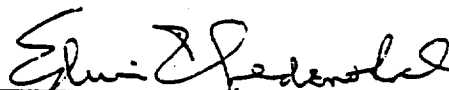


International Research and Development Corporation

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



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I. SYNOPSIS

FM-3422 was fed in the diet at levels of 30, 100, 300, 1,000, 3,000 and 10,000 ppm to Charles River CD rats for 90 days. Five male and five female rats were initiated at each dosage level and in the control group. The rats were observed twice daily for overt signs of toxicity and mortality. Individual body weights and sex-group food consumptions were recorded weekly. Hematological, biochemical and urinalysis studies were conducted during the pretest period and at 1 and 3 months of study.

All rats at the 1,000-, 3,000- and 10,000-ppm dosage levels died between days 9 and 29 of the study. Most of these rats exhibited one or more of the following signs of overt toxicity including: emaciation, altered posture, convulsions, reduced motor activity and/or increased sensitivity. Time-to-onset of signs of toxicity and length of life span decreased as the dosage level was increased.

At the 30-ppm dosage level, neither changes in appearance nor deaths were noted for either male or female rats. Females had a slightly depressed weight gain when compared to the controls. With the following exceptions, laboratory test values were within the expected range: at 1 month, γ -glutamyl transpeptidase (γ -GTP) levels were slightly elevated for two males; at 3 months, γ -GTP values were elevated for three males. One male rat with elevated γ -GTP (1 month) had a normal γ -GTP value at 3 months but slightly elevated plasma glutamic pyruvic and oxalacetic transaminase (PGPT and PGOT) values. Two male rats at the 30-ppm dosage level also showed slightly elevated blood urea nitrogen (BUN) values at 1 month of study.

At the 100-ppm dosage level, only one rat (a female) manifested any behavioral or appearance change (excessive salivation, week 4). A reduction in body weight gain occurred with both sexes. Food consumption was depressed for the females. Laboratory values were within the expected range.

At the 300-ppm dosage level, an increased incidence of possibly compound-related signs was noted. Two females died after the collection of blood for clinicopathology. One male and one female had an accumulation of material around the eye(s) and/or nose, and one female had a dilated pupil. Group mean body weight and food consumption levels were significantly lower ($p < 0.01$) for both males and females. At 3 months of study, erythrocyte counts, hemoglobin and hematocrit values for males and females at the 300-ppm dosage level were slightly lower when compared to the control values (statistically significant). Biochemical values showed some changes for alkaline phosphatase, PGPT, PGOT, γ -GTP and for BUN values for one or more rats of each sex at each sampling period.

Compound-related gross liver lesions consisting of enlargement, accentuated lobulations, brown discoloration and gray/yellow/white areas of discoloration were observed in the 300-ppm group and to a lesser extent in the 100-, 1,000- and 3,000-ppm groups. Brown kidney discoloration was observed in the 300-ppm group, and stomach hyperemia/congestion and red/brown foci/hemorrhages were noted in some rats from the 1,000-, 3,000- and 10,000-ppm groups. A statistically significant liver weight increase in 100- and 300-ppm rats was considered compound-related. Compound-related, microscopic, liver lesions consisting of hepatocellular hypertrophy and hyperplasia, hepatocellular vacuolation, hepatocellular necrosis and hepatocellular and Kupffer cell accumulation of brown pigment were observed to varying degrees in all treated groups. Compound-related, microscopic, kidney lesions consisting of tubular nephrosis, tubular proteinaceous casts, and intracellular accumulations of brown pigment and reddish brown hyaline droplets in tubular epithelial cells were observed in some rats from the 300-ppm group.

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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-03422 41-2700-3422-0	off-white to tan
Lot 784/ Net-35 DR-1	waxy substance

III. CLINICAL STUDIES

A. METHOD:

1. General Procedure:

Thirty-five male (240-306 g) and 35 female (180-226 g) Charles River CD rats purchased from The Charles River Breeding Laboratories, Inc., Portage, Michigan were used in this study. The rats were distributed among the groups, based on a computer-generated table of random numbers. The rats were housed individually in suspended wire mesh cages and maintained in a temperature-, humidity- and light-controlled room. During the pretest period, rats were provided Purina® Laboratory Chow® and water ad libitum. During the test period, the rats were provided the appropriate test diet and water ad libitum.

This study was initiated on November 4, 1977 with Groups I-VI (control, 100-, 300-, 1,000-, 3,000- and 10,000-ppm dosage levels). Group VII (30 ppm) was initiated on November 25, 1977 in accordance with an approved protocol modification. Surviving rats from Groups I-VI were sacrificed on February 2, 1978. The study was terminated by sacrifice of the Group VII rats on February 23, 1978.

2. Compound Administration:

The compound was mixed weekly with ground Purina® Laboratory Chow® (i.e., ground basal diet) to provide dosage levels of 30, 100, 300, 1,000, 3,000 and 10,000 ppm. Five male and five female rats were used at each dosage level and in a control group. The control rats received the basal diet only on the same regimen as treated rats. Diet samples (100 grams each) were taken immediately after preparation of each diet and after 7 days standing in weeks 1, 4 and 12. The samples were frozen and subsequently shipped to the sponsor. Diets were prepared in the following manner: an appropriate amount of FM-3422 was dissolved in 15 ml of ACS grade acetone. The resulting

solution was thoroughly mixed with 500 g of Purina® Laboratory Chow® in a Hobart blender to produce the premix. To provide the proper dosage levels, appropriate quantities of the premix were mixed with the ground basal diet using a twin-shell blender equipped with an intensifier bar. The diets were prepared weekly.

3. Observations:

The rats were observed twice daily for overt signs of toxicity and for mortality. Detailed observations normally were recorded weekly; daily observations were recorded whenever a specific abnormal condition existed. Individual body weights and food consumptions were recorded weekly during the pretest and treatment periods.

4. Laboratory Tests:

Once during the pretest period and at 1 month and 3 months of the study, blood (orbital sinus puncture technique) and overnight urine samples were obtained for analysis from all surviving rats. Food and water were withheld during sample collection.

a. Hematology:

Hematological studies included: hemoglobin¹, hematocrit², total erythrocytes³, reticulocytes⁴ and total³ and differential leucocyte counts.

b. Biochemistry:

Biochemical studies included: fasting glucose⁵, blood urea nitrogen (BUN)⁵, plasma glutamic pyruvic transaminase (PGPT)⁵ and plasma glutamic oxalacetic transaminase activity (PGOT)⁵, plasma alkaline phosphatase activity⁵, γ -glutamyl transpeptidase (γ -GTP)⁶, creatinine phosphokinase⁷ and calcium⁸. Alkaline phosphatase values from the pretest (baseline) period were not measured because of interference by the anticoagulant.

c. Urinalysis:

Urinalysis included description of color and appearance; measurement of volume, pH⁹ and specific gravity; qualitative tests for

protein⁹, glucose⁹, ketones⁹, bilirubin⁹ and occult blood⁹; and microscopic examination of the sediment.

d. Serum Samples:

Serum samples were obtained for all surviving rats at 13 weeks of study. The samples were pooled by sex and group, frozen and subsequently shipped to the sponsor.

5. Statistical Analysis:

All statistical analyses compared the treatment groups with the control group, by sex. Body weight (at 13 weeks), food consumption (weeks 1-13), hematological, biochemical and urinalysis parameters at 1 and 3 months, and absolute and relative terminal organ weights 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 Torrie¹⁰ using Dunnett's¹¹ multiple comparison tables to judge significance of differences.

B. RESULTS:

1. General Behavior, Appearance and Survival:

At the 30- and 100-ppm dosage levels, one male (30 ppm) had an accumulation of red material around the right eye from week 11 to week 13; one female (100 ppm) exhibited excessive salivation and rales during week 4. No other rats at these dosage levels manifested any signs of toxicity.

At 300-ppm dosage level, an increased frequency of possibly compound-related signs were noted. Two females died shortly after the collection of blood (one at 1 month; one at 3 months) without any signs of overt toxicity having been noted. One male had an accumulation of red material around the left eye and nose. One female rat had an accumulation of red material around the right eye and another female had a dilated right pupil (weeks 5 and 6).

All rats at the 1,000-, 3,000- and 10,000-ppm dosage levels died prior to the scheduled sacrifice. Most deaths occurred following manifestation of one or more of the following signs of overt toxicity: emaciation, altered posture (hunched back), reduced motor activity, convulsions following handling, increased sensitivity to outside stimuli, accumulation of red material (right eye and mouth or nose), accumulation of yellow material (anogenital region), dilation of the right pupil and excessive salivation and rales. The incidence of these findings was as follows:

Observation	No. of Rats/Observation/Dosage Level						-
	Control	30	100	300	1,000	3,000	10,000
		ppm	ppm	ppm	ppm	ppm	ppm
Emaciation					6	10	10
Alt. posture					4	8	10
Red. motor act.					1	1	7
Convulsions					3	5	
Inc. sensi- tivity					2		
Red material (eyes)	1	1		3		1	
Red material (nose, mouth)				1	2	2	1
Yellow material					2		2
Pupillary dilation				1			
Excessive salivation			1				

Survival after 3 months of compound consumption was as follows:

Treatment Group	No. Surviving/No. Initiated	
	MALE	FEMALE
Control	5/5	5/5
30 ppm	5/5	5/5
100 ppm	5/5	5/5
300 ppm	5/5	3/5
1,000 ppm	0/5	0/5
3,000 ppm	0/5	0/5
10,000 ppm	0/5	0/5

2. Body Weights (Tables 1-2):

Changes in body weight were similar for male rats at the 30-ppm and 100-ppm dosage levels when compared with control male rats. Female rats at the 30-ppm dosage level showed slightly lower gains in body weights and female rats at the 100-ppm dosage level showed moderately lower gains in body weight when compared with control female rats. Male and female rats at the 300-ppm dosage level showed markedly lower gains in body weight. The group mean body weights at 13 weeks of study were significantly lower for the females ($p < 0.05$) at the 100-ppm dosage level and for male and female rats ($p < 0.01$) at the 300-ppm dosage level when compared with control rats. Rats at the 1,000-, 3,000- and 10,000-ppm dosage level showed moderate to marked losses of body weight prior to death.

The group mean body weights (and the percent difference from the control group) at 13 weeks of study were as follows:

<u>Treatment Group</u>	<u>Group Mean Body Weights, g (% difference from Control)</u>	
	<u>MALE</u>	<u>FEMALE</u>
Control	501	286
30 ppm	491 (- 2.0)	269 (- 5.9)
100 ppm	482 (- 3.8)	248 (-13.3)
300 ppm	392 (-21.8)	227 (-20.6)

3. Food Consumption (Tables 3-4):

Group mean average for food consumption consistently declined as the dosage level was increased. Mean differences for the 300 ppm group (males and females) when compared with the control were statistically significant at $p < 0.01$.

<u>Treatment Group</u>	<u>Average Food Consumption (grams/rat/day)</u>	
	<u>MALE</u>	<u>FEMALE</u>
Control	27.6	19.9
30 ppm	27.2	19.3
100 ppm	27.4	18.6
300 ppm	24.2	15.1

4. Laboratory Tests (Tables 5-16):

a. Hematology:

Hematological values for rats at the 30- and 100-ppm dosage levels at 1 and 3 months of study and for rats at the 300-ppm dosage level at 1 month of study were within the expected range. The 3-month erythrocyte counts, hemoglobin and hematocrit values for male and female rats at the 300-ppm dosage level were slightly lower (statistically significant) when compared with the control values. All other hematologic values, at 3 months of study, for rats at the 300-ppm dosage level were within the expected range.

b. Biochemistry:

With the exceptions of the following findings, all biochemical values were within the expected range.

At the 30-ppm dosage level (1-month sampling period), two male rats had slightly elevated γ -GTP levels (9 units/ml/rat). At the 3-month sampling, one of these γ -GTP levels was still elevated and two other males had elevated γ -GTP levels (10 units/ml/rat). The group mean γ -GTP level for male rats at the 30-ppm dosage level was significantly lower ($p < 0.05$) when compared with the control group mean. One male rat (3-month sampling) had a slightly elevated PGPT (154 units/ml) and PGOT (299 units/ml); this rat had had a slightly elevated γ -GTP level at 1 month which had declined by 3 months. Two male rats at the 30-ppm dosage level also showed slightly elevated blood urea nitrogen values at 1 month of study.

At 100-ppm dosage level all biochemical values were within the expected range and showed no changes that could be attributed to the compound.

At the 300-ppm dosage level (1 month) plasma alkaline phosphatase levels were elevated for all females (statistically significant at $p < 0.01$ when the group mean was compared with the control

group mean). The group range for these values was 210 to 291 units/ml. One of these females also had an elevated PGOT (480 units/ml) value and an elevated PGPT (360 units/ml) value. Two male rats (at 1 month) had slightly elevated γ -GTP values (13 and 16 units/ml). At 3 months, three males and one female had elevated plasma alkaline phosphatase levels (227-281 units/ml). The group mean difference for these males was statistically significant when compared with the control mean. One male rat had a slightly elevated PGPT reading of 204 units/ml at 3 months. At 1 month of study, two female rats at the 300-ppm dosage level showed a slight and moderate increase in BUN. At 3 months of study, the BUN values for male rats at the 300-ppm dosage level generally were slightly higher than those of control male rats. The group mean blood urea nitrogen values for male rats at the 300-ppm dosage level was significantly higher ($p < 0.01$) than the control male rats at 3 months of study.

c. Urinalysis:

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

IV. PATHOLOGICAL STUDIES

A. METHODS:

1. Gross Pathology:

After completion of the compound administration period, all surviving rats were sacrificed by CO₂ inhalation and necropsied. The spleen, liver, kidneys and brain were weighed and representative tissues were collected in buffered neutral 10% formalin.* The adrenals, thyroid/parathyroid and pituitary were weighed after fixation. Liver samples, obtained from all of the rats at terminal sacrifice, were frozen and subsequently shipped to the sponsor.

Rats which died during the study period were necropsied as above with the exception that organ weights were not taken.

2. Histopathology:

Microscopic examination of fixed hematoxylin-eosin stained paraffin sections was performed for all rats in the control and 30-, 100-, 300-ppm dosage levels. The following tissues were examined:

adrenals	mammary gland
aorta	nerve (with muscle)
bone	spleen
brain (with segment of cervical cord attached)	pancreas
eyes	prostate/uterus
heart (with coronary vessels)	bone marrow (sternum)
duodenum	salivary gland
ileum	spinal cord (lumbar)
jejunum	pituitary
colon	stomach
kidneys	testes/ovaries
liver	thyroid
lung	parathyroid
thymus	urinary bladder
	mesenteric lymph node
and any other tissue with abnormalities.	

In addition, livers from rats in the 1,000-, 3,000- and 10,000-ppm dosage levels were processed and microscopically examined.

*Eyes fixed in Russell's fixative.

B. RESULTS:

1. Gross Pathology (Table 17) and Organ Weights (Tables 18-19):

Compound-induced, gross, liver lesions were observed in all 300-ppm rats which survived to terminal sacrifice. The lesions occurred singly or in combination and consisted of liver enlargement, accentuated lobulations, diffuse brown discoloration and gray/yellow/white areas of discoloration. Male rats appeared to be more severely affected. Similar, but less severe, liver lesions were observed in some rats from the 100-, 1,000- and 3,000-ppm groups. Additional compound-related gross lesions were observed in the stomachs (hyperemia/congestion, red/brown foci/hemorrhage) of some rats in the 1,000-, 3,000- and 10,000-ppm groups and kidneys (brown discoloration) of some rats from the 300-ppm group.

Statistically significant increases in absolute and relative liver weights in the 100- and 300-ppm groups were considered compound related with male rats more severely affected:

<u>Organ</u>	<u>Dosage Level (ppm)</u>	<u>Sex</u>	<u>Weight</u>	<u>Change</u>	<u>p<</u>
Liver	100	M	absolute, relative	increase	0.01, 0.01
		M	absolute, relative	increase	0.01, 0.01
	300	F	relative	increase	0.05

Other statistically significant organ weight variations observed in the 100- and 300-ppm groups were not accompanied by morphologic change and the biological significance of the variations is not known:

<u>Organ</u>	<u>Dosage Level (ppm)</u>	<u>Sex</u>	<u>Weight</u>	<u>Change</u>	<u>p<</u>
Kidneys	100	M	relative	increase	0.05
Brain	300	M	relative	increase	0.05
		F	relative	increase	0.05
Thyroid/Parathyroid	300	M	relative	increase	0.01
Pituitary	300	M	relative	increase	0.05

2. Histopathology (Tables 20-21):

Compound-induced microscopic alterations were observed in the livers from all treated groups and consisted of a very slight to marked enlargement (hypertrophy) of hepatocytes in the 30-, 100-, 300- and 1,000-ppm groups and increased numbers of hepatocytes (hyperplasia) in the 3,000- and 10,000-ppm groups. These alterations were centrilobular to panlobular in distribution with more liver involved as the dosage level increased.

A very slight-to-moderate increase in cytoplasmic vacuoles was observed in the livers of the 100- and 300-ppm groups. The vacuoles contained lipid (as verified by staining with oil red O) and were situated in a centrilobular to midzonal location.

Focal to multifocal coagulative hepatocellular necrosis of very slight-to-marked severity was observed in the 300-, 1,000-, 3,000- and 10,000-ppm groups. The lesion appeared to be primarily centrilobular to midzonal in location and there was a minimal amount of associated inflammatory infiltrate.

Increased intracytoplasmic accumulations of brown pigments in hepatocytes and sinusoidal macrophages (Kupffer cells) were observed primarily in livers from the 300-ppm group. Selected examples were stained for iron content using the Gomori's iron stain. Pigment in the Kupffer cells stained positive for iron while hepatocellular pigment was negative for iron.

Kidney lesions were observed in most rats of the 300-ppm group and consisted of a very slight-to-marked tubular nephrosis with associated proteinaceous cast formation and intracellular accumulation of brown pigment and reddish-brown hyaline droplets (protein) in tubular epithelial cells. The brown pigment was positive for iron as verified by the Gomori's iron stain. Mineralization of luminal tubular debris was observed in some rats. Whether the lesions developed as a result of a direct toxic effect of the compound on the renal parenchyma or indirectly

as a result of compound-effect on the liver with subsequent overload of the kidneys with bile and/or products of red blood cell breakdown could not be determined from histological examination.

Lesions observed in other tissues were not considered compound-related but were interpreted as spontaneous in origin.

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TABLE 1.

Group Mean Body Weights, Grams; Weight Ranges; and Survival.

Week of Study	Control			30 ppm			100 ppm			300 ppm			1,000 ppm			3,000 ppm			10,000 ppm		
	Mean Body Wt.	Weight Ranges	Survival	Mean Body Wt.	Weight Ranges	Survival	Mean Body Wt.	Weight Ranges	Survival	Mean Body Wt.	Weight Ranges	Survival	Mean Body Wt.	Weight Ranges	Survival	Mean Body Wt.	Weight Ranges	Survival	Mean Body Wt.	Weight Ranges	Survival
MALES:																					
-1	259	250-280	5/5	242	239-246	5/5	262	248-272	5/5	263	250-272	5/5	259	252-262	5/5	255	240-278	5/5	249	240-256	5/5
0	272	250-306	5/5	248	240-254	5/5	291	279-304	5/5	277	264-288	5/5	270	261-276	5/5	279	261-295	5/5	266	259-280	5/5
1	311	290-340	5/5	291	282-306	5/5	326	302-340	5/5	319	308-336	5/5	263	246-282	5/5	194	176-212	5/5	162	156-168	2/5
2	331	310-363	5/5	311	314-361	5/5	348	320-370	5/5	321	294-348	5/5	226	218-243	5/5			0/5			0/5
3	361	302-396	5/5	365	346-400	5/5	343	300-368	5/5	347	328-382	5/5	214	204-220	3/5						
4	377	360-416	5/5	363	336-400	5/5	379	354-398	5/5	351	326-389	5/5			0/5						
5	394	384-428	5/5	397	373-435	5/5	393	356-416	5/5	340	302-394	5/5									
6	419	404-456	5/5	426	400-464	5/5	422	388-447	5/5	371	340-426	5/5									
7	429	414-464	5/5	434	410-467	5/5	427	396-466	5/5	372	346-414	5/5									
8	455	442-500	5/5	454	421-494	5/5	446	407-490	5/5	389	353-436	5/5									
9	473	454-512	5/5	470	436-518	5/5	463	422-500	5/5	405	372-452	5/5									
10	477	460-521	5/5	480	442-535	5/5	459	418-505	5/5	393	365-430	5/5									
11	497	479-539	5/5	483	446-536	5/5	474	428-522	5/5	412	383-456	5/5									
12	511	496-544	5/5	496	448-546	5/5	487	434-544	5/5	414	384-445	5/5									
13	501	474-547	5/5	491	454-538	5/5	482	434-534	5/5	392**	342-414	5/5									
FEMALES:																					
-1	203	196-210	5/5	198	185-224	5/5	195	190-204	5/5	200	194-206	5/5	201	190-214	5/5	204	188-212	5/5	205	194-214	5/5
0	211	200-218	5/5	200	180-226	5/5	202	190-210	5/5	207	199-220	5/5	209	194-224	5/5	213	205-220	5/5	215	200-226	5/5
1	226	216-240	5/5	208	190-231	5/5	210	200-220	5/5	212	200-230	5/5	190	174-206	5/5	149	142-164	5/5			0/5
2	226	218-238	5/5	225	204-254	5/5	211	203-218	5/5	200	187-214	5/5	157	147-168	5/5						
3	231	206-246	5/5	239	212-264	5/5	224	214-230	5/5	202	164-224	5/5	157	142-168	5/5						
4	239	225-255	5/5	226	204-252	5/5	216	208-222	5/5	202	188-219	5/5			0/5						
5	248	227-266	5/5	243	222-268	5/5	219	214-225	5/5	209	186-230	4/5									
6	267	253-280	5/5	266	240-294	5/5	237	230-242	5/5	222	210-238	4/5									
7	263	246-278	5/5	254	225-281	5/5	237	232-242	5/5	222	212-238	4/5									
8	264	245-290	5/5	261	237-291	5/5	236	228-247	5/5	219	206-233	4/5									
9	285	264-306	5/5	267	240-294	5/5	254	248-262	5/5	241	230-258	4/5									
10	275	248-308	5/5	271	247-300	5/5	240	235-252	5/5	222	210-240	4/5									
11	279	258-305	5/5	273	247-303	5/5	245	239-252	5/5	230	212-248	4/5									
12	285	257-318	5/5	270	246-301	5/5	248	240-260	5/5	233	218-248	4/5									
13	286	258-320	5/5	269	240-300	5/5	248*	239-254	5/5	227**	203-241	3/5									

*Significantly different than Control group mean, p<0.05.

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

FM-3422 41-2700-3422-0:

Ninety Day Subacute Rat Toxicity Study.

TABLE 2. Individual Weekly Body Weights, Grams.

Group, Rat No.	Sex	Pratest		Week of Study												
		-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13*
Control:																
73961	M	254	259	304	325	338	371	388	418	422	445	468	465	482	496	474
73962	M	250	264	306	310	344	368	386	410	418	445	462	460	479	498	492
73963	M	250	250	290	317	302	360	386	408	414	442	454	463	485	500	488
73964	M	260	281	314	340	326	369	384	404	426	444	470	478	502	515	504
73965	M	280	306	340	363	396	416	428	456	464	500	512	521	539	544	547
73966	F	196	208	222	225	240	239	253	272	264	264	284	274	279	288	292
73967	F	210	218	234	230	246	255	266	280	278	290	304	308	305	318	320
73968	F	204	214	240	238	244	248	262	278	278	276	306	285	297	298	298
73969	F	210	213	220	218	206	228	227	254	250	245	268	260	258	264	262
73970	F	196	200	216	218	218	225	232	253	246	246	264	248	258	257	258
30 ppm:																
76231	M	242	252	290	340	374	382	422	448	452	476	486	494	494	508	506
76232	M	240	250	293	324	358	358	383	408	420	444	454	458	472	483	482
76233	M	243	254	306	361	400	400	435	464	467	494	518	535	536	546	538
76234	M	246	244	282	318	346	336	373	400	410	421	436	442	446	448	454
76235	M	239	240	286	314	347	340	374	410	419	436	458	473	468	493	476
76236	F	185	180	190	204	212	204	222	240	225	237	240	247	247	246	240
76237	F	192	196	206	223	234	220	241	264	253	254	266	270	269	268	270
76238	F	192	198	206	225	250	226	248	270	257	269	274	268	275	274	270
76239	F	197	200	206	220	233	228	235	260	252	254	263	270	270	263	267
76240	F	224	226	231	254	264	252	268	294	281	291	294	300	303	301	300
100 ppm:																
73971	M	272	304	340	370	348	392	416	447	466	490	500	505	522	544	534
73972	M	258	288	328	348	366	398	408	442	444	466	490	495	517	536	528
73973	M	248	279	320	340	300	357	375	402	402	423	436	423	440	445	444
73974	M	268	294	338	360	368	394	408	430	428	445	466	453	465	478	469
73975	M	266	289	302	320	334	354	356	388	396	407	422	418	428	434	434
73976	F	194	205	210	215	224	222	225	242	242	247	262	252	248	260	254
73977	F	204	210	220	215	228	208	217	234	238	235	254	240	252	248	248
73978	F	190	190	200	203	214	211	216	230	232	234	250	237	239	240	239
73979	F	190	206	212	218	230	222	224	240	240	235	258	235	245	249	253
73980	F	198	200	208	205	222	215	214	237	232	228	248	237	243	242	244
300 ppm:																
73981	M	264	282	328	333	360	359	356	380	384	402	412	412	427	428	414
73982	M	262	264	308	294	328	326	307	340	346	353	372	365	383	384	342
73983	M	272	276	316	310	336	345	343	365	364	380	394	377	401	416	407
73984	M	250	274	308	321	328	338	302	343	352	372	394	380	395	399	388
73985	M	268	288	336	348	382	389	394	426	414	436	452	430	456	445	410
73986	F	204	220	220	214	224	213	222	230	226	223	240	227	232	235	238
73987	F	206	213	230	202	218	219	230	238	238	233	258	240	248	248	241
73988	F	198	202	204	200	202	194	186	210	212	214	234	212	226	230	Died
73989	F	194	199	200	195	164	195	198	210	212	206	230	210	212	218	203
73990	F	200	200	208	187	204	188	Died								
1,000 ppm:																
73991	M	252	270	282	243	Died										
73992	M	260	273	266	220	Died										
73993	M	260	261	258	218	218	Died									
73994	M	262	276	264	228	204	Died									
73995	M	260	271	246	220	220	Died									
73996	F	192	202	194	155	160	Died									
73997	F	190	194	174	158	142	Died									
73998	F	214	224	206	168	168	Died									
73999	F	206	212	194	147	168	Died									
74000	F	204	214	180	158	146	Died									

*Terminal

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TABLE 2. Cont.

Individual Weekly Body Weights, Grams.

Group, Rat No.	Sex	Pretest		Week of Study												
		-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13*
<u>3,000 ppm:</u>																
74001	M	256	286	176	Died											
74002	M	240	261	200	Died											
74003	M	278	294	212	Died											
74004	M	262	281	198	Died											
74005	M	240	272	184	Died											
74006	F	212	220	164	Died											
74007	F	212	214	148	Died											
74008	F	208	214	146	Died											
74009	F	188	205	142	Died											
74010	F	202	214	146	Died											
<u>10,000 ppm:</u>																
74011	M	240	264	Died												
74012	M	256	259	Died												
74013	M	250	280	168	Died											
74014	M	250	260	156	Died											
74015	M	248	269	Died												
74016	F	202	216	Died												
74017	F	214	226	Died												
74018	F	194	205	Died												
74019	F	214	226	Died												
74020	F	200	200	Died												

*Terminal

TABLE 3.

Mean Food Consumption.

Week of Study	Control		30 ppm		100 ppm		300 ppm		1,000 ppm		3,000 ppm		10,000 ppm	
	g/ rat day	g/ kg/ day	g/ rat day	g/ kg/ day	g/ rat day	g/ kg/ day	g/ rat day	g/ kg/ day	g/ rat day	g/ kg/ day	g/ rat day	g/ kg/ day	g/ rat day	g/ kg/ day
MALES:														
1	23.3	75.0	26.7	91.9	26.3	80.6	25.4	79.5	17.3	65.8	6.1	31.5	0.9	5.3
2	26.1	78.7	28.9	87.4	27.4	78.7	25.8	80.5	13.6	60.2				
3	26.9	78.9	27.6	75.6	25.2	73.5	26.0	74.9	13.8	64.5				
4	28.1	74.6	23.9	66.0	27.6	72.8	24.9	70.9						
5	32.0	81.1	27.4	69.0	30.9	78.7	24.8	73.0						
6	29.9	71.3	26.9	63.2	29.8	70.5	27.0	72.7						
7	27.2	63.4	25.1	57.9	27.2	63.7	24.5	65.7						
8	27.3	60.0	25.8	56.8	27.7	62.1	24.4	62.7						
9	26.9	56.9	27.6 ^a	58.7 ^a	27.1	58.5	24.3	60.1						
10	26.9	56.4	28.8 ^b	59.9 ^b	25.3	55.0	22.4	57.0						
11	27.0	54.3	29.4	60.9	26.6	56.2	23.2	56.2						
12	27.5 ^a	53.8 ^a	28.2	56.9	27.3 ^a	56.0 ^a	25.3 ^a	61.0 ^a						
13	29.8	59.5	27.2 ^c	55.5 ^c	27.4	56.8	17.1	43.7						
FEMALES:														
1	17.8	78.9	20.6	99.2	17.3	82.2	16.2	76.3	9.6	50.5	3.8	25.3		
2	18.6	82.4	20.8	92.4	18.7	88.6	15.7	78.4	7.8	50.2				
3	21.0	90.8	20.7	86.4	19.4	86.5	15.5	76.7	11.6	73.9				
4	20.5	85.6	16.3	72.1	18.7	86.5	15.4	76.2						
5	23.7	95.7	19.3	79.6	21.6	98.8	15.7	75.2						
6	21.4	80.3	19.5	73.5	20.7	87.2	17.6	79.2						
7	19.4	73.9	17.1	67.2	20.1	84.6	14.9	66.9						
8	18.9	71.8	17.9	68.6	17.4	73.8	14.9	68.2						
9	19.7	69.2	20.4 ^a	76.4 ^a	19.2	75.7	15.2	63.1						
10	18.0	65.5	18.2 ^b	67.2 ^b	15.5	64.6	12.5	56.5						
11	18.8	67.5	21.1	77.4	18.3	74.6	14.1	61.3						
12	20.6 ^a	72.2 ^a	18.7	69.1	19.3 ^a	77.7 ^a	15.8 ^a	68.0 ^a						
13	19.7	68.8	19.9 ^c	73.9 ^c	15.5	62.6	13.4	59.2						

^aNine-day food consumption^bFive-day food consumption^cSix-day food consumption

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TABLE 4. T-test Comparison Between Means
of Control and Treated Groups, Food Consumption.

Study Week	Sex	Control	30 ppm	100 ppm	300 ppm
1-13	M	27.6	27.2	27.4	24.2*
	F	19.9	19.3	18.6	15.1*

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

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TABLE 5. MALES: Means and Significance of Hematological Values.

Hematology	Study Month	Control	30 ppm	100 ppm	300 ppm
Erythrocytes, 10 ⁶ /cmm	Pretest	6.08	5.95	5.69	6.03
	1	6.87	6.76	6.71	6.54
	3	7.69	7.30	7.64	6.81**
Hemoglobin, g/100 ml	Pretest	15.4	14.9	14.7	16.2
	1	16.1	16.0	16.1	15.8
	3	16.3	15.0*	15.9	14.7**
Hematocrit, %	Pretest	46	44	45	47
	1	49	50	47	49
	3	50	47*	48*	44**
Leucocytes, 10 ³ /cmm	Pretest	9.39	13.19	10.33	11.33
	1	10.43	10.78	12.25	14.45**
	3	9.79	11.21	11.35	9.11
Neutrophils, %	Pretest	14	28	11	9
	1	9	11	11	7
	3	13	15	12	10
Lymphocytes, %	Pretest	85	72	88	90
	1	89	87	88	91
	3	85	84	86	89
Eosinophils, %	Pretest	1	0	1	1
	1	1	1	1	1
	3	1	1	2	0
Monocytes, %	Pretest	0	0	0	0
	1	1	1	0	1
	3	1	0	0	1
Basophils, %	Pretest	0	0	0	0
	1	0	0	0	0
	3	0	0	0	0
Reticulocytes, %	Pretest	6.1	4.6	3.8	6.1
	1	2.6	2.2	2.6	2.8
	3	2.6	2.9	2.8	3.6**

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

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TABLE 5. Cont. FEMALES: Means and Significance of Hematological Values.

Hematology	Study Month	Control	30 ppm	100 ppm	300 ppm
Erythrocytes, 10 ⁶ /cmm	Pretest	6.41	6.26	6.33	6.47
	1	6.86	6.45	6.82	6.65
	3	7.56	7.14	7.27	6.81*
Hemoglobin, g/100 ml	Pretest	15.2	15.8	15.5	16.7
	1	16.1	15.9	16.1	16.0
	3	16.2	15.6	15.9	14.8*
Hematocrit, %	Pretest	46	45	47	48
	1	49	50	48	48
	3	48	48	47	45*
Leucocytes, 10 ³ /cmm	Pretest	10.50	11.75	7.38	9.29
	1	9.86	8.77	9.70	11.85
	3	9.08	8.85	6.47	8.62
Neutrophils, %	Pretest	12	25	15	14
	1	15	12	12	7*
	3	13	14	17	10
Lymphocytes, %	Pretest	87	73	84	84
	1	84	88	86	92
	3	85	84	81	87
Eosinophils, %	Pretest	1	1	1	2
	1	1	0	2	1
	3	1	1	2	2
Monocytes, %	Pretest	0	1	0	0
	1	0	0	0	0
	3	1	1	0	1
Basophils, %	Pretest	0	0	0	0
	1	0	0	0	0
	3	0	0	0	0
Reticulocytes, %	Pretest	2.7	4.4	2.9	3.5
	1	2.6	1.8	2.3	2.7
	3	3.0	3.3	2.7	2.0*

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

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

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TABLE 6. Individual Hematological Values - Pretest.

Group, Rat		Erythrocytes	Hemoglobin	Hematocrit	Leucocytes	Neutrophils		Lymphocytes	Eosinophils	Monoocytes	Basophils	Reticulocytes
Number	Sex	10 ⁶ /cmm	g/100 ml	%	10 ³ /cmm	Seg.	Non-Seg.	%	%	%	%	%
Control:												
73961	M	5.78*	15.2	45	9.82	14	1	84	1	0	0	5.2
73962	M	5.84*	14.3	46	10.25	9	0	90	1	0	0	8.5
73963	M	6.78*	17.0	51	10.17	12	0	88	0	0	0	4.5
73964	M	6.44*	15.3	46	8.17	16	0	81	3	0	0	8.3
73965	M	5.56*	15.0	44	8.54	16	0	82	2	0	0	4.0
Mean		6.08	15.4	46	9.39	14	0	85	1	0	0	6.1
73966	F	6.32*	14.6	45	6.03	19	0	80	1	0	0	4.4
73967	F	5.81*	15.4	45	10.79	9	0	89	2	0	0	2.7
73968	F	6.57*	14.8	46	11.11	6	0	94	0	0	0	1.1
73969	F	6.57*	15.6	48	15.82	18	0	80	2	0	0	4.7
73970	F	6.76*	15.4	47	8.74	9	0	91	0	0	0	0.7
Mean		6.41	15.2	46	10.50	12	0	87	1	0	0	2.7
30 ppm:												
76231	M	6.01*	14.9	45	15.44	25	0	75	0	0	0	4.6
76232	M	6.27*	15.6	47	10.98	33	0	65	2	0	0	4.1
76233	M	5.04*	12.4	38	13.16	30	0	70	0	0	0	5.8
76234	M	6.25*	14.8	45	15.21	35	0	65	0	0	0	4.0
76235	M	6.17*	16.9	45	11.18	15	0	85	0	0	0	4.6
Mean		5.95	14.9	44	13.19	28	0	72	0	0	0	4.6
76236	F	6.89*	16.3	47	15.03	40	0	57	1	2	0	4.0
76237	F	6.34*	15.7	47	9.10	26	0	73	0	1	0	4.5
76238	F	5.64*	14.8	42	8.62	24	0	76	0	0	0	4.0
76239	F	5.81*	14.8	41	15.13	24	0	75	1	0	0	6.1
76240	F	6.64*	17.4	47	10.85	12	0	84	2	2	0	3.6
Mean		6.26	15.8	45	11.75	25	0	73	1	1	0	4.4
100 ppm:												
73971	M	5.55*	13.8	42	13.56	13	0	86	1	0	0	4.7
73972	M	5.97*	15.8	46	10.05	13	0	87	0	0	0	5.2
73973	M	5.25*	14.2	46	11.21	9	0	91	0	0	0	3.9
73974	M	5.81*	14.9	48	8.56	8	0	90	2	0	0	3.0
73975	M	5.87*	14.7	44	8.27	11	0	89	0	0	0	2.3
Mean		5.69	14.7	45	10.33	11	0	88	1	0	0	3.8
73976	F	5.81*	13.5	42	11.19	25	0	74	1	0	0	4.7
73977	F	6.17*	16.3	49	6.34	16	0	82	2	0	0	0.5
73978	F	6.51*	15.5	47	6.01	10	0	89	1	0	0	2.8
73979	F	6.41*	15.4	47	7.85	14	0	85	1	0	0	3.4
73980	F	6.76*	16.9	48	5.49	9	0	90	1	0	0	3.0
Mean		6.33	15.5	47	7.38	15	0	84	1	0	0	2.9
300 ppm:												
73981	M	5.97*	15.7	47	12.62	14	0	85	1	0	0	11.1
73982	M	6.09*	17.2	49	13.56	5	0	93	2	0	0	3.7
73983	M	6.27*	16.5	49	12.31	6	0	93	1	0	0	4.9
73984	M	6.09*	16.3	46	9.02	9	0	90	1	0	0	6.5
73985	M	5.71*	15.3	45	9.14	10	0	89	1	0	0	4.3
Mean		6.03	16.2	47	11.33	9	0	90	1	0	0	6.1
73986	F	5.84*	15.6	46	9.10	15	0	83	2	0	0	4.6
73987	F	6.33*	16.3	47	8.91	10	0	88	2	0	0	2.2
73988	F	6.89*	16.8	46	8.63	9	0	86	5	0	0	3.2
73989	F	6.84*	18.3	52	11.56	16	0	84	0	0	0	3.1
73990	F	6.44*	16.4	47	8.26	18	0	81	1	0	0	4.6
Mean		6.47	16.7	48	9.29	14	0	84	2	0	0	3.3

*1+ Polychromasia

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TABLE 6. Cont.

Individual Hematological Values - Pretest.

Group, Rat Number	Sex	Erythro- cytes 10 ⁶ /cmm	Hemo- globin g/100 ml	Hemato- crit %	Leuco- cytes 10 ³ /cmm	Neutrophils Seg. Non-Seg.		Lympho- cytes %	Eosino- phils %	Mono- cytes %	Baso- phils %	Reticulo- cytes %
<u>1,000 ppm:</u>												
73991	M	4.98*	13.8	39	8.89	10	0	90	0	0	0	5.3
73992	M	6.08*	15.1	45	12.99	27	0	73	0	0	0	6.6
73993	M	6.21*	16.2	49	13.50	6	0	94	0	0	0	2.5
73994	M	5.97*	16.3	46	12.99	7	0	93	0	0	0	6.3
73995	M	5.69*	14.8	46	10.68	10	0	90	0	0	0	5.3
Mean		5.79	15.3	45	11.81	12	0	88	0	0	0	5.2
73996	F	5.99*	15.0	45	10.91	11	0	86	3	0	0	4.2
73997	F	5.82*	14.5	42	7.18	24	0	74	2	0	0	3.8
73998	F	6.44*	15.7	47	10.69	28	0	72	0	0	0	3.5
73999	F	6.47*	16.4	50	7.67	14	0	83	3	0	0	1.0
74000	F	6.30*	15.9	47	9.46	18	1	80	1	0	0	1.0
Mean		6.20	15.5	46	9.18	19	0	79	2	0	0	2.7
<u>3,000 ppm:</u>												
74001	M	5.13*	15.7	46	13.31	9	0	91	0	0	0	5.1
74002	M	5.96*	15.6	46	12.63	7	0	93	0	0	0	4.0
74003	M	6.01*	14.6	48	6.31	14	0	84	2	0	0	5.0
74004	M	5.56*	15.8	46	10.16	13	0	86	1	0	0	4.2
74005	M	6.15*	16.9	50	7.79	10	0	89	1	0	0	2.0
Mean		5.76	15.7	47	10.05	11	0	88	1	0	0	4.1
74006	F	5.80*	14.8	45	10.16	9	0	91	0	0	0	3.5
74007	F	6.25*	15.2	46	11.32	9	0	91	0	0	0	4.7
74008	F	5.83*	15.0	44	10.55	10	0	90	0	0	0	6.5
74009	F	6.47*	15.5	47	12.81	7	0	93	0	0	0	2.7
74010	F	6.28*	15.9	45	9.44	19	0	81	0	0	0	2.0
Mean		6.13	15.3	45	10.86	11	0	89	0	0	0	3.9
<u>10,000 ppm:</u>												
74011	M	5.93*	15.7	47	11.70	6	0	92	2	0	0	5.1
74012	M	5.55*	16.8	49	11.61	8	0	91	1	0	0	5.7
74013	M	6.42*	16.6	52	8.52	9	0	90	1	0	0	1.3
74014	M	5.94*	15.4	48	10.04	12	0	88	0	0	0	2.2
74015	M	6.13*	16.2	49	10.01	15	0	83	2	0	0	4.9
Mean		5.99	16.1	49	10.38	10	0	89	1	0	0	3.8
74016	F	6.18*	15.2	46	9.28	19	0	81	0	0	0	2.8
74017	F	6.13*	15.2	46	8.18	21	0	79	0	0	0	4.9
74018	F	5.90*	14.7	42	6.76	14	0	85	1	0	0	2.1
74019	F	5.93*	15.8	47	7.65	19	0	81	0	0	0	2.3
74020	F	6.38*	15.8	47	8.85	10	1	88	1	0	0	4.0
Mean		6.10	15.3	46	8.14	17	0	83	0	0	0	3.2

*1+ Polychromasia

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TABLE 7.

Individual Hematological Values - 1 Month.

Group, Rat		Erythro-	Hemo-	Hemato-	Leuco-	Neutrophils		Lympho-	Eosino-	Mono-	Baso-	Reticulo-
Number	Sex	cytes 10 ⁶ /cmm	globin g/100 ml	crit %	cytes 10 ³ /cmm	Seg. %	Non-Seg. %	cytes %	phils %	cytes %	phils %	cytes %
Control:												
73961	M	6.31	15.0	47	9.53	6	0	91	2	1	0	3.0
73962	M	6.53	15.2	47	10.89	11	0	88	1	0	0	2.6
73963	M	7.35	17.4	51	11.98	15	0	84	1	0	0	2.8
73964	M	7.16	16.4	51	9.61	6	0	89	0	5	0	2.2
73965	M	6.99	16.5	49	10.10	8	0	90	1	1	0	2.3
Mean		6.87	16.1	49	10.43	9	0	89	1	1	0	2.6
73966	F	6.88	15.9	47	6.32	20	0	75	4	1	0	2.0
73967	F	7.35	16.7	49	8.57	18	0	82	0	0	0	2.3
73968	F	6.83	16.9	51	10.56	10	0	89	1	0	0	2.5
73969	F	7.04	16.8	51	16.71	17	0	81	2	0	0	3.2
73970	F	6.21	14.3	46	7.12	11	0	89	0	0	0	3.0
Mean		6.86	16.1	49	9.86	15	0	84	1	0	0	2.6
30 ppm:												
76231	M	7.14	15.6	49	11.66	18	0	80	2	0	0	1.8
76232	M	7.46	16.5	52	10.23	9	0	90	1	0	0	1.7
76233	M	6.58*	15.6	50	11.27	12	0	83	1	4	0	2.9
76234	M	6.44	15.2	47	10.81	9	0	91	0	0	0	2.3
76235	M	7.12	17.1	53	9.92	9	0	88	0	3	0	2.4
Mean		6.95	16.0	50	10.78	11	0	87	1	1	0	2.2
76236	F	6.57	16.1	50	5.64	20	0	80	0	0	0	1.0
76237	F	6.53	15.9	50	8.46	13	0	86	1	0	0	1.9
76238	F	6.45	16.0	50	6.52	13	0	87	0	0	0	2.3
76239	F	6.45	16.0	51	14.30	10	0	89	1	0	0	1.7
76240	F	6.26	15.5	48	8.95	6	0	94	0	0	0	1.9
Mean		6.45	15.9	50	8.77	12	0	88	0	0	0	1.8
100 ppm:												
73971	M	6.78	16.0	51	15.44	6	0	93	0	1	0	2.1
73972	M	6.79	15.6	47	9.36	21	0	78	1	0	0	3.3
73973	M	6.38	16.5	48	16.80	7	0	92	1	0	0	3.0
73974	M	6.58	15.9	45	11.89	9	0	89	2	0	0	2.4
73975	M	7.04	16.4	46	7.76	10	0	89	1	0	0	2.3
Mean		6.71	16.1	47	12.25	11	0	88	1	0	0	2.6
73976	F	6.65	15.5	45	17.75	13	0	84	3	0	0	2.4
73977	F	6.91	16.9	51	10.26	15	0	85	0	0	0	2.2
73978	F	7.24	15.8	48	6.68	6	0	93	1	0	0	2.1
73979	F	6.61	16.1	48	8.31	10	0	89	1	0	0	2.4
73980	F	6.67	16.3	50	5.49	18	0	77	3	2	0	2.5
Mean		6.82	16.1	48	9.70	12	0	86	2	0	0	2.3
300 ppm:												
73981	M	6.23	15.1	47	14.70	5	0	93	1	1	0	2.8
73982	M	6.89	16.0	51	15.87	5	0	94	1	0	0	2.4
73983	M	6.85*	16.4	52	15.83	6	0	94	0	0	0	3.0
73984	M	6.44	15.5	48	12.75	11	1	85	1	2	0	3.1
73985	M	6.40	15.9	48	13.12	10	0	90	0	0	0	2.8
Mean		6.56	15.8	49	14.45	7	0	91	1	1	0	2.8
73986	F	6.48	15.7	47	13.83	9	0	90	1	0	0	2.0
73987	F	6.54	15.5	46	14.08	8	0	89	2	1	0	2.4
73988	F	6.50	15.5	47	9.33	6	0	92	2	0	0	2.3
73989	F	6.77	16.3	48	11.52	12	0	88	0	0	0	4.1
73990	F	6.95	17.2	52	10.48	4*	0	94	2	0	0	2.5
Mean		6.65	16.0	48	11.85	9	0	91	1	0	0	2.7

*Repeat determination.

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TABLE 8. Individual Hematological Values - 3 Months.

Group, Rat Number	Sex	Erythrocytes 10 ⁶ /cmm	Hemoglobin g/100 ml	Hematocrit %	Leucocytes 10 ³ /cmm	Neutrophils Seg. Non-Seg. % %		Lymphocytes %	Eosinophils %	Monocytes %	Basophils %	Reticulocytes %
Control:												
73961	M	7.56	16.6	50	11.72	12	0	87	1	0	0	2.1
73962	M	7.43	16.5	51	11.43	6	0	94	0	0	0	2.1
73963	M	8.05	17.3	52	10.66	16	0	80	1	3	0	2.6
73964	M	7.80	15.8	50	9.45	14	0	82	2	2	0	3.0
73965	M	7.62	15.4	48	5.70	16	0	82	2	0	0	2.8
Mean		7.69	16.3	50	9.79	13	0	85	1	1	0	2.6
73966	F	7.32	16.2	48	6.36	22	0	77	1	0	0	2.9
73967	F	7.76	15.6	47	8.00	16	0	83	1	0	0	3.4
73968	F	7.75	16.8	50	9.78	7	0	93	0	0	0	3.0
73969	F	7.65	16.8	50	12.06	11	0	87	1	1	0	3.0
73970	F	7.30	15.7	46	9.18	10	0	88	0	2	0	2.7
Mean		7.56	16.2	48	9.08	13	0	85	1	1	0	3.0
30 ppm:												
76231	M	7.48	14.5	46	11.12	19	0	80	1	0	0	2.5
76232	M	7.38	14.9	47	9.45	10	0	89	0	1	0	3.4
76233	M	6.52	14.1	44	12.35	19	0	77	4	0	0	2.8
76234	M	7.91	16.2	50	12.17	13	0	86	1	0	0	3.2
76235	M	7.19	15.4	47	10.96	13	0	86	1	0	0	2.6
Mean		7.30	15.0	47	11.21	15	0	84	1	0	0	2.9
76236	F	7.53	15.9	49	7.36	9	0	89	2	0	0	4.1
76237	F	7.33	16.5	50	8.52	23	0	76	1	0	0	3.8
76238	F	6.64	14.7	45	7.40	20	0	77	2	1	0	3.0
76239	F	7.49	15.8	49	11.98	9	0	89	2	0	0	2.3
76240	F	6.71	15.2	47	9.01	7	0	89	0	0	0	3.1
Mean		7.14	15.6	48	8.85	14	0	84	1	1	0	3.3
100 ppm:												
73971	M	7.85	15.3	48	13.71	16	0	82	2	0	0	2.2
73972	M	7.77	15.5	48	8.15	11	0	88	1	0	0	2.7
73973	M	7.20	15.7	48	11.47	5	0	92	3	0	0	3.8
73974	M	7.96	16.7	48	14.96	7	0	89	4	0	0	3.0
73975	M	7.40	16.4	48	8.46	21	0	78	0	1	0	2.4
Mean		7.64	15.9	48	11.35	12	0	86	2	0	0	2.8
73976	F	7.18	15.0	44	10.17	11	0	87	2	0	0	2.3
73977	F	7.24	16.8	48	6.26	19	0	79	2	0	0	2.7
73978	F	6.92	15.1	46	4.79	13	0	81	6	0	0	2.5
73979	F	7.11	15.9	48	6.63	26	0	74	0	0	0	3.3
73980	F	7.90	16.8	49	4.48	15	0	82	2	1	0	2.6
Mean		7.27	15.9	47	6.47	17	0	81	2	0	0	2.7
300 ppm:												
73981	M	6.88	15.6	47	11.70	7	1	92	0	0	0	3.4
73982	M	6.35	13.9	42	8.67	10	0	90	0	0	0	3.7
73983	M	6.87	15.3	45	9.32	8	0	91	0	1	0	3.5
73984	M	7.40	14.8	44	7.47	13	0	84	1	2	0	3.4
73985	M	6.53	13.8	41	8.40	9	0	90	1	0	0	3.8
Mean		6.81	14.7	44	9.11	9	0	90	0	1	0	3.6
73986	F	6.96	15.0	45	9.63	9	0	85	3	3	0	2.7
73987	F	6.44	14.0	43	8.34	7	0	92	1	0	0	2.2
73988	F	7.08	14.9	45	7.55	8	1	85	4	2	0	2.1
73989	F	6.77	15.1	45	8.95	14	0	85	1	0	0	2.0
73990	F	Died										
Mean		6.81	14.8	45	8.62	10	0	87	2	1	0	2.0

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TABLE 9. MALES: Means and Significance^a of Biochemical Values.

Biochemistry	Study Month	Control	30 ppm	100 ppm	300 ppm
Glucose, mg/100 ml	Pretest	74	62	82	76
	1	100	101	107	98
	3	126	123	120	119
B.U.N., mg/100 ml	Pretest	14.2	14.0	12.7	12.6
	1	14.6	21.6	14.5	19.3
	3	16.3	15.2	18.8	22.7**
γ-G.T.P., Sigma units/ml	Pretest	1	2	6	1
	1	1	5	1	7
	3	0	6*	0	0
C.P.K. ^b , Sigma units/ml	Pretest	25	16	5	10
	1	20	11	9	13
	3	9	5*	10	9
Alkaline Phos., int'l units/l	Pretest		216		
	1	172	170	179	128
	3	126	112	148	214**
P.G.O.T., int'l units/l	Pretest	133	83	116	112
	1	109	107	101	98
	3	104	140	101	93
P.G.P.T., int'l units/l	Pretest	113	74	95	95
	1	50	42	41	61
	3	40	66	40	116*
Calcium, meq/liter	Pretest	10.2	7.5	10.7	9.7
	1	9.0	9.7	8.6	8.4
	3	11.4	10.9	11.0	11.2

^aStatistical analyses not conducted on the pretest values.^bC.P.K. - Creatinine phosphokinase

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

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

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TABLE 9. Cont. FEMALES: Means and Significance^a of Biochemical Values.

Biochemistry	Study Month	Control	30 ppm	100 ppm	300 ppm
Glucose, mg/100 ml	Pretest	89	67	89	97
	1	118	109	109	108
	3	128	132	115	108*
B.U.N., mg/100 ml	Pretest	16.9	12.9	15.5	13.3
	1	15.6	16.7	16.9	28.9
	3	18.2	17.2	20.6	21.2
γ-G.T.P., Sigma units/ml	Pretest	1	1	1	1
	1	1	2**	0	1
	3	1	1	1	2
C.P.K. ^b , Sigma units/ml	Pretest	6	13	6	5
	1	8	15	10	13
	3	7	10	6	9
Alkaline Phos., int'l units/l	Pretest	+	140	+	+
	1	91	116	83	249**
	3	69	82	68	148
P.G.O.T., int'l units/l	Pretest	114	88	115	106
	1	91	121	79	196
	3	101	98	85*	115
P.G.P.T., int'l units/l	Pretest	103	68	97	95
	1	41	49	39	160
	3	28	32	33	83
Calcium, meq/liter	Pretest	9.8	7.7	9.7	9.6
	1	8.9	10.0	8.7	9.0
	3	11.3	11.2	11.2	11.4

^aStatistical analyses not conducted on pretest values.^bC.P.K. - Creatinine phosphokinase

+ = Not measured due to anticoagulant interference.

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

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

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TABLE 10.

Individual Biochemical Values - Pretest.

Group, Rat Number	Sex	Glucose mg/100 ml	B.U.N. mg/100 ml	γ -G.T.P. Sigma units/ml	C.P.K.* Sigma units/ml	Alk. Phos. int'l units/ml	P.G.O.T. int'l units/ml	P.G.P.T. int'l units/ml	Calcium meq/ liter
<u>Control:</u>									
73961	M	75	12.0	2	5	**	105	90	10.2
73962	M	75	15.3	1	12	**	144	117	10.8
73963	M	69	13.8	1	69	**	171	174	10.1
73964	M	75	18.0	0	3	**	96	93	10.2
73965	M	75	12.0	1	35	**	147	93	9.8
Mean		74	14.2	1	25		133	113	10.2
73966	F	90	18.3	1	5	**	96	120	10.2
73967	F	87	16.2	1	15	**	120	105	10.0
73968	F	105	18.0	1	3	**	117	114	9.5
73969	F	90	17.7	1	3	**	117	87	10.0
73970	F	75	14.4	1	3	**	120	90	9.5
Mean		89	16.9	1	6		114	103	9.8
<u>30 ppm:</u>									
76231	M	75	16.2	2	15		93	81	8.3
76232	M	51	11.7	1	24		84	72	5.8
76233	M	66	12.3	2	20		87	75	7.4
76234	M	72	15.0	2	14		84	81	7.9
76235	M	45	15.0	1	8		66	60	8.1
Mean		62	14.0	2	16		83	74	7.5
76236	F	57	15.0	1	8		108	81	8.1
76237	F	66	13.5	2	5		78	66	7.1
76238	F	87	15.0	1	6		90	60	7.6
76239	F	63	9.6	1	25		81	60	7.4
76240	F	60	11.4	1	19		84	72	8.5
Mean		67	12.9	1	13		88	68	7.7
<u>100 ppm:</u>									
73971	M	72	11.4	1	4	**	105	87	9.9
73972	M	90	12.3	1	4	**	132	102	9.8
73973	M	75	12.0	0	3	**	102	84	10.1
73974	M	90	15.3	1	3	**	99	90	10.2
73975	M	81	12.3	25	10	**	144	111	13.7
Mean		82	12.7	6	5		116	95	10.7
73976	F	99	19.2	2	7	**	117	99	9.4
73977	F	90	16.5	2	4	**	105	90	10.1
73978	F	87	13.5	1	6	**	120	96	9.5
73979	F	84	13.2	1	7	**	120	108	9.8
73980	F	87	15.0	1	8	**	111	90	9.7
Mean		89	15.5	1	6		115	97	9.7
<u>300 ppm:</u>									
73981	M	81	10.5	1	7	**	111	90	9.5
73982	M	66	12.0	1	22	**	147	105	9.5
73983	M	87	14.7	1	3	**	105	90	10.1
73984	M	72	13.8	1	3	**	93	99	9.4
73985	M	75	12.0	1	17	**	102	90	10.2
Mean		76	12.6	1	10		112	95	9.7
73986	F	99	12.0	0	4	**	90	90	9.2
73987	F	81	15.6	2	6	**	120	93	9.9
73988	F	105	15.0	2	5	**	120	96	10.1
73989	F	93	12.0	1	4	**	93	102	9.6
73990	F	105	12.0	1	5	**	108	93	9.4
Mean		97	13.3	1	5		106	95	9.6

*Creatinine phosphokinase

**Alkaline phosphatase not measured due to anticoagulant

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TABLE 10. Cont.

Individual Biochemical Values - Pretest.

Group, Rat Number	Sex	Glucose mg/100 ml	B.U.N. mg/100 ml	(-G.T.P. Sigma units/ml	C.P.K.* Sigma units/ml	Alk. Phos. int'l units/ml	P.G.O.T. int'l units/ml	P.G.P.T. int'l units/ml	Calcium meq/ liter
<u>1,000 ppm:</u>									
73991	M	99	9.0	1	11	**	123	90	9.7
73992	M	93	17.7	1	10	**	135	99	10.3
73993	M	81	13.8	1	8	**	114	90	9.7
73994	M	72	12.0	1	30	**	123	108	10.3
73995	M	102	18.0	1	10	**	114	90	10.0
Mean		89	14.1	1	14		122	95	10.0
73996	F	87	16.2	1	11	**	111	90	10.1
73997	F	117	12.0	1	5	**	75	78	9.6
73998	F	105	18.0	1	6	**	105	93	9.6
73999	F	93	12.0	1	11	**	120	78	10.0
74000	F	93	12.0	1	7	**	117	96	9.3
Mean		99	14.0	1	8		106	87	9.7
<u>3,000 ppm:</u>									
74001	M	78	12.0	1	8	**	96	120	10.0
74002	M	78	12.9	1	4	**	108	93	10.2
74003	M	75	12.0	1	7	**	132	90	9.5
74004	M	87	17.4	2	7	**	123	102	9.9
74005	M	87	10.2	1	15	**	90	102	9.8
Mean		81	12.9	1	8		110	101	9.9
74006	F	99	15.0	1	5	**	102	102	9.7
74007	F	102	15.0	2	18	**	108	135	9.8
74008	F	87	15.0	1	8	**	93	90	10.1
74009	F	93	15.3	2	13	**	111	114	9.7
74010	F	102	18.0	1	7	**	90	117	10.3
Mean		97	15.7	1	10		101	112	9.9
<u>10,000 ppm:</u>									
74011	M	78	16.5	2	5	**	105	126	10.2
74012	M	78	14.7	1	8	**	126	93	10.0
74013	M	96	14.7	1	8	**	120	153	10.2
74014	M	81	15.3	1	5	**	90	96	9.7
74015	M	84	14.7	2	8	**	108	90	9.9
Mean		83	15.2	1	7		110	112	10.0
74016	F	84	15.3	1	12	**	120	135	9.3
74017	F	105	15.0	0	7	**	108	114	9.8
74018	F	90	17.7	1	9	**	105	120	9.7
74019	F	78	15.3	1	10	**	105	102	10.1
74020	F	90	15.3	2	15	**	126	159	10.5
Mean		89	15.7	1	11		113	126	9.9

*Creatinine phosphokinase

**Alkaline phosphatase not measured due to anticoagulant

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TABLE 11.

Individual Biochemical Values - 1 Month.

Group. Rat Number	Sex	Glucose mg/100 ml	B.U.N. mg/100 ml	γ -G.T.P. Sigma units/ml	C.P.K.* Sigma units/ml	Alk. Phos. int'l units/ml	P.G.O.T. int'l units/ml	P.G.P.T. int'l units/ml	Calcium meq/ liter
<u>Control:</u>									
73961	M	96	11.7	1	14	192	93	42	8.7
73962	M	102	18.0	0	43	162	126	51	9.4
73963	M	96	14.7	1	15	174	111	78	9.4
73964	M	108	16.8	0	15	186	93	36	9.5
73965	M	99	12.0	1	12	144	120	45	8.0
Mean		100	14.6	1	20	172	109	50	9.0
73966	F	120	15.0	1	9	90	84	42	8.6
73967	F	120	18.3	0	4	96	84	42	9.1
73968	F	132	17.7	1	9	102	102	48	8.7
73969	F	114	15.3	1	7	84	120	51	9.2
73970	F	105	11.7	1	9	81	66	24	8.8
Mean		118	15.6	1	8	91	91	41	8.9
<u>30 ppm:</u>									
76231	M	90	14.7	2	12	195	108	42	9.4
76232	M	102	14.4	3	7	153	120	45	9.4
76233	M	108	30.9	9	11	195	114	42	9.6
76234	M	105	32.4	9	16	159	78	36	10.5
76235	M	102	15.6	2	8	147	117	45	9.8
Mean		101	21.6	5	11	170	107	42	9.7
76236	F	90	20.7	2	10	90	123	48	9.6
76237	F	111	17.4	2	18	138	150	69	9.2
76238	F	120	15.0	2	15	138	132	48	9.9
76239	F	114	16.5	2	17	102	105	42	8.8
76240	F	111	14.1	2	15	111	93	39	12.4
Mean		109	16.7	2	15	116	121	49	10.0
<u>100 ppm:</u>									
73971	M	108	12.0	0	8	132	108	42	8.6
73972	M	105	15.0	1	10	213	93	48	9.3
73973	M	102	15.3	0	10	162	99	39	8.5
73974	M	102	14.7	1	13	192	90	36	8.9
73975	M	117	15.3	1	4	195	114	42	7.5
Mean		107	14.5	1	9	179	101	41	8.6
73976	F	120	19.8	0	7	48	78	42	8.5
73977	F	108	18.3	0	5	96	84	48	8.4
73978	F	108	14.7	0	7	93	75	42	8.7
73979	F	105	19.2	0	22	108	96	30	9.2
73980	F	102	12.3	0	7	72	60	33	8.6
Mean		109	16.9	0	10	83	79	39	8.7
<u>300 ppm:</u>									
73981	M	102	24.3	13	12	168	117	72	8.7
73982	M	96	17.7	2	13	78	96	57	8.0
73983	M	96	15.6	16	14	135	93	57	7.4
73984	M	93	21.0	2	13	144	93	63	8.6
73985	M	102	17.7	2	15	117	90	57	9.2
Mean		98	19.3	7	13	128	98	61	8.4
73986	F	111	20.4	1	10	291	87	66	8.5
73987	F	105	18.0	1	8	210	480	360	8.8
73988	F	108	51.0	0	9	267	96	75	9.2
73989	F	102	18.6	1	19	225	135	147	9.1
73990	F	114	36.6	0	17	252	180	150	9.2
Mean		108	28.9	1	13	249	196	160	9.0

*Creatinine phosphokinase

FM-3422 41-2700-3422-0:

Ninety Day Subacute Rat Toxicity Study.

TABLE 12.

Individual Biochemical Values - 3 Months.

Group, Rat Number	Sex	Glucose mg/100 ml	B.U.N. mg/100 ml	γ -G.T.P. Sigma units/ml	C.P.K.* Sigma units/ml	Alk. Phos. int'l units/ml	P.G.P.T. int'l units/ml	P.G.O.T. int'l units/ml	Calcium meq/ liter
<u>Control:</u>									
73961	M	121	15.5	0	10	140	32	82	11.6
73962	M	124	17.2	0	8	120	39	106	11.2
73963	M	120	17.0	0	9	135	45	120	11.3
73964	M	139	17.9	0	9	140	34	81	11.9
73965	M	124	13.9	0	10	96	52	133	10.9
Mean		126	16.3	0	9	126	40	104	11.4
73966	F	125	19.6	0	6	91	31	94	11.1
73967	F	131	18.8	1	9	65	29	90	11.0
73968	F	145	20.8	1	8	89	20	101	11.9
73969	F	132	17.9	0	8	51	33	110	11.6
73970	F	106	13.9	1	6	49	27	110	10.8
Mean		128	18.2	1	7	69	28	101	11.3
<u>30 ppm:</u>									
*76231	M	114	13.9	10	3	144	33	85	10.6
76232	M	120	13.9	10	6	94	47	106	10.2
76233	M	124	15.1	2	3	134	154	299	11.3
76234	M	125	17.1	9	4	98	39	91	11.5
76235	M	130	16.0	0	8	91	58	118	11.0
Mean		123	15.2	6	5	112	66	140	10.9
76236	F	125	21.1	2	10	77	34	95	11.2
76237	F	125	18.1	1	11	100	30	128	11.1
76238	F	140	16.3	1	10	91	32	102	11.5
76239	F	130	17.4	1	3	56	37	96	10.8
76240	F	140	12.9	0	15	88	28	69	11.4
Mean		132	17.2	1	10	82	32	98	11.2
<u>100 ppm:</u>									
73971	M	126	18.1	1	5	112	43	100	10.6
73972	M	114	18.1	0	25	160	50	104	10.7
73973	M	117	17.0	0	7	116	31	88	11.5
73974	M	119	19.6	0	7	139	36	96	11.3
73975	M	123	21.2	0	7	213	42	118	10.8
Mean		120	18.8	0	10	148	40	101	11.0
73976	F	122	23.2	1	7	44	43	92	10.8
73977	F	112	24.6	1	6	99	34	83	10.6
73978	F	114	19.9	1	6	82	31	90	11.9
73979	F	117	20.5	0	7	67	28	88	11.8
73980	F	108	14.9	0	5	49	28	72	10.9
Mean		115	20.6	1	6	68	33	85	11.2
<u>300 ppm:</u>									
73981	M	120	23.1	0	6	227	78	81	10.8
73982	M	118	20.1	1	11	151	142	103	11.1
73983	M	131	22.1	0	8	270	89	92	11.0
73984	M	109	23.1	0	10	147	204	119	11.9
73985	M	115	25.1	0	9	274	68	72	11.0
Mean		119	22.7	0	9	214	116	93	11.2
73986	F	103	21.4	1	9	114	50	91	11.3
73987	F	113	18.9	0	11	107	46	89	11.3
73988	F	100	24.8	0	11	281	166	184	11.0
73989	F	116	19.5	5	5	90	69	95	12.1
73990	F	Died							
Mean		108	21.2	2	9	148	83	115	11.4

*Creatinine phosphokinase

FM-3422 41-2700-3422-0: Ninety Day Subacute Rat Toxicity Study.

TABLE 13. MALES: Means and Significance^a of Urinalysis Values.

Urinalysis	Study Month	Control	30 ppm	100 ppm	300 ppm
Volume, ml	Pretest	3.8	6.2	5.4	4.7
	1	5.9	1.7**	5.0	4.3
	3	5.2	3.7	6.6	6.8
pH	Pretest	7.1	7.0	7.4	7.3
	1	6.7	6.5	6.9	5.9
	3	6.9	6.3	6.6	6.1*
Specific Gravity	Pretest	1.032	1.036	1.032	1.031
	1	1.050	1.076*	1.050	1.067
	3	1.047	1.057	1.051	1.045

^aStatistical analyses not conducted on pretest values.*Significantly different from Control group mean, $p < 0.05$.**Significantly different from Control group mean, $p < 0.01$.

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TABLE 13. Cont. FEMALES: Means and Significance^a of Urinalysis Values.

Urinalysis	Study Month	Control	30 ppm	100 ppm	300 ppm
Volume, ml	Pretest	3.4	4.2	1.8	4.1
	1	2.9	1.2	2.8	4.4
	3	2.0	1.1	3.8	3.9
pH	Pretest	7.0	6.9	6.9	7.0
	1	5.8	7.3**	6.3	6.4
	3	6.3	6.8	6.4	6.3
Specific Gravity	Pretest	1.031	1.037	1.036	1.027
	1	1.057	1.065	1.060	1.046
	3	1.071	1.084	1.044	1.043

^aStatistical analyses not conducted on pretest values.*Significantly different from Control group mean, $p < 0.05$.**Significantly different from Control group mean, $p < 0.01$.

TABLE 14.

Individual Urinalysis Values - Pretest.

Group, Rat Number	Sex	Volume ml	Color and Appear.	pH	Spec. Grav.	Total Protein	Glucose	Billirubin	Occult Blood	Ketones	Leucocytes	Erythrocytes	Epi. Cells	Amor. Urates	Triple Phos.	Cal. Ox.	Uric Acid Crystals	Bacteria	Comments
Control:																			
71961	H	1.0	LS-C	7.1	1.043	N	N	N	N	N	-	occ	1-3	occ	F	-	-	N	-
71962	H	5.0	S-cl	7.7	1.028	N	N	N	tr	N	-	1-3	occ	F	F	-	-	N	-
71963	H	2.0	LS-C	6.8	1.034	N	N	N	N	N	-	-	-	occ	occ	-	-	F	-
71964	H	6.0	LS-C	6.7	1.026	N	N	N	tr	N	-	-	-	occ	F	-	-	F	-
71965	H	5.0	S-cl	7.0	1.031	N	N	N	tr	N	-	-	-	occ	F	-	-	N	-
71966	F	5.0	LS-C	7.6	1.022	N	N	N	tr	N	-	-	-	occ	F	-	-	N	-
71967	F	1.0	LS-C	6.9	1.034	N	N	N	N	N	-	1-3	-	occ	occ	-	-	F	-
71968	F	5.0	LS-C	6.9	1.024	N	N	N	N	N	-	-	-	occ	occ	-	-	F	-
71969	F	2.5	LS-C	7.2	1.036	N	N	N	tr	N	-	-	occ	occ	F	-	-	N	-
71970	F	1.5	LS-C	6.5	1.037	N	N	N	N	N	-	1-3	-	occ	occ	-	-	F	-
10 ppm:																			
76231	H	7.0	LS-C	7.3	1.034	N	N	N	tr	N	-	-	-	occ	occ	-	-	F	-
76232	H	5.0	LS-C	6.6	1.037	N	N	N	N	N	-	-	-	occ	occ	-	-	F	-
76233	H	6.0	S-cl	7.4	1.035	N	N	N	1+	N	-	occ	-	occ	F	-	-	N	-
76234	H	5.0	S-cl	7.0	1.042	N	N	N	tr	N	-	-	-	occ	occ	-	-	N	-
76235	H	8.0	LS-cl	6.9	1.031	N	N	N	tr	N	-	-	-	occ	occ	occ	-	N	-
76236	F	1.0	S-C	6.7	1.038	N	N	N	1+	N	-	-	-	occ	F	-	-	F	-
76237	F	1.0	LS-C	6.5	1.048	N	N	N	N	N	-	occ	-	occ	occ	-	-	N	-
76238	F	5.0	S-cl	7.1	1.060	N	N	N	1+	N	-	-	-	occ	occ	-	-	N	-
76239	F	5.0	LS-cl	7.1	1.027	N	N	N	N	N	-	-	occ	occ	occ	-	-	N	-
76250	F	5.0	LS-cl	7.1	1.034	N	N	N	N	N	-	occ	-	occ	F	-	-	N	-
100 ppm:																			
71971	H	2.0	S-C	6.9	1.048	N	N	N	N	N	-	occ	-	occ	F	-	-	N	-
71972	H	6.0	S-C	7.0	1.029	N	N	N	N	N	-	occ	occ	occ	F	-	-	N	-
71973	H	6.0	DS-cl	8.1	1.027	N	N	N	tr	N	-	1-3	-	occ	F	-	-	N	-
71974	H	8.0	LS-C	6.9	1.026	N	N	N	N	N	-	-	occ	occ	occ	-	-	N	-
71975	H	5.0	S-cl	7.9	1.030	N	N	N	tr	N	-	occ	occ	occ	occ	-	-	N	-
71976	F	0.5	S-C	6.8	1.042	N	N	N	4+	N	-	occ	-	occ	F	-	-	N	-
71977	F	1.0	LS-C	6.5	1.036	N	N	N	tr	N	-	-	occ	occ	F	-	-	N	-
71978	F	2.0	LS-C	6.4	1.036	N	N	N	N	N	-	-	-	occ	F	-	-	N	-
71979	F	1.0	LS-C	6.5	1.026	N	N	N	N	N	-	-	-	occ	occ	-	-	F	-
71980	F	1.0	DS-cl	8.2	1.038	N	N	N	4+	N	-	-	-	occ	occ	-	-	F	-

Code:

tr - Trace

1+ - Trace to slight

2+ - Slight to moderate

1+ - 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

- = None seen

117-086

FH-1422 41-2700-1422-0:

Ninety Day Subacute Rat Toxicity Study.

TABLE 14. Cont.

Individual Urinalysis Values - Pretest.

Group, Rat Number	Sex	Volume ml	Color and Appear.	pH	Spec. Grav.	Total Protein	Glu- cose	Billi- rubin	Occult Blood	Ke- tones	Leuco- cytes	Erythro- cytes	Epi. Cells	Amor. Urates	Triple Phos.	Cal. Ox.	Uric Acid Crystals	Bac- teria	Casts
300 ppm:																			
73981	M	4.0	LS-cl	6.5	1.033	N	N	N	N	N	-	-	-	occ	F	-	-	F	-
73982	H	5.0	S-C	7.5	1.035	N	N	N	N	N	-	occ	-	occ	F	-	-	N	-
73983	H	2.0	LS-C	6.8	1.035	N	N	N	N	N	-	-	occ	occ	F	-	-	N	-
73984	M	6.0	LS-C	7.0	1.030	N	N	N	N	N	-	-	-	occ	F	-	-	N	-
73985	H	6.5	LS-C	8.5	1.024	N	N	N	N	N	-	-	-	occ	F	-	-	N	-
73986	F	5.0	S-cl	7.9	1.027	N	N	N	3+	N	-	1-3	1-3	F	F	-	-	N	-
73987	F	1.0	LS-C	6.5	1.034	N	N	N	N	N	-	occ	-	F	F	-	-	F	-
73988	F	5.0	LS-C	6.9	1.023	N	N	N	N	N	-	-	-	occ	occ	-	-	F	-
73989	F	1.5	LS-C	6.9	1.029	N	N	N	2+	N	-	-	-	occ	occ	-	-	N	-
73990	F	4.0	LS-C	7.0	1.023	N	N	N	N	N	-	occ	-	occ	F	-	-	F	-
1,000 ppm:																			
73991	H	3.0	LS-C	7.2	1.026	N	N	N	tr	N	-	-	-	occ	occ	-	-	F	-
73992	H	6.0	LS-C	7.0	1.026	N	N	N	tr	N	-	-	-	occ	F	-	-	N	-
73993	H	4.0	LS-C	7.0	1.028	N	N	N	tr	N	-	-	-	occ	occ	-	-	N	-
73994	H	1.5	LS-C	7.1	1.035	N	N	N	N	N	-	occ	-	occ	F	-	-	F	-
73995	H	8.0	LS-C	7.7	1.027	N	N	N	N	N	-	-	occ	occ	F	-	-	N	-
73996	F	1.0	LS-C	7.8	1.033	N	N	N	tr	N	-	-	-	F	occ	-	-	N	-
73997	F	2.0	LS-cl	8.2	1.030	N	N	N	1+	N	3-5	1-3	-	occ	occ	-	-	N	-
73998	F	4.5	S-C	7.0	1.032	N	N	N	1+	N	-	1-3	occ	F	N	-	-	N	-
73999	F	1.0	LS-C	6.2	1.074	N	N	N	N	N	-	occ	occ	occ	occ	-	-	F	-
74000	F	2.5	LS-C	6.9	1.027	N	N	N	N	N	-	-	-	occ	occ	-	-	F	-
2,000 ppm:																			
74001	H	6.5	LS-C	7.0	1.029	N	N	N	N	N	-	-	-	occ	F	-	-	N	-
74002	H	4.0	LS-C	7.0	1.035	N	N	N	N	N	-	occ	-	occ	occ	-	-	N	-
74003	H	3.0	S-C	7.0	1.041	N	N	N	N	N	-	-	-	occ	F	-	-	N	-
74004	H	6.0	LS-C	7.0	1.031	N	N	N	N	N	-	-	-	occ	F	-	-	F	-
74005	H	8.0	LS-C	7.5	1.025	N	N	N	N	N	-	-	-	occ	occ	-	-	N	-
74006	F	1.0	S-C	7.0	1.044	N	N	N	N	N	-	occ	-	F	F	-	-	N	-
74007	F	1.0	DS-cl	8.0	1.040	N	N	N	3+	N	-	1-3	-	F	F	-	-	N	-
74008	F	6.0	LS-C	6.8	1.028	N	N	N	N	N	-	-	-	occ	F	-	-	F	-
74009	F	2.0	DS-cl	7.9	1.036	N	N	N	2+	N	-	1-3	-	F	occ	-	-	N	-
74010	F	3.0	LS-C	8.1	1.024	N	N	N	tr	N	-	occ	-	F	F	-	-	N	-

Code:

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

S - Straw
LS - Light Straw
DS - Dark Straw
LA - Light Amber
DA - Dark Amber
cl - Cloudy
C - Clear

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

- = None seen

117-086

FH-1422 41-2700-1422-0:

Ninety Day Subacute Rat Toxicity Study.

TABLE 14. Cont.

Individual Urinalysis Values - Pretest.

Group, Rat Number	Sex	Volume ml	Color and Appear.	pH	Spec. Grav.	Total Protein	Glu- cose	Billi- rubin	Occult Blood	Ke- tones	Leuco- cytes	Erythro- cytes	Epi. Cells	Amor. Urates	Triple Phos.	Cal. Ox.	Uric Acid Crystals	Bac- teria	Costs
10,000 ppm:																			
74011	M	5.0	LS-C	7.0	1.026	N	N	N	N	N	-	-	-	occ	F	-	-	N	-
74012	M	1.0	S-cl	6.5	1.046	N	N	N	N	N	-	occ	1-3	F	occ	-	-	N	-
74013	M	2.0	S-C	6.5	1.044	N	N	N	1+	N	-	occ	-	occ	H	-	-	N	-
74014	M	7.0	LS-C	6.9	1.028	N	N	N	N	N	-	1-3	-	occ	F	-	-	F	-
74015	M	5.5	LS-C	7.0	1.033	N	N	N	tr	N	-	-	-	F	F	-	-	N	-
74016	F	0.5	S-cl	7.1	1.043	N	N	N	2+	N	-	1-3	-	occ	F	-	-	N	-
74017	F	2.0	LS-C	6.2	1.038	N	N	N	N	N	-	-	-	occ	occ	-	-	F	-
74018	F	2.0	LS-C	6.2	1.044	N	N	N	N	N	-	-	-	occ	F	-	-	F	-
74019	F	3.0	LS-cl	6.8	1.035	N	N	N	tr	N	-	occ	-	occ	F	-	-	N	-
74020	F	2.0	LS-C	6.1	1.038	N	N	N	N	N	-	1-3	-	occ	F	-	-	F	-

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

- = None seen

117-086

TABLE 15.

Individual Urinalysis Values - 1 Month.

Group, Rat Number	Sex	Volume ml	Color and Appear.	pH	Spec. Grav.	Total Protein	Glucose	Billi- rubin	Occult Blood	Ke- tones	Leuco- cytes	Erythro- cytes	Epi. Cells	Amor. Urates	Triple Phos.	Cal. Ox.	Uric Acid Crystals	Bac- teria	Costa
Control:																			
73961	M	8.0	S-cl	7.2	1.045	N	N	N	1+	N	-	-	-	occ	F	occ	-	M	-
73962	M	5.5	S-cl	6.0	1.045	N	N	N	tr	N	-	8-10	-	occ	F	-	-	M	-
73963	M	7.0	DS-cl	7.5	1.045	N	N	N	1+	N	-	occ	-	occ	M	F	-	M	-
73964	M	5.0	S-cl	6.0	1.050	N	N	N	tr	N	-	-	-	occ	F	-	-	M	-
73965	M	4.0	DS-cl	7.0	1.065	N	N	N	1+	N	-	1-3	occ	occ	F	-	-	M	-
73966	F	3.0	S-C	6.0	1.055	N	N	N	N	N	-	1-3	occ	occ	F	-	-	M	-
73967	F	1.5	S-C	5.5	1.080	N	N	N	N	N	-	occ	-	occ	F	-	-	M	-
73968	F	2.0	S-C	5.7	1.073	N	N	N	N	N	-	-	occ	occ	F	-	-	M	-
73969	F	4.0	S-C	6.0	1.040	N	N	N	N	N	-	-	occ	occ	M	-	-	M	-
73970	F	4.0	S-cl	6.0	1.038	N	N	N	N	N	-	-	occ	F	M	occ	-	M	-
30 ppm:																			
76231	M	1.0	LS-cl	6.0	1.094	N	N	N	N	N	-	-	R	-	R	-	-	-	-
76232	M	2.0	LS-cl	6.3	1.084	N	N	N	N	N	-	R	R	-	R	R	-	R	-
76233	M	2.0	DS-cl	7.0	1.072	N	N	N	tr	N	-	R	-	-	R	-	-	-	-
76234	M	2.0	LS-cl	6.3	1.074	N	N	N	N	N	-	-	-	-	-	-	-	-	-
76235	M	1.5	DS-cl	7.1	1.056	N	N	N	N	N	-	-	-	-	R	-	-	-	-
76236	F	0.0																	
76237	F	0.0																	
76238	F	1.5	LS-cl	6.9	1.070	N	N	N	tr	N	R	-	-	-	occ	-	-	occ	-
76239	F	1.5	DS-cl	8.0	1.076	N	N	N	2+	N	occ	-	-	-	-	-	-	-	-
76240	F	3.0	S-cl	7.0	1.050	N	N	N	N	N	occ	-	-	-	R	R	-	-	-

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

- = 0 Seen

PM-1422 41-2700-1422-01

Ninety Day Subacute Rat Toxicity Study.

TABLE 15. Cont.

Individual Urinalysis Values - 1 Month.

Group, Rat Number	Sex	Volume ml	Color and Appear.	pH	Spec. Grav.	Total Protein	Glu- cose	Billi- rubin	Occult Blood	Ke- tones	Leuco- cytes	Erythro- cytes	Epi. Cells	Amor. Uraten	Triple Phos.	Cal. Ox.	Uric Acid Crystals	Bac- teria	Casts
100 ppm:																			
71971	M	3.0	DS-cl	7.0	1.065	N	N	N	N	N	-	occ	-	F	M	occ	-	M	-
71972	M	6.0	S-C	8.2	1.050	N	N	N	tr	N	-	-	occ	occ	M	-	-	M	-
71973	M	7.5	S-cl	6.3	1.035	N	N	N	N	N	-	occ	1-3	occ	F	-	-	M	-
71974	M	5.0	S-C	7.0	1.045	N	N	N	N	N	-	occ	-	occ	F	-	-	M	-
71975	M	3.5	S-cl	6.2	1.055	N	N	N	N	N	-	1-3	occ	occ	F	-	-	M	-
71976	F	2.0	S-C	6.2	1.075	N	N	N	N	N	-	occ	-	occ	occ	-	-	M	-
71977	F	2.0	S-C	6.2	1.080	N	N	N	N	N	-	occ	occ	F	M	F	-	M	-
71978	F	3.5	S-C	6.0	1.050	N	N	N	N	N	-	occ	occ	F	occ	-	-	M	-
71979	F	3.0	DS-cl	7.0	1.055	N	N	N	N	N	-	occ	occ	occ	occ	-	-	M	-
71980	F	3.5	S-C	6.2	1.040	N	N	N	N	N	-	-	occ	F	occ	-	-	M	-
300 ppm:																			
71981	M	3.5	S-cl	5.5	1.090	N	N	N	N	2+	-	occ	occ	occ	occ	-	-	F	-
71982	M	2.0	S-cl	6.0	1.080	N	N	N	N	1+	-	-	-	occ	M	-	-	F	-
71983	M	2.5	S-cl	5.0	1.065	N	N	N	N	2+	-	occ	occ	F	F	-	-	M	-
71984	M	8.5	S-cl	6.2	1.040	N	N	N	N	N	-	-	occ	F	F	F	-	M	-
71985	M	5.0	DS-cl	7.0	1.058	N	N	N	N	N	-	-	occ	occ	M	-	-	M	-
71986	F	4.0	S-cl	7.2	1.040	N	N	N	N	N	-	-	occ	occ	F	-	-	M	-
71987	F	1.0	S-C	6.0	1.060	N	N	N	N	N	-	-	occ	occ	F	-	-	M	-
71988	F	5.0	S-C	6.8	1.036	N	N	N	N	N	-	-	occ	occ	occ	-	-	M	-
71989	F	7.0	S-C	6.7	1.031	N	N	N	N	N	-	occ	1-3	occ	occ	-	-	M	-
71990	F	3.0	S-C	5.5	1.065	N	N	N	N	N	-	-	occ	occ	F	-	-	M	-

Code:

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

S - Straw
 LS - Light Straw
 DS - Dark Straw
 LA - Light Amber
 DA - Dark Amber
 cl - Cloudy
 C - Clear

N - Negative
 F - Few
 L - Loaded
 M - Many
 R - Rare
 occ - Occasional
 - = None seen

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FM-3422 41-2/00-3422-0;

Ninety Day Subacute Rat Toxicity Study.

TABLE 16.

Individual Urinalysis Values - 3 Months.

Group, Rat Number	Sex	Volume ml	Color and Appear.	pH	Spec. Grav.	Total Protein	Glucose	Billi- rubin	Occult Blood	Ke- tones	Leuco- cytes	Erythro- cytes	Epi. Cells	Amor. Urates	Triple Phos.	Cal. Ox.	Uric Acid Crystals	Bac- teria	Casts
<u>Control:</u>																			
73961	M	6.0	LS-C	6.9	1.038	N	N	N	tr	N	-	-	-	occ	occ	-	-	N	-
73962	M	5.0	DS-cl	7.8	1.050	N	N	N	2+	N	-	occ	occ	F	occ	-	-	M	-
73963	M	4.0	LS-C	6.5	1.048	N	N	N	N	N	-	occ	-	F	F	-	-	M	-
73964	M	6.5	LS-C	6.2	1.046	N	N	N	tr	N	-	1-3	-	F	F	-	-	F	-
73965	M	4.5	S-C	6.9	1.053	N	N	N	tr	N	-	occ	-	F	F	-	-	F	-
73966	F	1.0	DS-cl	7.3	1.088	tr	N	N	2+	N	-	-	occ	M	F	-	-	M	-
73967	F	1.0	S-C	6.0	1.094	N	N	N	N	N	-	occ	-	F	M	-	-	M	-
73968	F	4.5	LS-C	5.9	1.040	N	N	N	tr	N	-	-	-	occ	F	-	-	F	-
73969	F	1.5	LS-C	6.0	1.062	N	N	N	N	N	-	-	occ	occ	F	-	-	F	-
73970	F	0.0																	
<u>30 ppm:</u>																			
76231	M	5.0	LS-C	6.0	1.040	N	N	N	N	N	-	-	-	F	F	-	-	F	-
76232	M	5.0	S-cl	6.0	1.055	N	N	N	N	N	-	occ	occ	F	occ	-	-	M	-
76233	M	2.5	S-C	6.0	1.072	N	N	N	N	N	-	1-3	occ	F	occ	-	-	F	-
76234	M	3.0	S-cl	6.8	1.052	N	N	N	N	N	-	1-3	occ	F	F	-	-	M	-
76235	M	3.0	S-cl	6.8	1.065	N	N	N	N	N	-	occ	occ	F	M	-	-	M	-
76236	F	1.0	DS-cl	6.3	1.094	N	N	N	N	N	-	1-3	1-3	M	M	-	-	M	-
76237	F	1.0	LS-C	5.1	1.088	N	N	N	N	N	-	occ	occ	F	F	-	-	F	-
76238	F	0.0																	
76239	F	1.0	DS-cl	8.0	1.084	1+	N	tr	2+	N	-	1-3	occ	F	M	-	-	M	-
76240	F	1.5	S-cl	7.8	1.070	N	N	N	N	N	-	occ	occ	F	M	-	-	M	-

171-086

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

- = 0 Seen

FM-1422 41-2700-1422-01

Ninety Day Subacute Rat Toxicity Study.

TABLE 16. Cont.

Individual Urinalysis Values - 3 Months.

Group, Rat Number	Sex	Volume ml	Color and Appear.	Spec. pH	Spec. Grav.	Total Protein	Glucose	Bilirubin	Occult Blood	Ketones	Leucocytes	Erythrocytes	Epi. Cells	Amor. Urates	Triple Phos.	Cal. Ox.	Uric Acid Crystals	Bacteria	Casts
100 ppm:																			
71971	M	5.0	DS-cl	6.9	1.058	N	N	N	N	N	-	1-3	occ	H	H	-	-	H	-
71972	M	4.0	S-cl	6.0	1.074	N	N	N	N	N	-	occ	occ	F	F	-	-	H	-
71973	M	11.0	LS-C	6.1	1.039	N	N	N	N	N	-	-	-	occ	F	-	-	F	-
71974	M	7.0	DS-cl	6.9	1.044	tr	N	N	N	N	-	-	-	F	F	-	-	H	-
71975	M	6.0	S-cl	7.0	1.041	N	N	N	N	N	-	-	occ	occ	F	-	-	H	-
71976	F	0.0																	
71977	F	2.0	DS-cl	6.1	1.057	N	N	N	N	N	-	-	-	F	F	-	-	F	-
71978	F	4.5	DS-cl	6.0	1.046	N	N	N	N	N	-	-	occ	F	occ	-	-	F	-
71979	F	<0.5	DS-cl	7.5	1.038	N	N	N	2+	N	-	1-3	-	F	F	-	-	N	-
71980	F	5.0	LS-C	6.0	1.036	N	N	N	N	N	-	-	occ	F	occ	-	-	F	-
100 ppm:																			
71981	M	7.5	S-C	5.9	1.043	N	N	N	N	N	-	-	occ	F	F	-	-	F	-
71982	M	5.5	DS-cl	6.0	1.045	N	N	N	N	N	-	-	occ	occ	F	-	-	F	-
71983	M	6.0	S-cl	6.1	1.051	N	N	N	N	N	-	-	occ	F	occ	-	-	H	-
71984	M	6.0	S-C	6.0	1.043	N	N	N	N	2+	-	-	occ	occ	occ	-	-	F	-
71985	M	9.0	S-C	6.3	1.042	N	N	N	N	N	-	-	occ	F	F	occ	-	F	-
71986	F	2.0	S-C	7.0	1.056	N	N	N	N	N	-	-	-	F	H	-	-	H	-
71987	F	2.5	S-C	5.8	1.058	N	N	N	2+	N	-	-	occ	occ	F	-	-	F	-
71988	F	5.0	S-C	6.2	1.033	N	N	N	N	N	-	occ	occ	occ	F	-	-	F	-
71989	F	6.0	LS-C	6.1	1.026	N	N	N	N	N	-	-	-	occ	occ	-	-	F	-
71990	F	Died																	

Code: tr - Trace
1+ - Trace to slight
2+ - Slight to moderate
H - 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
H - Many
R - Rare
occ - Occasional

- = 0 Seen

TABLE 17.

Summary of Necropsy Observations, Terminal Sacrifice and Deaths.

Site Lesion	Terminal Sacrifice								Deaths							
	Control		30 ppm		100 ppm		300 ppm		300 ppm		1,000 ppm		3,000 ppm		10,000 ppm	
	M	F	M	F	M	F	M	F	F		M	F	M	F	M	F
Number necropsied	5	5	5	5	5	5	5	3	2*		5	5	5	5	5	5
No gross lesions	3	5	2	4	5	1	0	0	0		0	0	0	0	0	1
External																
red-brown material, eyes/nose/mouth	1						1					3	2		3	
emaciation												2	1	2	1	
incomplete fracture, femur											1					
yellow material, anogenital region											1	4			1	
Lungs																
congestion											1		2	1		
red foci									1		2					
gray/yellow/white foci	1		2	1		2										
Liver																
congestion													1			
adhesions						1										
accentuated lobulations						2	2	2			1					
brown discoloration							5	3			1					
gray/yellow/white areas							5	3			1		1			
enlarged							5				1	1				
yellow mottling											1					
red foci															1	
Stomach																
hyperemia/congestion, mucosa									1				2	1	3	2
red foci/brown areas/hemorrhages							1				1	3	2	4	3	3
brown-red mucoid contents							1						2	1	1	1
Spleen																
pale											1					
Mesenteric Lymph Nodes																
dark red																1
Small Intestine																
red/black/brown contents												1	2	1		1
Adrenals																
dark red														1		
Kidneys																
hydronephrosis			1			1										
brown discoloration							2	2								1

*Died after blood collection.

TABLE 17. Cont.

Summary of Necropsy Observations, Terminal Sacrifice and Deaths.

Site Lesion	Terminal Sacrifice								Deaths							
	Control		30 ppm		100 ppm		300 ppm		300 ppm		1,000 ppm		3,000 ppm		10,000 ppm	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Uterus hydrometra								2								
Testes small															1	

*Died after blood collection.

TABLE 18.

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

Group Sex	Body Wt. g	Spleen		Liver		Kidneys		Brain		Adrenals		Thyroid/ Parathyroid		Pituitary	
		g	%	g	%	g	%	g	%	mg	$\times 10^{-2}$	mg	$\times 10^{-2}$	mg	$\times 10^{-2}$
Control:															
M	484	0.82	0.17	17.51	3.61	3.75	0.77	2.19	0.45	61	1.27	24	0.50	15	0.32
F	270	0.62	0.23	11.48	4.23	2.36	0.88	1.99	0.74	77	2.88	21	0.78	17	0.63
30 ppm:															
M	439	0.75	0.18	18.24	4.30	3.66	0.86	2.29	0.55	63	1.46	26	0.60	16	0.35
F	257	0.60	0.23	10.59	4.14	2.46	0.96	2.08	0.81	80	3.12	22	0.87	17	0.67
100 ppm:															
M	462	0.82	0.17	24.89**	5.37**	4.24	0.91*	2.22	0.48	55	1.19	30	0.66	15	0.32
F	237	0.52	0.22	11.67	5.00	2.15	0.92	1.90	0.82	75	3.17	20	0.84	16	0.68
300 ppm:															
M	372	0.68	0.18	31.52**	8.51**	4.73	1.30	2.17	0.59*	76	2.11	27	0.72**	14	0.38*
F	208	0.47	0.22	15.01	7.22*	1.99	0.96	2.04	0.98*	73	3.52	17	0.81	13	0.64

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

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

TABLE 19.

Individual Organ Weights.

Group, Rat No.	Sex	Body Wt. g	Spleen g	Liver g	Kidneys g	Brain g	Adrenals mg	Thyroid/ Parathyroid mg	Pituitary mg
Control:									
73961	M	459	0.82	14.72	3.56	2.09	53	18	15
73962	M	475	0.74	16.71	3.42	2.24	63	24	15
73963	M	470	0.84	16.50	3.85	2.22	71	25	17
73964	M	490	0.80	20.06	3.92	2.20	64	28	15
73965	M	526	0.89	19.54	3.99	2.19	55	27	15
73966	F	270	0.66	9.42	2.47	2.18	72	22	14
73967	F	304	0.81	10.51	2.38	1.82	77	20	17
73968	F	278	0.59	19.88	2.21	1.87	85	20	18
73969	F	253	0.66	9.42	2.30	1.92	80	19	16
73970	F	245	0.38	8.18	2.45	2.15	73	23	20
30 ppm:									
76231	M	496	0.73	20.76	3.75	2.08	65	29	19
76232	M	467	0.73	12.60	3.48	2.17	64	29	19
76233	M	327	0.94	21.11	4.05	2.94	63	21	10
76234	M	438	0.71	18.86	3.56	2.14	69	25	15
76235	M	465	0.63	17.85	3.44	2.12	53	28	15
76236	F	232	0.53	10.08	2.28	2.06	81	20	17
76237	F	257	0.61	10.85	2.53	1.92	88	27	16
76238	F	256	0.72	9.74	2.33	2.12	74	22	19
76239	F	253	0.46	10.95	2.48	2.03	66	21	12
76240	F	285	0.69	11.35	2.68	2.25	88	22	22
100 ppm:									
73971	M	516	0.98	29.15	4.43	2.19	56	32	14
73972	M	509	0.69	24.28	4.66	2.30	59	28	17
73973	M	422	9.72	22.81	4.23	2.19	52	27	14
73974	M	448	-	-	-	-	56	29	15
73975	M	413	0.80	23.32	3.63	2.21	50	34	14
73976	F	244	0.77	11.92	2.62	1.71	72	20	18
73977	F	230	0.47	11.53	1.93	1.94	63	15	17
73978	F	250	-	-	-	-	68	19	18
73979	F	234	0.47	11.40	2.05	2.16	97	25	13
73980	F	226	0.38	11.81	2.00	1.80	75	20	15
300 ppm:									
73981	M	392	0.68	35.44	4.47	2.05	52	23	14
73982	M	324	0.76	31.39	6.77	2.23	132	24	12
73983	M	381	0.48	28.51	4.12	2.17	58	32	16
73984	M	368	0.78	31.78	4.13	2.15	68	32	15
73985	M	394	0.69	30.44	4.18	2.24	71	22	13
73986	F	217	0.58	16.64	2.15	1.84	73	16	14
73987	F	221	0.44	14.69	2.02	2.22	76	20	14
73989	F	187	0.39	11.71	1.81	2.05	70	15	12

- - Not available

TABLE 20.

Histomorphologic Observations.

Tissue Lesion	Group, Rat Number	Sex	Control								30 ppm								100 ppm								300 ppm																	
			M	M	M	M	M	F	F	F	F	M	M	M	M	F	F	F	F	M	M	M	M	F	F	F	F	M	M	M	M	F	F	F	F									
			73961	73962	73963	73964	73965	73966	73967	73968	73969	73970	76231	76232	76233	76234	76235	76236	76237	76238	76239	76240	73971	73972	73973	73974	73975	73976	73977	73978	73979	73980	73981	73982	73983	73984	73985	73986	73987	73988*	73989	73990*		
Liver							1	1	1									1																										
hematopoiesis				2	2				2	2																	2		2															
hepatocellular vacuolation			2																																									
focal/multifocal mononuclear infiltrate - parenchymal				2	3			2	2	2	2	2	2	2	2					2	2		3	3	4	2	2						2	3	3	4	2	2	2	3				
focal/multifocal mononuclear infiltrate - periportal									3	2					2		2				2		2		2									3							2			
bile duct proliferation									2						2												2															2		
hepatocellular hypertrophy																																												
hepatocellular accumulation of brown pigment													3	2	3	3	3	2	2				4	4	4	3	4	3	3	2	2	4	5	5	5	5	4	4	4	3	3			
focal chronic inflammation																																												
focal/multifocal inflammatory infiltrate - parenchymal																																												
focal/multifocal hepatocellular necrosis																																												
mineralization of necrotic debris																																												
accumulation of brown pigment in sinusoidal macrophages (Kupffer cells)																																												
Brain																																												
focal lymphocytic infiltrate - meninges				1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Cervical Spinal Cord				-	-	-	-	-	-	-	-	-	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Lumbar Spinal Cord				1	1	1	-	1	1	-	-	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Peripheral Nerve				1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Eyes				1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
retinal rosette - right eye																																												
retinal atrophy - bilateral																																												
Pituitary																																												
cyst with duct-like structures adjacent to cyst wall				1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Thyroid																																												
ultramicrobursal cysts				x				x	x	x							x						x		x								x		x	x	x	x	x	x	x	x	x	
Parathyroid				1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Adrenal				1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
vacuolated cells - zona fasciculata				3																																								
focal/multifocal mononuclear infiltrate - zona fasciculata																																												
focal cortical degeneration																																												
diffuse mononuclear infiltrate - zona reticularis																																												
hypertrophy and hyperplasia of cortical epithelial cells - zona fasciculata																																												

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

TABLE 20. Cont.

Histomorphologic Observations.

Tissue Lesion	Group, Rat Number Sex	Control										30 ppm										100 ppm										300 ppm												
		M	M	M	M	M	F	F	F	F	F	M	M	M	M	M	F	F	F	F	F	M	M	M	M	M	F	F	F	F	F	M	M	M	M	M	F	F	F	F	F			
		73961	73962	73963	73964	73965	73966	73967	73968	73969	73970	76231	76232	76233	76234	76235	76236	76237	76238	76239	76240	73971	73972	73973	73974	73975	73976	73977	73978	73979	73980	73981	73982	73983	73984	73985	73986	73987	73988*	73989	73990*			
Lung																																												
peribronchial/peribronchiolar lymphoid hyperplasia		2		3	2	2	2	2	2			4	3	2	2	3	3	2	2	2		2	1	2		2	2	1	2	2	2	2	2			1			2		3			
focal accumulation of alveolar macrophages		2															2																							2				
atelectasis			2	2	2	3	2		4	4	2	3	4		2	3	3	2	3	3		2		2	3	2	4		2		3	2	2	2	3			2	1	1				
perivascular lymphoid infiltrate				2								4	3				3																											
interstitial inflammatory infiltrate							2															2										2												
interstitial edema																				3					3		3						3		2	3					3			
hemorrhage																																											2	
Heart																																												
focal/multifocal mononuclear infiltrate-myocardium			1				1	1	1						1	1	1	1	1	1	1	1					1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
focal/multifocal fibrosis		3	2		3	2		2		2		2	2	2									2	2	2	2				2														
focal mineralization - myocardium								2																									2											
Aorta				1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Spleen																																												
hematopoiesis		1				1			1	1										1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
hemosiderosis			2	3	2		2	3	3			3	3	2	3	2	2	3	2	3			2																					
Mesenteric Lymph Nodes																																												
congestion		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Thymus																																												
hemorrhage		1	1	1			1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
degeneration of cortical thymocytes				3	2																													3							3			
Bone Marrow																																												
focal myeloid hyperplasia		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
edema																	2																											
Bone																																												
Salivary Gland																																												
focal/multifocal mononuclear infiltrate		1	1	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Stomach																																												
submucosal inflammatory infiltrate		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
focal inflammatory infiltrate - serosa																																												
multifocal mucosal necrosis																																												
submucosal hemorrhage																																												
focal degeneration and early mineralization of smooth muscle - tunica muscularis																																												
congestion - mucosal vessels																																												

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

TABLE 20, Cont.

Histomorphologic Observations.

Tissue Lesion	Group, Rat Number	Sex	Control								30 ppm								100 ppm								300 ppm																
			M	M	M	M	F	F	F	F	M	M	M	M	F	F	F	F	M	M	M	M	F	F	F	F	M	M	M	M	F	F	F	F									
			73961	73962	73963	73964	73965	73966	73967	73968	73969	73970	76231	76232	76233	76234	76235	76236	76237	76238	76239	76240	73971	73972	73973	73974	73975	73976	73977	73978	73979	73980	73981	73982	73983	73984	73985	73986	73987	73988*	73989	73990*	
Small Intestine			1	1	1	1	1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
focal vasculitis - mesentery								2																																			
focal mucosal fibrosis																					2																				2		
Large Intestine (Colon)			1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Pancreas			1	1	1	1			1	1			1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
focal perivascular and periductular inflammatory infiltrate								2						1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
focal/multifocal mononuclear infiltrate									3					2		2								4	2			3						2				2					
focus of hypertrophied acinar cells									x																																		
focal interlobular inflammatory infiltrate											3																																
focal/multifocal fibrosis with acinar atrophy																																											
focal fibrosis with pancreatic duct proliferation																																											
Kidney			1			1	1	1					1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
focal/multifocal tubular regeneration				2																																							
subacute nephritis					2	2			2		3					2					3	3		2	2	2	2	2	2													3	
cyst							x																																				
focal acute inflammatory infiltrate - renal hilus											3																																
chronic nephritis													2		3																												
tubular nephrosis																																											
thickening of glomerular basement membrane with eosino- philic proteinaceous droplets in glomerular space																																											
tubular proteinaceous casts																																											
tubular mineralized debris																																											
intracellular yellowish brown pigment - tubular epithelial cells																																											
intracellular reddish brown hyaline droplets - tubular epithelial cells																																											
hydronephrosis																																											
Urinary Bladder			1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
focal mononuclear infiltrate - tunica muscularis																																											
Testes			1	1	1	1	1						1	1	1	1	1						1	1	1	1	1																
Ovaries																																											
cystic ovarian bursa																																											
focal inflammatory infiltrate - para ovarian adipose tissue																																											
cystic corpus luteum																																											

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

TABLE 20. Cont.

Histomorphologic Observations.

Tissue Lesion	Group, Rat	Sex	Control								30 ppm								100 ppm								300 ppm																	
			M	M	M	M	M	F	F	F	F	M	M	M	M	F	F	F	F	M	M	M	M	F	F	F	F	M	M	M	M	F	F	F	F									
			73961	73962	73963	73964	73965	73966	73967	73968	73969	73970	76231	76232	76233	76234	76235	76236	76237	76238	76239	76240	73971	73972	73973	73974	73975	73976	73977	73978	73979	73980	73981	73982	73983	73984	73985	73986	73987	73988*	73989	73990*		
Prostate			1	1	1	1					1	1	1	1								1	1	1						1	1	1												
focal inflammatory infiltrate alveolus																						3																						
multifocal inflammatory infiltrate - alveolus																																		4	3									
interstitial mononuclear infiltrate																																	3											
Uterus							1	1	1	1	1						1	1	1	1						1		1												1	1	1	1	
hydrometra																												x	x															
Skeletal Muscle			1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Mammary Gland			1	1	1	1	-	1	1	1	1	-	-	1	-	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
hyperkeratosis - skin																																	3							2				

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

TABLE 21.

Histomorphologic Observations.

Tissue Lesion	Group, Rat Number Sex	1,000 ppm										3,000 ppm										10,000 ppm									
		M	M	M	M	M	F	F	F	F	F	M	M	M	M	M	F	F	F	F	F	M	M	M	M	M	F	F	F	F	F
		73991	73992	73993	73994	73995	73996	73997	73998	73999	74000	74001	74002	74003	74004	74005	74006	74007	74008	74009	74010	74011	74012	74013	74014	74015	74016	74017	74018	74019	74020
Liver																															
congestion		3																				-									
hepatocellular hypertrophy		4	5	5	4	4	3	4	4	4	4			3							2			2							2
focal/multifocal hepatocellular necrosis		3	5	4		3	3	4	5	3	4	3	4	4	3		2						4	3	2	4					
focal/multifocal inflammatory infiltrate - paren-																															
cymal				2	2									2													3		2		
focal fibrosis			2													2															
accumulation of brown pigment in sinusoidal macro-																															
phages (Kupffer cells)						2	2		2		2																				
hepatocellular hyperplasia												4	4	3		4	5	4	5	3	4		3		4	3	4	4	5	4	
hepatocellular vacuolation													3										2	3							
hemorrhage															2																
bile duct proliferation																															
hepatocellular accumulation of brown pigment																								2							2

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