>																
7470	M	40	LS-C	7.4	1.019	N	N	N	N	-	-	occ	F	F	-	F
7479	M	35	LS-C	7.5	1.027	N	N	N	N	-	occ	occ	F	occ	-	F
7493	F	50	LS-C	7.9	1.030	N	N	N	N	-	-	occ	F	occ	-	F
7495	F	45	LS-cl	7.8	1.031	N	N	N	N	-	-	-	F	occ	-	H
<u>1 mg/kg/day:</u>																
7467	M	15	LS-C	8.3	1.032	N	N	N	N	-	-	-	F	F	-	H
7473	M	50	LS-C	7.8	1.021	N	N	N	N	-	-	occ	F	occ	-	H
7489	F	50	LS-cl	7.5	1.019	N	N	N	N	-	occ	occ	F	F	-	H
7492	F	5	LS-cl	8.7	1.031	N	N	N	N	-	1-3	1-3	F	F	-	H
<u>3 mg/kg/day:</u>																
7469	M	40	LS-C	7.5	1.028	N	N	N	N	-	-	occ	F	occ	-	F
7474	M	125	LS-C	7.9	1.019	N	N	N	N	-	-	occ	F	F	-	H
7487	F	50	LS-cl	6.8	1.029	N	N	N	N	-	-	-	F	F	-	F
7497	F	45	LS-C	7.9	1.016	N	N	N	N	-	-	-	F	F	-	H
<u>10 mg/kg/day:</u>																
7475	M	50	LS-C	8.0	1.026	N	N	N	N	-	-	-	F	F	H	H
7480	M	50	LS-C	6.2	1.031	N	N	N	N	-	occ	occ	F	F	-	F
7491	F	20	LS-C	7.1	1.038	N	N	tr	N	-	-	-	F	occ	-	F
7498	F	40	LS-C	7.5	1.029	N	N	N	N	-	occ	-	F	F	-	H
<u>30 mg/kg/day:</u>																
7472	M	30	LS-C	8.0	1.029	N	N	N	N	-	-	-	F	F	occ	H
7477	M	30	LS-cl	8.8	1.035	N	N	N	N	-	occ	occ	F	F	occ	H
7490	F	100	LS-C	7.8	1.013	N	N	N	N	-	-	-	F	F	occ	F
7499	F	30	LS-C	8.2	1.032	N	N	N	N	-	-	-	F	F	F	H

137-088

Code: tr - Trace S - Straw N - Negative LAm - Light Amber
 1+ - Trace to slight LS - Light straw F - Few DAm - Dark Amber
 2+ - Slight to moderate DS - Dark straw H - Many occ - Occasional
 3+ - Moderate cl - Cloudy L - Loaded - - None seen
 4+ - Marked C - Clear R - Rare

FM-1422:

Ninety Day Subacute Rheus Monkey Toxicity Study.

TABLE 10.

Individual Urinalysis Values - 3 Months.

Group, Monkey Number	Sex	Volume ml	Color and Appear.	pH	Spec. Grav.	Protein	Glucose	Occult Blood	Ke- tones	leuco- cytes	Erythro- cytes	Epi. Cells	Urate	Triple Phos.	Calc. Ox.	Bac- teria
Control:																
7470	M	55	LS-cl	6.5	1.020	N	N	tr	N	-	-	occ	F	occ	-	M
7479	M	50	LS-cl	7.0	1.026	N	N	N	N	-	-	-	F	F	-	F
7493	F	45	S-cl	8.5	1.033	N	N	tr	N	-	occ	occ	F	F	-	M
7495	F	35	S-cl	8.0	1.035	N	N	N	N	-	-	occ	F	F	-	F
1 mg/kg/day:																
7467	M	45	S-cl	9.0	1.034	N	N	N	N	-	occ	-	F	F	F	F
7473	M	250	LS-cl	6.5	QNS	N	N	N	N	-	-	occ	F	occ	-	M
7489	F	35	S-cl	9.0	1.012	N	N	2+	N	-	18-20	occ	M	occ	-	M
7492	F	35	S-cl	8.5	1.032	N	N	3+	N	-	-	-	F	occ	-	M
3 mg/kg/day:																
7469	M	60	LS-cl	7.5	1.027	N	N	N	N	-	-	occ	F	F	occ	M
7474	M	110	LS-cl	8.0	1.017	N	N	N	N	-	-	occ	F	occ	-	F
7487	F	35	S-cl	7.5	1.035	N	N	N	N	-	-	occ	F	F	-	M
7497	F	125	LS-cl	7.5	1.012	N	N	N	N	-	-	-	F	occ	-	F
10 mg/kg/day:																
7475	M	50	LS-cl	8.0	1.026	N	N	tr	N	-	-	-	F	F	-	F
7480	M	60	LS-cl	6.5	1.024	N	N	N	N	-	occ	-	F	F	-	F
7491	F	45	LS-cl	8.0	1.025	N	N	2+	N	-	-	-	F	F	-	M
7498	F	25	LS-cl	8.5	1.031	N	N	2+	N	-	-	occ	F	F	-	F
30 mg/kg/day:																
7472	M	5	S-cl	6.8	1.043	N	N	N	N	-	-	occ	F	F	-	F
7477	M	45	LS-cl	8.5	1.032	N	N	N	N	-	-	-	F	F	-	F
7499	F	35	LS-cl	7.0	1.033	N	N	N	N	-	occ	-	F	F	-	M
7490	F	Died														

117-088

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

S - Straw
 LS - Light straw
 DS - Dark straw
 cl - Cloudy
 C - Clear

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

LAm - Light Amber
 DAm - Dark Amber
 occ - Occasional
 QNS - Quantity not sufficient
 - None seen

FM-3422:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 11.

Necropsy Observations.

Site Lesion	Sex	Age	Control				1 mg/kg/day				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day			
			M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
			7470	7479	7493	7495	7467	7473	7489	7492	7469	7474	7487	7497	7475	7480	7491	7498	7472	7477	7490*	7499
No gross lesions					x	x							x				x					
Lymph nodes (bronchial, mediastinal)																						
black discoloration													x						x			
Lung																						
yellow-red-gray foci (mice lesions)			x					x	x			x	x			x	x			x		x
pleural adhesions			x						x							x	x					
yellow focus																x						
black discoloration																			x			
Heart																						
subendocardial hemorrhages, I-V																						
septum																					x	
Abdominal cavity																						
esophagostomum nodules, mesentery			x	x																		
Liver																						
gray foci				x																		
adhered to diaphragm								x														
abscess with necrosis/gray-yellow																						
area of necrosis																x				x		
red-yellow mottling																			x			x
Stomach																						
mucosal congestion, mucoid contents																					x	
mucosal thickening, fundic region				x																		
area of hemorrhage/red focus,																						
fundic region								x				x										
Small intestine																						
mucoid contents																					x	
Large intestine																						
mucosal congestion, ileocolic orifice																						x
red foci/erosions, mucosa												x										x
esophagostomum nodules			x	x					x	x	x				x	x	x					x
soft to firm fecal contents																				x		

*died

TABLE 12.

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

Group, Monkey Number	Sex	Body Wt. kg	Spleen		Liver		Adrenals		Kidneys		Testes/ Ovaries		
			g	Z	g	Z	g	Zx10	g	Z	g	Zx10 ²	
Terminal Sacrifice:													
Control:													
7470	H	3.55	5.74	0.15	70.00	1.97	0.68	0.19	17.47	0.49	1.15	0.03	
7479	H	3.10	3.51	0.11	61.88	2.00	0.89	0.29	12.88	0.42	0.83	0.03	
Mean		3.33	4.43	0.13	65.94	1.98	0.79	0.24	15.18	0.45	0.99	0.03	
7493	F	3.55	4.16	0.12	74.63	2.10	0.76	0.21	16.50	0.46	0.45	1.27	
7495	F	2.75	2.22	0.08	54.72	1.99	0.77	0.28	14.07	0.51	0.16	0.58	
Mean		3.15	3.19	0.10	64.68	2.05	0.77	0.25	15.29	0.49	0.31	0.92	
1.0 mg/kg/day:													
7467	H	3.85	2.86	0.07	74.19	1.93	0.91	0.24	15.70	0.41	1.72	0.04	
7473	H	2.90	3.27	0.11	59.39	2.05	0.71	0.24	12.37	0.43	1.21	0.04	
Mean		3.38	3.07	0.09	66.79	1.99	0.81	0.24	14.04	0.42	1.47	0.04	
7489	F	3.10	2.83	0.09	74.11	2.39	0.75	0.24	13.82	0.45	0.29	0.94	
7492	F	3.45	3.81	0.11	65.96	1.91	0.55	0.16	15.86	0.46	0.28	0.81	
Mean		3.28	3.32	0.10	70.04	2.15	0.65	0.20	14.84	0.45	0.29	0.87	
3.0 mg/kg/day:													
7469	H	4.10	4.24	0.10	90.74	2.21	0.60	0.15	17.31	0.42	0.88	0.02	
7474	H	3.55	3.35	0.09	84.32	2.38	0.80	0.23	17.70	0.50	1.22	0.03	
Mean		3.83	3.80	0.10	87.53	2.29	0.70	0.19	17.51	0.46	1.05	0.03	
7487	F	3.10	1.81	0.06	77.79	2.51	0.75	0.24	15.08	0.49	0.22	0.71	
7497	F	3.05	3.43	0.11	62.79	2.06	0.64	0.21	12.45	0.41	0.26	0.85	
Mean		3.08	2.62	0.09	70.29	2.28	0.70	0.23	13.77	0.45	0.24	0.78	
10.0 mg/kg/day:													
7475	H	3.45	4.28	0.12	84.65	2.45	0.60	0.17	16.40	0.48	1.40	0.04	
7480	H	3.55	2.39	0.07	92.28	2.60	0.82	0.23	18.48	0.52	2.53	0.07	
Mean		3.50	3.34	0.10	88.47	2.53*	0.71	0.20	17.44	0.50	1.97	0.06	
7491	F	3.05	4.90	0.16	86.57	2.84	0.98	0.32	15.19	0.50	0.24	0.79	
7498	F	2.95	3.60	0.12	87.14	2.82	0.90	0.31	13.82	0.47	0.27	0.92	
Mean		3.00	4.25	0.14	84.86	2.83	0.94	0.31	14.51	0.48	0.26	0.85	
30.0 mg/kg/day:													
7472	H	3.05	3.79	0.12	97.06	3.18	0.76	0.25	14.26	0.47	1.01	0.03	
7477	H	3.75	3.24	0.09	108.04	2.88	0.84	0.22	16.26	0.43	11.79	0.31	
Mean		3.40	3.52	0.11	102.55*	3.03**	0.80	0.24	15.26	0.45	6.40	0.17	
7499 ^a	F	2.65	3.13	0.12	94.62	3.57	0.70	0.26	15.07	0.57	0.22	0.83	
Deaths:													
30.0 mg/kg/day:													
7490 ^a	F	2.85	3.23	0.11	131.72	4.62	1.42	0.50	15.77	0.55	0.34	1.19	

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, $p < 0.05$.^aNot included in statistical analysis.**Significantly different from Control group mean, $p < 0.01$.

TABLE 12. Cont. Absolute (Grams) and Relative (% Body Weight) Organ Weights, Terminal Sacrifice and Deaths.

Group, Monkey Number	Sex	Body Wt. kg	Heart		Thyroid/ Parathyroid		Brain		Pituitary	
			g	%	g	%x10	g	%	g	%x10
Terminal Sacrifices:										
Control:										
7470	M	3.55	14.60	0.41	0.693	0.20	96.38	2.71	0.072	0.20
7479	M	3.10	15.15	0.49	0.771	0.25	92.88	3.00	0.028	0.09
Mean		3.33	14.88	0.45	0.732	0.22	94.63	2.86	0.050	0.15
7493	F	3.55	16.53	0.47	0.950	0.27	80.59	2.27	0.052	0.15
7495	F	2.75	11.56	0.42	0.624	0.23	84.39	3.07	0.068	0.25
Mean		3.15	14.05	0.44	0.787	0.25	82.49	2.67	0.060	0.20
1.0 mg/kg/day:										
7467	M	3.85	14.34	0.37	1.062	0.28	96.23	2.50	0.072	0.19
7473	M	2.90	12.18	0.42	0.455	0.16	93.87	3.24	0.044	0.15
Mean		3.38	13.26	0.40	0.759	0.22	95.05	2.87	0.058	0.17
7489	F	3.10	16.12	0.52	0.913	0.29	77.08	2.49	0.058	0.19
7492	F	3.45	16.25	0.47	0.820	0.24	81.03	2.35	0.072	0.21
Mean		3.28	16.19	0.50	0.867	0.27	79.06	2.42	0.065	0.20
3.0 mg/kg/day:										
7469	M	4.10	18.06	0.44	0.856	0.21	91.86	2.24	0.094	0.23
7474	M	3.55	16.21	0.46	1.545	0.44	90.12	2.54	0.058	0.16
Mean		3.83	17.14	0.45	1.201	0.32	90.99	2.39	0.076	0.20
7487	F	3.10	13.88	0.45	0.710	0.23	82.44	2.66	0.069	0.22
7497	F	3.05	13.29	0.44	0.533	0.17	82.78	2.71	0.054	0.18
Mean		3.08	13.59	0.44	0.622	0.20	82.61	2.69	0.062	0.20
10.0 mg/kg/day:										
7475	M	3.45	14.38	0.42	0.818	0.24	79.36	2.30	0.050	0.14
7480	M	3.55	16.04	0.45	0.679	0.19	82.96	2.34	0.062	0.17
Mean		3.50	15.21	0.43	0.749	0.21	81.16**	2.32	0.056	0.16
7491	F	3.05	13.69	0.45	0.903	0.30	77.70	2.55	0.056	0.18
7498	F	2.95	13.24	0.45	0.431	0.15	79.31	2.69	0.051	0.17
Mean		3.00	13.47	0.45	0.667	0.22	78.51	2.62	0.054	0.18
30.0 mg/kg/day:										
7472	M	3.05	12.87	0.42	0.620	0.20	84.67	2.78	0.062	0.20
7477	M	3.75	15.30	0.41	0.670	0.18	85.63	2.28	0.062	0.17
Mean		3.40	14.09	0.41	0.645	0.19	85.15*	2.53	0.062	0.18
7494 ^u	F	2.65	13.69	0.52	0.493	0.19	76.87	2.90	0.052	0.20
Deaths:										
20 mg/kg/day:										
7490 ^u	F	2.85	16.01	0.56	0.445	0.16	83.29	2.92	0.110	0.39

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

FM-3422:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 13.

Microscopic Observations.

Tissue Lesion	Group Monkey Number	Control				1 mg/kg/day				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day			
		M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
Brain		7470	7479	7493	7495	7467	7471	7489	7492	7469	7474	7487	7497	7475	7486	7491	7498	7472	7477	7490*	7499
small focus of neutrophil infiltrate in leptomeninges		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1		1
																				3	
Spinal Cord		1	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
focus of perivascular lymphoid infiltrates in arachnoid						3															
Peripheral Nerve			1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
focus of perivascular lymphoid infiltrate in perineural tissue		2																			
Eye		1		1		1	1		1	1	1	3				1		1			
acute conjunctivitis																					
focus of lymphoid infiltrate in ciliary muscle			2											2							
follicular conjunctivitis					4			2						3	2						
foci of interstitial lymphoid infiltrates in lacrimal gland																					2
Sarcocystis sp. in ocular muscle																					x
foci of lymphoid infiltrates in palpebral/ocular conjunctiva												2			2		3		2		
Pituitary			-	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
small parenchymal cyst		x																			
Thyroid		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Parathyroid		1	-	1	1	1	-	1	-	1	-	1	1	1	1	-	1	-	1	-	1
Adrenal			1		1			1	1			1		1	1		1		1		
small focus/foci of dystrophic mineralization		x		x		x	x			x	x	x		x						x	
small foci of lymphoid infiltrates in cortical sinusoids																		3			
diffuse congestion																					
diffuse lipid depletion																		5		5	3
acidophilic degeneration of individual to small groups of cells																					3
Trachea						1	1			1	1			1							
foci of inflammatory cell infiltrates in lamina propria		2										2		2		2				2	
foci of inflammatory cell infiltrates in lamina propria and mucosa			3	3	2			3	2			2				3		2	3		3
focal cystic dilatation of tracheal glands		3							3					2							

Code:

x - condition present
 1 - not remarkable
 2 - very slight
 3 - slight

4 - moderate
 5 - marked
 6 - extreme
 - not available
 *died

FM-3422:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 13. Conc.

Microscopic Observations.

Tissue Lesion	Group, Monkey Number	Control				1 mg/kg/dav				3 mg/kg/dav				10 mg/kg/dav				30 mg/kg/dav			
		M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
Lung		7470	7479	7493	7495	7467	7473	7489	7492	7469	7474	7487	7497	7475	7480	7491	7498	7472	7477	7490*	7499
acarian pigment (peribronchial, peribronchiolar, perivascular)		2	2	2	2	2	3	2	2	2	2	3	3	3	2	2		4	3	3	3
focus/foci of perivascular lymphoid infiltrates		3			3																
foci of peribronchial/peribronchiolar lymphoid aggregates		2	2	3	3	3	2	3	3	3	3	2	2	2	2	3		3	4	2	3
lung mite in bronchiolar lumina					x				x									x			x
acute focal bronchopneumonia																		2			
chronic focal pleuritis																		3			
interstitial pneumonia		3				3															3
acarian pigment in bronchial lymph node								3				3	4					4			
focal hemorrhage							3														3
Heart		1				1	1			1	1							1			
focus/foci of interstitial lymphoid infiltrates			2	2	2		2	2		2	2			2	2	2	2		2	3	3
focal subepicardial hemorrhage																			3		
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	1		1	1	1	1	1	1	1	1
diffuse congestion												3									
Lymph Nodes		-	1	-		1	1	1	1	1	1			1	1	1					-
parasitic granuloma														x							
focal aggregates of hemosiderin-laden macrophages					3					2	3							3	2		3
Thymus		1	1	1	1	1	1	1	1	1	1	-		1	1	1	1	1	1	-	1
cyst										x											
Tonsil		-	1							1	-			1	-	-	1	1			
keratin-filled cyst						x												x			
foci of interstitial lymphoid infiltrates in muscle						2				2											
foci of inflammatory cell infiltrates in mucosal epithelium and lamina propria								3	3			2						2	2	3	
Sarcocystis sp. in muscle		x																			
Gongylonema sp. in mucosal epithelium			x																		
foci of inflammatory cell infiltrates in surface epithelium and tonsillar crypts								3													
Tongue																					
Sarcocystis sp.		x																			
foci of inflammatory cell infiltrates in lamina propria and mucosal epithelium		3	3	2	2	2	3	3		2	2	2	2	2	2	2		3	3	3	3
foci of inflammatory cell infiltrates in muscle		2												2							
foci of ballooning degeneration of mucosal epithelium																					3
foci of hyaline degeneration of muscle			3	3		3	3	3	3	3	3	3		3				3	3	4	2
foreign body granuloma										x											

Code:

x - condition present
 1 - not remarkable
 2 - very slight
 3 - slight

4 - moderate
 5 - marked
 6 - extreme
 - not available
 *died

FM-3422:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 13. Cont.

Microscopic Observations.

Tissue Lesion	Group, Monkey Number	Control				1 mg/kg/dav				3 mg/kg/dav				10 mg/kg/dav				30 mg/kg/dav			
		M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
Salivary gland								1			1										
foci of interstitial lymphoid infiltrates		3	3	3	3	2	3	2		2		2	2	3	3	2	2	2	2	2	2
Esophagus					1	1	1			1											
foci of inflammatory cell infiltrates in lamina propria		3	2	2		2	2			2	2	2		2	2	2	2		2	2	2
foci of interstitial lymphoid infiltrates in muscularis		3	2							2	2	2		2				2			
Gongylonema sp. in epithelium														x							
foci of black pigment aggregates in periesophageal lymph node																		3			
Stomach																					
foci of inflammatory cell infiltrates in lamina propria		3				2	4			2				3	3	3	2	3	3	3	
foci of inflammatory cell infiltrates in lamina propria and submucosa		3			4					3	3	3						4			
foci of inflammatory cell infiltrates in lamina propria, submucosa and muscularis								3	3												
foci of inflammatory cell infiltrates in lamina propria, submucosa, muscularis and serosa					4																
foci of inflammatory cell infiltrates in muscularis and serosa														2							
cystic gastric gland														x							
diffuse congestion																				3	
Small Intestine																					
encapsulated abscess in mesentery		-	1	1	1	1	1	1		1	1	1	1		1	1	1	1	1	1	1
parasitic granuloma in lamina propria									x												
														x							
Cecum																					
parasitic granuloma in submucosa		1	1	1		1	1	1				1	1			1		1		1	
parasitic granuloma in muscularis and mesentery										x	x							x			
parasitic granuloma in serosa		x												x							
parasitic granuloma in mesentery									x							x					x
focal aggregates of hemosiderin pigment in muscularis/mesentery									3		3										
focal inflammatory cell infiltrates in mesentery and muscularis																3					
parasitic granuloma in muscularis																x					

Code:

x - condition present
 1 - not remarkable
 2 - very slight
 3 - slight

4 - moderate
 5 - marked
 6 - extreme
 - not available
 *died

FM-3422:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 13. Cont.

Microscopic Observations.

Tissue Lesion	Group. Monkey Number	Control				1 mg/kg/day				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day			
		M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
Colon						1	1			1	1	1				1	1			1	1
parasitic granuloma in submucosa			x					x													x
parasitic granuloma in muscularis		x						x					x								x
parasitic granuloma in serosa		x	x																		
parasitic granuloma in mesentery								x	x												
foci of inflammatory cell infiltrates in muscularis, serosa and mesentery		3		3				3	3												
foci of inflammatory cell infiltrates in mesentery			2		2				3								2				
foci of inflammatory cell infiltrates in muscularis																					3
focal aggregates of hemosiderin pigment in muscularis								3													3
foci of inflammatory cell infiltrates in serosa			2							3					2						2
small focus of mucosal hemorrhage																					
Rectum		1		1		1		1	1	1	1	1	1	1	1	1	1	1		1	1
foci of inflammatory cell infiltrates in muscularis			3		2													2			
foci of inflammatory cell infiltrates in lamina propria			3		3																
focal hyaline degeneration of muscle			3		3																
focal aggregates of hemosiderin pigment in submucosa								3													
Pancreas		1	1	1	1	1	1			1	1	1	1			1	1			1	1
decreased cell size, loss of zymogen granules																				4	4
focal periductal lymphoid infiltrates								3						2	3					3	
focal interstitial lymphoid infiltrates									3						3						
Liver																					
portal inflammatory cell infiltrates		2	3	4	3	2	3	3	3	2	3	4		2		4		3	2	2	2
focal/multifocal bile duct proliferation			3		2												3				
acidophilic degeneration of individual to small groups of hepatocytes			3	2	3	3	2	2	2	3		3		3	2		4		2	2	2
diffuse congestion																					
small focus/foci of inflammatory cell infiltrates in parenchyma		2	2	3	2		2	3	2	2	2	2	3		2	3	2		3	2	
several large areas of coagulation necrosis																				4	
focal capsular fibrosis								3													
focal cholangiohepatitis			4																		
focal parenchymal fibrosis			3																		
focal cytoplasmic vacuolation of hepatocytes			2																		

Code: x - condition present 4 - moderate
 1 - not remarkable 3 - marked
 2 - very slight 5 - extreme
 3 - slight - not available
 *died

137-088

FM-3422:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 13. Cont.

Microscopic Observations.

Tissue Lesion	Group, Monkey Number	Control				1 mg/kg/day				3 mg/kg/day				10 mg/kg/day				30 mg/kg/day			
		M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
		7470	7479	7493	7495	7467	7473	7489	7492	7469	7474	7487	7497	7475	7480	7491	7498	7472	7477	7490*	7499
Gallbladder																		1	1	1	
foci of inflammatory cell infiltrates in lamina propria				3	3	2				2		2		3							3
foci of inflammatory cell infiltrates in lamina propria and muscularis			3			2				3	3			2							
foci of inflammatory cell infiltrates in lamina propria, muscularis and serosa		3						3	3							3	3				
foci of hemorrhage in lamina propria and muscularis		3																			
Kidney														1							
focus/foci of interstitial lymphoid infiltrates		2	3	2	2	2	3	3	2	3	3	2	3	2	2	2	2	2	2	2	2
small foci of dystrophic mineralization		2				2		2				2						2	2		
diffuse congestion																				3	
multinucleated lining epithelium in papillary ducts										x										x	
brown pigment in tubular epithelium												3									
ectopic adrenal in cortex								x													
Urinary Bladder						1		-	1												
foci of inflammatory cell infiltrates in lamina propria				3	2			2				3		3	2	2	2	2	2	2	2
foci of inflammatory cell infiltrates in lamina propria and muscularis			3																		
foci of inflammatory cell infiltrates in lamina propria, muscularis and serosa		3				3				2	2										
Testes																		1			
prepubertal development		x	x			x	x			x	x			x	x			x			
foci of inflammatory cell infiltrates in capsule										3				3							
small focus of dystrophic mineralization						x															
Ovaries				1	1			1				1			1	1			1		
small foci of dystrophic mineralization corpus luteum								x				x								x	
Prostate																					
foci of interstitial lymphoid infiltrates		3	3			2	3			3	2			3	3			3			
focus of lymphoid infiltrates in ganglion																		3			
lymphoid nodule(s)/infiltrates in corpus cavernosum		x	x			x				x				x	x			x			

Code:

x - condition present
 1 - not remarkable
 2 - very slight
 3 - slight

4 - moderate
 5 - marked
 6 - extreme
 - not available
 a - autolyzed
 *died

FM-3422:

Ninety Day Subacute Rhesus Monkey Toxicity Study.

TABLE 13. Cont.

Microscopic Observation.

Tissue Lesion	Group, Monkey Number	Control				1 mg/kg/dav				1 mg/kg/dav				10 mg/kg/dav				30 mg/kg/dav			
		M		F		M		F		M		F		M		F		M		F	
		7470	7479	7493	7495	7467	7473	7489	7492	7469	7474	7487	7497	7475	7480	7491	7498	7472	7477	7490*	7499
Uterus				1	1							1	1			1				1	1
foci of lymphoid infiltrates in broad ligament and myometrium																3					
loss of endometrial surface epithelium, blood in lamina propria and uterine glands								3	3												
Vagina																					
foci of lymphoid infiltrates in mucosal epithelium and lamina propria				3	4			3	4			3	3			3	3			3	4
foci of lymphoid infiltrates in muscularis				2	3			3				2	2			2	2			2	4
Skeletal Muscle			1	1	1					1	1	1	1	1	1			1	1	1	
Sarcocystis sp.	x									x											x
foci of interstitial lymphoid infiltrates						2	2	2	2							2	2				2
Mammary Gland																					
dermal inflammatory cell infiltrates		2	2	3	2	3		3	2	2	2	3		2	2	3	3	2	2		
few inflammatory cells in alveolar lumina				x				x				x	x	x		x	x	x		x	
hyperkeratosis							3	3				3	3			3	3			3	
focal hemorrhage						3															
small focus of epidermal hydropic degeneration																	x				
brown pigment in dermis			x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Skin																					
dermal inflammatory cell infiltrates			3			3	3	2													2
diffuse acanthosis			3																		
hyperkeratosis						3						3				3				3	
focal hemorrhage						4															
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
Femur		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Rib		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	-	1	1

Code:

x - condition present
 1 - not remarkable
 2 - very slight
 3 - slight

4 - moderate
 5 - marked
 6 - extreme
 - not available
 *diad