Abortion Studies

T-3351

SPONSOR: 3M Company

COMPOUND: Fluorad® Fluorochemical Surfactant FC-95

SUBJECT: 90-Day Subacute Rhesus Monkey Toxicity Study.

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I. SYNOPSIS

Fluorad® Fluorochemical Surfactant FC-95 was administered to rhesus monkeys, in aqueous suspension at dosage levels of 10, 30, 100 and 300 mg/kg/day for 20 days. Two male and two female monkeys were initiated at each dosage level and also in a control group. The control group was treated only with distilled water. The monkeys were observed twice daily for general physical appearance and behavior and pharmacotoxic signs. Body weights were recorded weekly. Hematological, biochemical and urine studies were conducted only in the control period. The study was terminated after 20 days because of the early deaths of the monkeys in all treatment groups.

The monkeys treated with 300 mg/kg/day died between the 2nd and 4th days after the initiation of the study. From the first through the second day, the following signs of toxicity were observed: anorexia, decreased activity (from slight to severe before death), emesis with some diarrhea, body stiffening, general body trembling and twitching, weakness, convulsions and prostration.

The administration of 100 mg/kg/day of the test compound led to death of all monkeys between the 3rd and 5th day of study. The monkeys treated at 30 mg/kg/day died between the 7th and 10th day and those treated at 10 mg/kg/day died between the 11th and 20th day of study. At each of these dosage levels the toxic symptoms were the same as for the monkeys at the 300-mg/kg/day dosage level. However, the time of appearance of the toxic symptoms was related to dosage level.

All deaths were considered as resulting from compound effect. A yellowish-brown liver coloration noted at necropsy in several monkeys from the 100 and 300 mg/kg/day levels was the only gross finding which was considered compound-related. No histomorphologic basis for this finding was observed. Other gross and microscopic lesions were of an agonal nature or were those which are commonly seen in untreated monkeys. Organ weights of treated monkeys were considered within normal limits.

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II. COMPOUND

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

Label	Description
Fluorad® Flurochemical Surfactant FC-95 3M 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. METHODS:

1. General Procedure:

Ten male (weighing from 3.05 to 3.80 kg) and ten female (weighing from 2.75 to 4.10 kg) rhesus monkeys obtained from Primate Imports, Port Washington, New York were initiated into this study. The monkeys were housed individually in hanging wire mesh "squeeze-type" cages and maintained in a temperature-, humidity- and light-controlled room. 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. Prior to initiation of compound administration complete physical examinations were conducted by a staff veterinarian. Only monkeys in good health were selected.

This study was initiated on January 10, 1978. The study was terminated on January 30, 1978 because of the deaths of the monkeys.

2. Compound Administration:

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

Group	Number of Monkeys		Dosage Level
	Male	Female	mg/kg/day
I	2	2	Control
II	2	2	10
III	2	2	30
IV	2	2	100
V	2	2	300

The test compound, suspended in distilled water, was administered 7 days each week by gavage. All doses were contained in the same volume of water. Also the same 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 only in the control period, because of the early deaths of all treated monkeys.

4. Clinical Laboratory Tests:

Blood and urine samples were obtained for analysis from all monkeys only in the control period. The monkeys were fasted overnight prior to the collection of blood and urine samples.

a. Hematology:

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

b. Biochemistry:

Biochemical studies included: blood glucose[8], blood urea nitrogen[8], serum alkaline phosphatase[8], serum glutamic oxalacetic transaminase[8], serum glutamic pyruvic transaminase[8], cholesterol[9], total protein[9], albumin[8], sodium[10], potassium[10], chloride[9], inorganic phosphate[9], γ-glutamyl transpeptidase[11], creatinine phosphokinase[12].

c. Urinalysis:

Urinalysis included: measurement of volume, pH[13] and specific gravity; description of color and appearance; qualitative tests for protein[13], glucose[13], ketones[13], occult blood[13] and microscopic examination of the sediment.

d. Statistical Analysis:

No statistical analysis on the laboratory tests was performed because the laboratory tests were obtained for the control period only, however statistical analysis of body weights were conducted.

B. RESULTS:

1. General Behavior, Appearance and Survival:

The monkeys from the 300-mg/kg/day dosage level group died between the 2nd and 4th day of the study. From the 1st or 2nd day the following signs of toxicity were observed: anorexia, decreased activity (slight to severe), emesis (frothy or food like emesis) and occasional diarrhea. Antemortem observations were body stiffening and stiffened limbs, general body trembling and twitching, convulsions and prostration.

The monkeys at the 100-mg/kg/day dosage level died between the 3rd and the 5th day of the study. The same toxic symptoms as the previous group were noted from the 2nd day.

The administration of 30 mg/kg/day led to the same indications of toxicity, but appeared some days later. The deaths also occurred later; from the 7th to the 10th day of the study. The monkeys at the 10-mg/kg/day dosage level died between day 11 and 20 of the study. The signs of toxicity which appeared in the second week of the study were: anorexia, diarrhea, decreased activity, emesis, marked

weakness, prostration, general body trembling and tremoring and stiffening of the limbs. One of the monkeys had black stools and one had erythema of the face.

There were no deaths nor unusual behavior in the control group. Occasionally, soft stools were noted.

2. Body Weights (Table 1):

The monkeys from all treated groups lost body weight when the terminal body weight was compared with the initial body weight.

In the first week of the study, there was no statistically significant decrease in the body weight of monkeys at the 10- and 30-mg/kg/day dosage levels.

3. Laboratory Tests:

a. Hematology:

The control period values are contained in Table 2.

b. Biochemistry:

The control period values are contained in Table 3.

c. Urinalysis:

The control period values are contained in Table 4.

IV. PATHOLOGICAL STUDIES

A. METHODS:

1. Gross Pathology:

All experimental monkeys died during the study period. 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. A new study was initiated (137-092) utilizing the control monkeys from this study.

2. Histopathology:

Microscopic examination of the following formalin fixed hematoxylin and eosin stained paraffin sections was performed for all animals in the experimental groups:

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

and any other tissue(s) with lesions

B. RESULTS:

1. Gross Pathology (Table 5) and Organ Weights (Table 6):

All deaths which occurred during the course of study were considered due to compound effect. Significant compound related gross pathologic findings were limited to the liver where yellowish-brown discoloration was observed in several monkeys from the 100 and 300 mg/kg/day groups. Other gross findings in these monkeys were of agonal nature or were those which are commonly seen in untreated monkeys. While contemporary control organ weight values were not available for comparison, the organ weight values of these monkeys appeared to be within normal limits.

2. Histopathology (Table 7):

No consistent histopathologic changes which were considered to represent a direct compound effect were observed in any tissues examined microscopically. Many agonal changes, including congestion, hemorrhage and lipid depletion of the adrenal cortex, were seen in monkeys from all experimental groups. No microscopic basis was seen for the yellowish-brown discoloration noted at necropsy in several monkeys from the 100 and 300 mg/kg/day groups.

TABLE 1. Individual Body Weights, Kilograms.

Group, Monkey Number	Sex	Control 1	Control 2	Week of Study 1	Week of Study 2	Week of Study 3
Control:						
7355	M	3.10	3.10	3.10	3.20	
7358	M	3.70	3.75	3.70	3.75	
7368	F	3.05	3.10	3.10	3.25	
7372	F	3.55	3.60	3.60	3.65	
Mean		3.35	3.39	3.38	3.46	
10 mg/kg/day:						
7347	M	3.40	3.40	3.05	2.90	2.50* Died
7354	M	3.05	3.10	3.05	2.65	2.40* Died
7369	F	3.10	3.10	3.05	2.70	2.55* Died
7371	F	3.85	4.00	3.70	3.25* Died	
Mean		3.35	3.40	3.21	2.75	
30 mg/kg/day:						
7349	M	3.45	3.45	3.05	2.90* Died	
7351	M	3.65	3.70	3.05	3.10* Died	
7370	F	3.05	3.10	2.60	2.65* Died	
7377	F	3.50	3.30	2.95	2.50* Died	
Mean		3.41	3.39	2.91		
100 mg/kg/day:						
7356	M	3.80	3.80	3.50* Died		
7359	M	3.10	3.10	2.70* Died		
7373	F	3.80	3.80	3.20* Died		
7374	F	2.85	2.80	2.45* Died		
Mean		3.39	3.38			
300 mg/kg/day:						
7357	M	3.00	3.05	2.80* Died		
7360	M	3.60	3.65	3.40* Died		
7375	F	4.05	4.10	3.35* Died		
7379	F	2.70	2.75	2.60* Died		
Mean		3.34	3.39			

*Terminal weight not included in mean.

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TABLE 2. Individual Hematological Values - Control Period.

Group, Monkey Number	Sex	Erythrocytes 10^6/cmm	Hemoglobin g/100 ml	Hematocrit %	Platelets 10^3/cmm	Reticulocytes %	Prothrombin Time sec	Activated P.T.T. sec	Leucocytes 10^3/cmm	Neutrophils Seg. %	Neutrophils Non-Seg. %	Lymphocytes %	Eosinophils %	Monocytes %	Basophils %	MCV μ^3	MCH µµg	MCHC g/100 ml
Control:																		
7355	M	4.48	11.3	34	185	0.8	13	26	5.95	33	0	66	1	0	0	76	25	33
7358	M	4.56	12.0	38	219	1.8	12	28	8.59	17	0	78	5	0	0	83	26	32
7368	F	4.51	10.8	35	138	0.8	13	31	4.82	38	0	62	0	0	0	78	24	31
7372	F	5.10	11.8	35	197	0.7	14	32	8.66	42	0	54	4	0	0	69	23	34
Mean		4.66	11.5	36	185	1.0	13	29	7.01	33	0	64	3	0	0	77	25	33
10 mg/kg/day:																		
7347	M	4.34	11.8	37	173	0.3	13	27	11.22	17	0	81	2	0	0	85	27	32
7354	M	5.04	12.6	39	167	0.2	13	28	7.42	23	0	76	1	0	0	77	25	32
7369	F	4.94	12.4	38	113	0.5	14	28	7.65	31	0	68	1	0	0	77	25	33
7371	F	4.96	12.1	39	236	0.6	13	33	6.79	68	0	32	0	0	0	79	24	31
Mean		4.82	12.2	38	172	0.4	13	29	8.27	35	0	64	1	0	0	80	25	32
30 mg/kg/day:																		
7349	M	4.69	11.6	38	107	0.3	13	31	6.76	33	0	65	2	0	0	81	25	31
7351	M	5.09	12.1	39	130	0.4	14	31	10.80	68	0	32	0	0	0	77	24	31
7370	F	4.48	12.5	39	137	1.1	14	31	8.99	40	0	59	1	0	0	87	28	32
7377	F	4.41	11.1	35	171	0.3	14	29	6.95	55	0	41	4	0	0	79	25	32
Mean		4.67	11.8	38	136	0.5	14	31	8.38	49	0	49	2	0	0	81	26	32
100 mg/kg/day:																		
7356	M	4.70	11.6	38	234	0.3	13	26	11.61	38	0	61	1	0	0	81	25	31
7359	M	4.99	12.5	38	189	0.6	14	29	6.12	18	0	82	0	0	0	76	25	33
7373	F	4.55	11.6	38	134	0.6	13	28	5.64	47	1	49	3	0	0	84	25	31
7374	F	4.31	11.4	36	318	0.8	14	28	6.84	52	0	45	2	0	1	80	25	32
Mean		4.69	11.8	38	219	0.6	14	28	7.55	39	0	59	2	0	0	80	25	32
300 mg/kg/day:																		
7357	M	4.46	11.0	35	172	0.4	13	29	6.90	49	0	48	2	1	0	78	25	31
7360	M	4.76	12.2	40	174	1.0	14	30	5.95	47	0	53	0	0	0	84	26	31
7375	F	4.01	11.7	36	278	0.6	13	26	5.61	63	0	35	2	0	0	90	29	33
7379	F	4.84	12.8	39	186	0.1	13	30	7.11	45	0	52	2	0	1	81	26	33
Mean		4.52	11.9	38	203	0.5	13	29	6.39	51	0	47	2	0	0	83	27	32

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TABLE 3. Individual Biochemical Values - Control Period.

Group, Monkey Number	Sex	Glucose mg/100 ml	B.U.N. mg/100 ml	Alk. Phos. int'l units/l	S.G.O.T. int'l units/l	S.G.P.T. int'l units/l	Cholesterol mg/100 ml	Total Protein g/100 ml	Albumin g/100 ml	Sodium meq/l	Potassium meq/l	Chloride meq/l	Inorganic Phosphate mg/100 ml	γ - Glutamyl Transpeptidase Sigma u/ml	Creatinine Phosphokinase Sigma u/ml
Control:															
7355	M	122	20.0	1023	46	245	170	8.70	4.81	153	4.1	111	5.7	49	20
7358	M	103	18.2	1185	50	93	147	8.64	4.71	157	5.1	110	6.6	56	11
7368	F	144	34.0	1116	30	90	146	9.08	5.00	156	4.6	112	5.3	35	16
7372	F	106	26.4	1023	41	76	206	9.00	4.74	156	4.0	111	5.0	29	20
Mean		119	24.7	1087	42	126	167	8.86	4.82	156	4.5	111	5.7	42	17
10 mg/kg/day:															
7347	M	130	26.8	1140	42	102	182	7.92	5.49	165	5.7	112	8.4	49	10
7354	M	77	43.6	1020	52	140	226	9.88	5.60	165	7.0	116	7.5	55	24
7369	F	111	32.0	924	50	94	149	8.14	5.07	154	5.8	112	5.8	26	7
7371	F	104	23.6	1080	30	109	143	8.34	5.20	162	5.9	116	5.4	47	10
Mean		106	31.5	1041	44	111	175	8.57	5.34	162	6.1	114	6.8	44	13
30 mg/kg/day:															
7349	M	110	23.0	1020	30	93	180	8.70	5.01	159	5.3	113	7.0	54	9
7351	M	96	22.6	765	32	102	213	8.64	5.20	158	5.7	113	5.8	67	16
7370	F	115	23.0	1524	60	121	151	9.22	4.80	159	4.8	110	5.6	65	8
7377	F	99	21.0	460	29	65	194	9.40	5.12	153	4.1	110	4.8	34	11
Mean		105	22.4	942	38	95	185	8.99	5.03	157	5.0	112	5.8	55	11
100 mg/kg/day:															
7356	M	107	25.1	1461	48	130	214	9.10	5.45	163	5.5	110	7.0	77	16
7359	M	81	24.5	743	33	47	177	9.08	4.80	150	3.8	109	6.0	44	78
7373	F	100	23.9	1290	30	86	201	9.08	5.51	162	5.4	112	6.6	30	11
7374	F	117	25.1	910	36	100	163	8.74	5.30	159	5.3	114	6.4	47	26
Mean		101	24.7	1101	37	91	189	9.00	5.27	159	5.0	111	6.5	50	33
300 mg/kg/day:															
7357	M	86	25.0	867	46	125	180	9.28	5.26	160	5.6	110	6.8	44	10
7360	M	66	27.8	1110	50	107	227	8.50	4.99	156	4.7	110	5.4	46	30
7375	F	84	28.0	1470	35	95	127	8.74	5.51	157	4.6	111	5.7	40	11
7379	F	145	26.2	1437	55	126	183	8.98	5.44	162	4.5	111	6.1	47	8
Mean		95	26.8	1221	47	113	179	8.88	5.30	159	4.9	111	6.0	44	15

TABLE 4. Individual Urinalysis Values.

Group, Monkey Number	Sex	Volume ml	Color and Appear.	pH	Spec. Grav.	Protein	Glucose	Occult Blood	Ketones	Leuco-cytes	Erythro-cytes	Epi. Cells	Urates	Triple Phos.	Cal. Oxal.	Uric Acid Crystals	Bacteria	Casts
Control:																		
7355	M	30	S-cl	7.6	1.030	N	N	N	N	-	-	-	F	occ	-	-	M	-
7358	M	15	DS-cl	7.5	1.040	N	N	N	N	-	-	occ	M	occ	occ	-	M	-
7368	F	30	LS-C	7.0	1.021	N	N	N	N	-	occ	occ	occ	occ	-	-	F	-
7372	F	50	S-cl	7.5	1.032	N	N	N	N	-	-	-	F	-	-	-	F	-
Mean		31		7.4	1.031													
10 mg/kg/day:																		
7347	M	25	S-cl	7.6	1.044	N	N	N	N	-	1-3	occ	occ	occ	-	-	F	-
7354	M	10	S-cl	7.6	1.035	N	N	N	3+	-	-	occ	occ	occ	-	-	F	-
7369	F	20	S-cl	6.3	1.031	N	N	N	N	-	-	occ	occ	occ	-	-	M	-
7371	F	32	S-cl	9.0	1.021	N	N	N	N	-	occ	-	F	occ	-	-	F	-
Mean		22		7.6	1.033													
30 mg/kg/day:																		
7349	M	30	S-cl	7.6	1.023	N	N	N	1+	-	occ	-	F	-	-	-	F	-
7351	M	12	S-cl	7.2	1.040	N	N	N	N	-	-	-	occ	F	-	-	F	-
7370	F	40	LS-cl	8.2	1.009	N	N	1+	N	-	-	occ	F	-	F	-	M	-
7377	F	20	S-cl	7.8	1.027	N	N	N	3+	-	-	occ	occ	-	-	-	F	-
Mean		26		7.7	1.025													
100 mg/kg/day:																		
7356	M	14	S-cl	7.8	1.040	N	N	tr	N	-	occ	-	F	-	-	-	F	-
7359	M	25	LS-cl	8.0	1.024	N	N	N	N	-	-	-	F	-	-	-	M	-
7373	F	13	S-cl	5.9	1.041	N	N	N	N	-	-	occ	occ	-	occ	-	F	-
7374	F	33	S-C	8.5	1.038	N	N	N	N	-	-	-	occ	occ	-	-	F	-
Mean		21		7.6	1.036													
300 mg/kg/day:																		
7357	M	10	S-cl	8.0	1.041	N	N	N	tr	-	-	occ	F	F	-	-	M	-
7360	M	35	S-cl	6.5	1.031	N	N	N	N	-	-	-	F	F	-	-	M	-
7375	F	30	DS-cl	8.0	1.029	N	N	N	N	-	-	-	occ	-	-	-	F	-
7379	F	30	S-C	7.3	1.040	N	N	tr	N	-	-	-	occ	occ	-	-	F	-
Mean		26		7.5	1.035													

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

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TABLE 5. Gross Necropsy Observations of Deaths.

Tissue Lesion	10 mg/kg/day				30 mg/kg/day				100 mg/kg/day				300 mg/kg/day			
Group, Monkey Number	M 7347	M 7354	F 7369	F 7371	M 7349	M 7351	F 7370	F 7377	M 7356	M 7359	F 7373	F 7374	M 7357	M 7360	F 7375	F 7379
External																
scant body fat	x															
accessory nipple				x												
red fluid around mouth								x			x	x	x			
skin, dark red areas, chin area											x					
emaciated													x			
foamy material around mouth																x
Lungs																
yellow foci	x				x		x									
purplish/dark red foci	x												x			
adhesions to, and between parietal pleura		x		x											x	
congestion, edema			x							x		x		x	x	
yellowish mite lesions				x	x				x	x		x			x	
reddish purple discoloration											x					
emphysema												x			x	
failed to collapse; yellow air filled focus													x			x
Trachea, Bronchi																
bloody fluid															x	
Heart																
hemorrhage, subendocardial			x				x	x				x			x	
dark red foci, subendocardial/papillary muscle				x	x				x	x						
Esophagus																
hyperemia						x										
Abdominal Cavity																
mesenteric vessels congested		x														
esophagostomum nodules												x				
Thymus																
involuted														x		
Stomach																
light brown mucoid contents															x	
clear frothy mucoid contents	x															
distended with normal ingesta			x													
hemorrhage, pyloric area			x					x								
slightly thickened mucosa									x							
congestion											x					
dark red foci												x				
Small Intestine																
yellow/pale mucoid material	x										x					x
dark red areas	x															
pasty/pale yellow ingesta					x		x									
thickened, mucosa									x							
blood stained ingesta										x						
green mucoid material and gas													x			

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TABLE 5. Cont. Gross Necropsy Observations of Deaths.

Tissue Lesion	10 mg/kg/day				30 mg/kg/day				100 mg/kg/day				300 mg/kg/day			
Group, Monkey Number	M 7347	M 7354	F 7369	F 7371	M 7349	M 7351	F 7370	F 7377	M 7356	M 7359	F 7373	F 7374	M 7357	M 7360	F 7375	F 7379
Large Intestines																
hemorrhage, mucosa		x					x	x		x						
petechiae, colon			x													
semi fluid contents						x										
thickened mucosa									x							
congestion mucosa									x							
tapeworm in lumen									x							
esophagostomum nodules												x				
raised reddish foci, mucosa												x				x
Ileo-Colic Orifice																
congested			x												x	
Gallbladder																
distended with dark green bile	x															
Liver																
white linear area	x															
dark red									x					x		
yellowish brownish discoloration											x		x			x
nodule												x				
accentuated lobulations													x			
Kidney																
hydronephrosis	x															
pale												x				
congestion										x						

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TABLE 6. Absolute (Grams) and Relative (% Body Weight) Organ Weights, Deaths.

Group, Monkey Number	Sex	Body Wt. kg	Spleen g	Spleen %	Liver g	Liver %	Adrenals g	Adrenals %x10	Kidneys g	Kidneys %	Testes/ Ovaries g	Testes/ Ovaries %x10 ^{2}
10 mg/kg/day:												
7347	M	2.50	2.00	0.08	84.62	3.38	1.16	0.54	20.42	0.82	1.34	0.05
7354	M	2.40	2.24	0.09	85.19	3.55	1.18	0.49	14.05	0.59	3.10	0.13
7369	F	2.55	2.03	0.08	73.21	2.87	1.49	0.58	15.33	0.60	0.26	1.02
7371	F	3.25	1.46	0.04	89.12	2.74	1.51	0.46	16.87	0.52	0.15	0.46
30 mg/kg/day:												
7349	M	2.90	2.17	0.07	98.89	3.41	1.48	0.51	18.07	0.62	3.02	0.10
7351	M	3.10	1.99	0.06	99.69	3.22	1.39	0.45	16.57	0.53	1.17	0.04
7370	F	2.65	2.09	0.08	73.99	2.79	0.94	0.35	16.34	0.62	0.17	0.64
7377	F	2.50	1.30	0.05	65.68	2.63	1.21	0.48	14.70	0.59	0.21	0.84
100 mg/kg/day:												
7356	M	3.50	2.44	0.07	126.72	3.62	0.88	0.25	20.72	0.59	3.88	0.11
7359	M	2.70	3.38	0.13	76.92	2.85	1.10	0.41	14.44	0.53	0.78	0.03
7373	F	3.20	2.02	0.06	104.07	3.25	1.17	0.37	18.18	0.57	0.18	0.56
7374	F	2.45	1.65	0.07	65.75	2.68	1.16	0.47	15.27	0.62	0.12	0.49
300 mg/kg/day:												
7357	M	2.80	2.60	0.09	82.97	2.96	1.02	0.36	13.06	0.47	0.63	0.02
7360	M	3.40	2.62	0.08	90.53	2.66	1.09	0.32	15.31	0.45	1.48	0.04
7375	F	3.35	1.60	0.05	98.57	2.94	1.33	0.40	19.75	0.59	0.32	0.96
7379	F	2.60	1.45	0.06	73.12	2.81	0.85	0.33	14.70	0.57	0.09	0.35

TABLE 6. Cont. Absolute (Grams) and Relative (% Body Weight) Organ Weights, Deaths.

Group, Monkey Number	Sex	Body Wt. kg	Heart		Thyroid		Brain		Pituitary	
			g	%	g	%x10	g	%	g	%x10[2]
10 mg/kg/day:										
7347	M	2.50	14.14	0.57	0.38	0.15	79.12	3.16	0.050	0.20
7354	M	2.40	14.09	0.59	0.46	0.19	111.28	4.64	0.038	0.16
7369	F	2.55	13.46	0.53	0.71	0.28	74.90	2.94	0.077	0.30
7371	F	3.25	15.15	0.47	0.47	0.14	84.48	2.60	0.082	0.25
30 mg/kg/day:										
7349	M	2.90	14.37	0.50	0.72	0.25	85.03	2.93	0.038	0.13
7351	M	3.10	18.09	0.58	0.38	0.12	86.88	2.80		
7370	F	2.65	12.78	0.48	0.44	0.17	81.33	3.07	0.048	0.18
7377	F	2.50	14.46	0.58	0.59	0.24	80.52	3.22	0.051	0.20
100 mg/kg/day:										
7356	M	3.50	17.06	0.49	1.05	0.30	89.07	2.54	-	-
7359	M	2.70	13.23	0.49	0.90	0.33	82.35	3.05	0.064	0.24
7373	F	3.20	15.04	0.47	0.61	0.19	80.78	2.52	0.066	0.21
7374	F	2.45	12.48	0.51	0.33	0.13	77.71	3.17	0.051	0.21
300 mg/kg/day:										
7357	M	2.80	13.07	0.47	0.88	0.31	96.22	3.44	0.050	0.18
7360	M	3.40	15.20	0.45	0.73	0.21	86.18	2.53	-	-
7375	F	3.35	19.62	0.59	0.65	0.19	95.96	2.86	0.070	0.21
7379	F	2.60	11.60	0.45	0.75	0.29	88.92	3.42	0.058	0.22

- = not available

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TABLE 7. Microscopic Observations, Deaths.

	10 mg/kg/day				30 mg/kg/day				100 mg/kg/day				300 mg/kg/day			
Sex	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
Monkey Number	7347	7354	7369	7371	7349	7351	7370	7377	7356	7359	7373	7374	7357	7360	7375	7379
Tissue Lesion																
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	-
Peripheral nerve	1	1	1	1	1	-	1	1	1	1	1		1	1	1	1
focal lymphoid infiltrate in connective tissue												3				
Eyes	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Pituitary	1	1	1				1		1		1	1	1		1	
small focal hemorrhage in pars nervosa					3			3						3		3
small focal dystrophic mineralization																x
small parenchymal cysts				x		x				x						
Thyroid	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
Adrenal																
diffuse lipid depletion	5	5	5	5	5	5	5	5	5	5	5	5	4	5	5	5
small to large focal dystrophic mineralization		x				x	x	x			x			x		x
focal lymphoid infiltrate				4										3		
accessory adrenal tissue															x	
congestion	3	4	3	3	4		2		2	2	2	2		2		
focal hemorrhage				4												
large focal necrosis with cholesterol clefts				x												
Trachea							1	1								
focal lymphoid infiltrate in lamina propria	2	3	3	3	3	2			3	3	2	3	3	2	2	2
Lung																
acarian pigment	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
focal peribronchial/peribronchiolar lymphoid infiltrate			3	3	2	2	2	2	3	3	2	3	3	3	3	2
focal hemorrhage	3	2			3	2	2	2	3	2	3	3	2		4	
diffuse congestion			4		4		3		3	4	3					
focal edema	2		4												3	
lung mite in bronchiolar lumen			x	x					x	x			x		x	
bronchiectasis	x		x							x					x	
interstitial inflammatory cell infiltrate	3			3	4							4				
focal perivascular lymphoid infiltrate	3		3													
focal bronchiolar smooth muscle hypertrophy					3											
focal aggregates of alveolar macrophages		3														
Heart					1				1				1			1
small focal myocardial necrosis	2			2				3				2		2		
focal interstitial lymphoid infiltrate				2				2			3	3			3	
focal subendocardial hemorrhage	3		3	3			4	5		3		4			3	
focal subepicardial lymphoid infiltrate		3	3	3		3	3	2								
focal interstitial neutrophil infiltrate				2				2								

Code: x - condition present; 1 - not remarkable; 2 - very slight; 3 - slight; 4 - moderate; 5 - marked; 6 - extreme; - = not available

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TABLE 7. Cont. Microscopic Observations, Deaths.

	10 mg/kg/day				30 mg/kg/day				100 mg/kg/day				300 mg/kg/day			
Sex	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
Monkey Number	7347	7354	7369	7371	7349	7351	7370	7377	7356	7359	7373	7374	7357	7360	7375	7379
Tissue Lesion																
Aorta	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Spleen										1		1				
diffuse congestion	3	3	3		3		3		3					3	3	3
atrophy of lymphatic follicles			3	3	3	4		4			3		4	3	4	3
Mesenteric lymph node		1		1						1		1	1			1
atrophy of lymphatic follicles	4		4		3	3	3	3	3					3	4	
focal hemorrhage											4					
Retropharyngeal lymph node	1		1	1	1	1			-	-	1	-	1	-	1	1
congestion		3														
atrophy of lymphatic follicles							3	3								
Thymus	-		1	1	1		-	-	1	1	1	-	1	1	1	1
cyst		x				x										
Bone marrow (rib junction)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Bone	-	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Submandibular salivary gland				1			1									
diffuse atrophy of serous alveolar cells			4					4				4	3		4	
focal interstitial lymphoid infiltrate	3	2			2	3		3	2	2	3	3	3	3	2	2
Esophagus		1	-	1	1		1		1	1	1				1	1
focal lymphoid infiltrate in lamina propria						3						2	2	2		
acute focal esophagitis	3															
focal hemorrhage in lamina propria						3										
focal neutrophil infiltrate in mucosa and lamina propria						3										
Gongylonema sp.								x								
Tongue		1	1	1		1	1				1			1	1	
focal hemorrhage								2					3			
focal lymphoid infiltrate in lamina propria	2							2	3	2		3				3
focal interstitial lymphoid infiltrate in muscularis	2															
focal neutrophil infiltrate in mucosal epithelium					3			3				3				
small focal necrosis in mucosal epithelium								3				3				
focal edema								3								
focal interstitial neutrophil infiltrate in muscularis								4				3				
focal neutrophil infiltrate in lamina propria												4				
Tonsil		-	-			-		-	-	-	-				-	-
focal neutrophil infiltrate in tonsillar epithelium	2			2	3		2					2	3	3		
atrophy of lymphatic follicle	3															

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TABLE 7. Cont. Microscopic Observations, Deaths.

	10 mg/kg/day				30 mg/kg/day				100 mg/kg/day				300 mg/kg/day			
Sex	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
Tissue / Lesion — Monkey Number	7347	7354	7369	7371	7349	7351	7370	7377	7356	7359	7373	7374	7357	7360	7375	7379
Stomach																
focal lymphoid infiltrate in lamina propria/ submucosa	3	4	2	3		3	4	2	3	3	2	3	3	3	3	3
focal submucosal edema	4				5											
focal submucosal hemorrhage								3								
Small intestine		1		1				1	1	1	1		1		1	1
atrophy of lymphatic nodule	2		2		3	2	3					3		2		
Large intestine		1		1	1			1			1					1
microgranuloma in muscularis													x			
atrophy of lymphatic nodule	2		3			3	2		2	3		3		2	2	
focal lymphoid infiltrate in submucosa			3						2							
focal hemorrhage in mucosa							4									
submucosal congestion										4						
Pancreas	1	a	a			1	1		1	a	a				a	
focal interstitial/periductal lymphoid infiltrate				2	2			3				3	2	3		3
Liver																
diffuse congestion	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
portal inflammatory cell infiltrate				3	2	2	2			3	3		2		2	3
focal bile duct proliferation								3								
small necrotic focus									2							
dark brown pigment-laden Kupffer cells												3				
parasitic granulomas												x				
large focal cytoplasmic vacuolation of hepatocytes													4			
Gallbladder	a	a	a	1	a	1	a		a	a	a		1	1	a	1
focal lymphoid infiltrate in lamina propria								2				2				
Kidney																
cyst													x			
diffuse congestion	3	4		4	3	3	4	3	4	4	3	3		4	4	
focal lymphoid infiltrate in connective tissue			3											3		
focal interstitial lymphoid infiltrate	2	2	2	3	3	4	2	3	2	2	3				2	3
multinucleated lining epithelium in papillary duct								x								x
microlith in renal tubules			x				x									
ectopic adrenal rest			x													
Urinary bladder		1	-		1					1	1			1	-	
focal lymphoid infiltrate in lamina propria	2			2		3	3	3	3				3			3
focal neutrophil infiltrate in lamina propria																3
Testis									1							
prepuberal development	x	x			x	x				x			x	x		
interstitial fibrosis		4														

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TABLE 7. Cont. Microscopic Observations, Deaths.

	10 mg/kg/day				30 mg/kg/day				100 mg/kg/day				300 mg/kg/day			
Sex	M	M	F	F	M	M	F	F	M	M	F	F	M	M	F	F
Monkey Number	7347	7354	7369	7371	7349	7351	7370	7377	7356	7359	7373	7374	7357	7360	7375	7379
Tissue Lesion																
Ovary			1					1				1			1	1
small focal dystrophic mineralization				x			x				x					
Prostate	-				-				1	-				1		
focal interstitial lymphoid infiltrate		3				2							3			
Uterus			1				1				1	1			1	
erythrocytes and inflammatory cells in lumen of endometrial glands				2				2								
focal hemorrhage in endometrium																2
Vagina												-				1
focal lymphoid infiltrate in lamina propria			4	3			3	3			3				3	
Skeletal muscle	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1
Sarcocystis sp.				x												
Skin															1	
focal aggregates of dark brown pigment in dermis	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
focal lymphoid infiltrate in dermis											3	2		2		
diffuse acanthosis								3						3		
Mammary gland															1	
focal aggregates of dark brown pigment in dermis	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
focal lymphoid infiltrate in intra- and interlobular connective tissue							3				2	3				3
epidermal inclusion cyst			x													
hyperkeratosis							4				3	3				
proteinaceous fluid in dilated ducts							x									
focal lymphoid infiltrate in dermis								2				2				
accessory nipple				x												
Skin (tattoo)								1								
focal aggregates of black/dark brown pigment in dermis	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x
focal hemorrhage in dermis																3
focal hemorrhage in subcutis				3			3									
Miscellaneous																
focal lymphoid infiltrate, corpus spongiosum									3							
congestion and hemorrhage, chin skin											4					

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