



E. I. DU PONT DE NEMOURS & COMPANY
INCORPORATED
WILMINGTON, DELAWARE 19898

LEGAL DEPARTMENT

January 14, 1966

Mr. Walter M. Schaefer
Food and Drug Officer
Petitions Control Branch
Food and Drug Administration
Department of Health, Education and Welfare
Washington, D. C. 20204

Dear Mr. Schaefer:

Food Additive Petition No. 5B1747

It was recommended that 90-day feeding studies in the rat and dog be undertaken to assist you in evaluating the above Petition. These studies have been completed and we are hereby enclosing for filing three copies each of the following studies:

Ninety-Day Feeding Study of (b) (4) [redacted]
Paper Fluorodizer in the Rat by
International Research and Development
Corporation dated November 30, 1965;

Ninety-Day Feeding Study of (b) (4) [redacted]
Paper Fluorodizer in the Dog by
International Research and Development
Corporation dated November 30, 1965.

These studies substantiate the toxicity data originally filed with the Petition and indicate that the proposed use is not hazardous.

We hope you will now be able to make a final determination on the Petition.

Very truly yours,

[Redacted signature block]

Richard H. Rea PC

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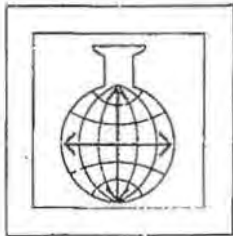
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International Research and Development Corporation

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International Research and Development Corporation

SPONSOR: E. I. duPont de Nemours and Company

COMPOUND: (b) (4)

SUBJECT: 90-Day Feeding Study in the Beagle Dog.


Francis X. Wažeter, Ph.D.
Director of Research
International Research and
Development Corporation

Collaborators:

R. H. Buller, Ph.D., Director of Pharmacology
R. G. Geil, D.V.M., Director of Pathology

Date: November 30, 1965

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I. SYNOPSIS

In a 90-day oral toxicity study (b) (4) was fed 7 days each week to male and female beagle dogs at dietary levels of 100, 500 or 2500 ppm. After 35 days of feeding, the 500 ppm. and 2500 ppm. dietary levels were increased to 1000 ppm. and 5000 ppm., respectively for the duration of the 90 days of treatment.

No pharmacodynamic and/or gross toxic signs were observed. Detailed physical examination revealed all dogs to be essentially normal.

No adverse body weight changes occurred among any dogs used for this study. Food consumption values remained relatively constant, and average daily water intake and urine output were not meaningfully different from values obtained in the control period.

No alterations in hematologic parameters were observed which could be related to feeding the test compound.

No biologically meaningful changes occurred with respect to plasma glucose, protein, albumin, urea nitrogen or albumin-to-globulin ratios.

A biologically significant increase in plasma cholesterol was found for 5-of-6 dogs at the 2500 ppm. dietary level.

Prothrombin time determinations and serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxalacetic transaminase (SGOT) activities remained within the usual ranges at all periods of measurement. Alkaline phosphatase activities exhibited an upward trend in 2 of 6 dogs at the high dietary level.

Urinalysis did not reveal compound-related changes at any period of examination.

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Although no gross compound-related lesions were observed at necropsy, a slight compound-related liver weight increase occurred at the middle and high dietary levels. Compound-related microscopic lesions consisted of hypertrophy of centrilobular liver parenchymal cells in 4-of-6 dogs from the 5000 ppm. dietary level group. No compound-related lesions were seen in other tissues from these dogs or in livers from dogs at the lower dietary levels.

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II. COMPOUND

The test compound was received from E. I. duPont de Nemours and Company, Wilmington, Delaware, on June 19, 1965. It was a brown amorphous solid in containers bearing the label "MPD-3110A - (b) (4) (b) Active Ingredient, Haskell No. 4212."

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III. CLINICAL STUDIES

A. METHODS:

1. General Procedure:

Twelve male and 12 female young, purebred beagle dogs in apparent good health, were used for a 90-day feeding study of (b) (4)

The dogs were separated into one control and 3 treated groups of 3 males and 3 females each, and were housed individually in metabolism cages in temperature and humidity controlled quarters throughout the course of study. Powdered Purina Dog Chow without (b) (4) and the same chow with the prescribed dietary levels of the test compound were available, as was water, at all times to the respective groups of dogs. Food consumption and individual body weights were measured and recorded once each week. Water intake and urine output were measured and recorded daily during each clinical laboratory test interval week.

Prior to the initiation of the compound administration phase of this study, stool flotation studies were conducted for the detection of intestinal parasites. Positive findings were followed by appropriate vermifuge therapy.

During the control period and again during the period of compound administration, all dogs were subjected to detailed physical examination. Heart sounds were examined by five point auscultation; pulse rates were determined by palpation; the ocular fundi were viewed for abnormalities; and reflexes were evaluated.

In addition to the routine physical examination described above, all dogs were observed several times daily, 7 days each week, for signs of pharmacodynamic and/or toxic effects.

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After 90 consecutive days of compound administration, all dogs were sacrificed and subjected to necropsy examination. (see section on Pathology for detailed methodology.)

2. Laboratory Tests:

At least 3 times during the control period, and again after 1, 2 and 3 months of compound administration, blood and 24-hour urine samples were obtained for clinical laboratory studies.

a. Hematology:

Routine hematologic studies included total¹ and differential leucocyte counts, hematocrits², hemoglobin concentrations³, erythrocyte sedimentation rates⁴, and total erythrocyte counts¹.

b. Biochemical Studies:

(1) Plasma: Chemical determination on plasma routinely included quantitative tests for glucose⁵, total protein⁶, total albumin⁷, and urea nitrogen⁸. Albumin-to-globulin ratios were calculated.

¹ Coulter Particle Size Counter, Model A., Coulter Electronics, 590 W. 20th Street, Hialeah, Florida.

² Miller, S., Microcapillary Method, Textbook of Clinical Pathology, 1960, Williams and Wilkins Company, Philadelphia, Pa., p. 43.

³ Miller, S., Cyanmethemoglobin Method, Textbook of Clinical Pathology, 1960, Williams and Wilkins Company, Philadelphia, Pa., p. 35.

⁴ Miller, S., Westergren Method, Textbook of Clinical Pathology, 1960, Williams and Wilkins Company, Philadelphia, Pa., p. 48.

⁵ Hoffman, W. S., Modified Hoffman Method, J. Biol. Chem., 120: 51, 1937. (Auto Analyzer).

⁶ Stevens, D. L., Modified Biuret Method, Amer. J. Clin. Path. 7: 40, 1946. (Auto Analyzer).

⁷ Stevens, D. L., Stevens Adaptation for Auto Analyzer, J. Clin. Invest., 33: 211, 1954.

⁸ Skeggs, L. T., Diacetyl Monoxime Method, Amer. J. Clin. Path. 28: 311, 1957. (Auto Analyzer).

(2) Liver Function: Plasma alkaline phosphatase activity⁹, prothrombin time¹⁰ determinations, serum glutamic oxalacetic (SGOT) and serum glutamic pyruvic (SGPT) transaminase activities¹¹, and cholesterol¹² determinations, were used as an indication of liver function. In addition, serum albumin electrophoretic patterns (cellulose strip method) were obtained once during the control period and again after one and 3 months of compound administration¹³.

(3) Urinalysis: Observations for abnormality in gross appearance and color and qualitative tests for the detection of bilirubin¹⁴, occult blood,^{15,16,17} albumin,^{18,19,20,21} and glucose,^{21,22,23} were conducted on the 24-hour urine specimen. Urinary pH,²⁴ specific gravity and volume were measured, and the urinary sediments were examined microscopically.

⁹ Marsh, W., Modified King-Armstrong Method, Clin. Chem. 5: 119, 1959. (Auto Analyzer).

¹⁰ Quick, A. J., Hemorrhagic Diseases, 1957, Lea & Febiger, Phila., Pa.

¹¹ Reitman, S., and Frankel, S., Colorimetric Method for the Determination of Serum Transaminase Activity, Am. J. of Clin. Path., 28: 56, 1957.

¹² Hycel Cholesterol Procedures - Hycel, Inc., Houston, Texas, Revised Dec. 1962.

¹³ "Sephophore 111", Gelman Technical Manual No. 51199-A, 1963.

¹⁴ "Ictotest" (Ames Reagent Tablets).

¹⁵ "Hemastix" (Ames Reagent Strips).

¹⁶ "Hematest" (Ames Reagent Tablets).

¹⁷ "Occultest" (Ames Reagent Tablets).

¹⁸ "Albustix" (Ames Reagent Strips).

¹⁹ "Bumintest" (Ames Reagent Tablets).

²⁰ Heller's Ring Test, Practical Physiologic Chemistry, Hawk, Oser and Summerson, 13th Ed., p. 830.

²¹ "Combistix" (Ames Reagent Strips).

²² "Clinistix" (Ames Reagent Strips).

²³ "Clinitest" (Ames Reagent Tablets).

²⁴ Beckman Expanded Scale pH Meter, Model No. 76.

c. Special Sampling:

Twenty-four hour urine and fecal samples were obtained from all dogs during the period of compound administration. These were frozen and delivered to the sponsor for analysis of (b) (4) content. Similarly, representative tissue samples (see section on Pathology) were provided following necropsy examination.

3. Compound Administration:

The test compound (b) (4) was incorporated into the basic laboratory diet (powdered Purina Dog Chow) and fed to the respective groups of dogs throughout the study. The 3 treated groups of dogs were fed diets containing (b) (4) at initial concentrations of 100, 500, or 2500 ppm. for a continuous period of 35 days. From the 6th week of compound administration to the termination of the study the 500 ppm. dietary level was increased to 1000 ppm. and the 2500 ppm. dietary level was increased to 5000 ppm. The dogs at the lowest dietary level continued to receive a diet containing 100 ppm. of the test agent throughout the study. The diets were freshly prepared each week and were constantly available to the dogs in self-feeding hoppers.

The control group of 3 male and 3 female dogs was maintained on a regimen identical to that of the treated groups except that the powdered basic laboratory diet did not contain (b) (4).

B. RESULTS:

1. Behavior, Appearance and Mortality:

No alterations in behavior or appearance which could be considered to be compound-related were seen among any of the control or treated dogs employed in this study.

Incidental alterations included one female dog (65-038) in

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the control group that exhibited 3 small 1-to-2 cm. areas of alopecia on the back throughout the study; one male dog (65-072, 100 ppm.) that exhibited slight alopecia of the right rear leg during the last half of the study; one female dog (65-085, 100 ppm.) that exhibited an enlarged right Harderian gland throughout the study; one male dog (65-087, 1000 ppm.) that exhibited conjunctivitis and opacity of the right cornea during the last 4 compound administration weeks; and one female dog (65-094, 1000 ppm.) that exhibited slight dermatitis of the right foreleg during the last month of compound administration.

All dogs survived the 90-day period of compound administration.

2. Physical Examination:

Routine physical examinations conducted during the study revealed all dogs to be essentially normal in behavior and appearance at all times. Heart sounds were not unusual; pulse rates were normal; reflexes were unimpaired and fundoscopic examination of the eyegrounds revealed no changes.

3. Body Weight (Table 1):

All control and treated dogs exhibited essentially normal body weights throughout the 90-day period of treatment. No differences in body weight gain were seen between the control and the treated groups of dogs.

4. Food Consumption (Table 2):

All dogs consumed essentially the same quantities of food each week during the compound administration period as they did during the control period. No differences in food consumption were seen between the control and the treated groups of dogs.

5. Compound Consumption:

Compound consumption was calculated in mg./kg./day based on the average food consumption and body weight of each animal. The results of these calculations appear in Table 3.

6. Water Intake and Urine Output (Table 4):

Although considerable variation in average daily water intake and urine output was found for most dogs employed in this study, the values obtained during the period of treatment were not consistently different from values obtained during the corresponding control period. No biologically meaningful differences were found between the control and test animals.

7. Laboratory Tests (Tables 5 through 28-A):

a. Hematology:

No compound-related hematologic changes occurred among dogs used for this study.

Incidental changes, not related to compound administration, included low borderline hemoglobin and hematocrit values and mild to marked hypochromasia of the erythrocytes. The incidence of occurrence was similarly distributed in the control and treated groups, particularly in the control examination periods and in the first examination (1 month) interval after the beginning of treatment. These values tended to fall into the usual acceptable ranges as the study progressed.

An elevated total leucocyte count was observed in Dog 65-083 (control; male) and Dog 65-078 (male; 500 ppm.) in the final control examination period prior to treatment, and Dog 65-092 (female; 500 ppm.) after 3 months of compound administration.

A decrease in the polymorphonuclear leucocyte-to-lymphocyte

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ratio was observed at one or more periods of examination in 3-of-6 control dogs and 9-of-18 treated dogs during the period of study.

An occasional elevation in erythrocyte sedimentation rate was observed in the control and treated groups of dogs at one of the control periods of examination. One dog (65-187, male; 500 ppm.) exhibited an elevation in this parameter in the treatment period. This was observed at the 60-day examination period and had returned to normal by the terminal examination.

b. Biochemical Studies:

(1) Plasma: No compound-related changes in plasma biochemistry were found among dogs used for this study.

(2) Liver Function Tests: A dose-related increase in plasma cholesterol was found in 5-of-6 dogs after 3 months of compound administration at the 2500 - 5000 ppm. level. No consistent biologically meaningful changes in plasma cholesterol were found at the lower dietary levels (Table 28-A).

In addition, a slight upward trend in plasma alkaline phosphatase activity was noted for Dogs 65-090 (male) and 65-099 (male) at the 2500 - 5000 ppm. level.

Prothrombin time determinations and serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxalacetic transaminase (SGOT) values remained within the usual acceptable ranges at all periods of examination for all groups of dogs in this study. No unusual changes were noted in the serum albumin electrophoretic patterns.

(3) Urinalysis: Urinalysis examination failed to reveal changes which were considered to be related to treatment with (b) (4)

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Incidental findings, not related to compound administration, included slight bilirubinuria for one control (65-086, male) and 3 treated (65-078, 65-079 and 65-087, males) dogs at the 2-month examination period. Bilirubinuria again was found at the terminal examination, for one of these dogs (65-079, male; 500 - 1000 ppm.)

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IV. PATHOLOGICAL STUDIES

A. METHODS:

1. Gross Examination:

At the completion of the compound administration period, all dogs were anesthetized with sodium pentobarbital, sacrificed by exsanguination and subjected to necropsy examination. Major organs were weighed and representative tissues were collected into 10 per cent buffered neutral formalin for subsequent histologic processing and microscopic examination. Fresh specimens of brain, liver, kidneys, spleen, fat, muscle, testes and blood were collected from each dog, frozen and forwarded to the sponsor.

2. Microscopic Examination:

The following tissues from each of the control and 5000 ppm. dosage group dogs were paraffin embedded, sectioned, stained with hematoxylin and eosin and examined microscopically:

brain	aorta	pancreas
spinal cord	spleen	liver
peripheral nerve	lymph node	gall bladder
eye	thymus	kidney
pituitary	bone marrow	urinary bladder
thyroid	salivary gland	testes or ovary
parathyroid	esophagus	prostate or uterus
adrenal	stomach	skeletal muscle
trachea	small intestine	skin
lung	large intestine	bone
heart		

Liver sections from all 100 and 1000 ppm. dosage level dogs were also processed as above and examined microscopically.

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B. RESULTS:

1. Gross Pathology (Table 29) and Organ Weights (Table 30):

No compound-related gross pathologic lesions were observed in any dogs subjected to necropsy examination. Organ weights of treated dogs were within the normal range except the liver weights of the 5000 ppm. dosage group dogs which were slightly increased. The liver weights of the 1000 ppm. dosage group dogs were also greater than the liver weights of the control dogs in this study although they were still within the normal range.

2. Histopathology (Tables 31 and 32):

Compound-related changes were limited to the liver of 3-of-3 male and 1-of-3 female dogs from the 5000 ppm. dosage level group. These changes consisted of slight hypertrophy of centrilobular parenchymal cells. The cytoplasm of affected cells was more homogeneous and less coarsely granular than the cytoplasm of hepatocytes at the periphery of the lobule or of hepatocytes in control livers. These changes were not seen in any of the livers from the 100 or 1000 ppm. dosage level dogs.

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Ninety-Day Feeding Study in the Dog.

TABLE 1. Individual Weekly Body Weights, Kilograms.

Dog Number	Sex	Control Period			Compound Administration Weeks												
		1	2	3	1	2	3	4	5	6	7	8	9	10	11	12	13
<u>Control:</u>																	
65-038	F	7.7	7.9	8.1	8.2	8.5	8.4	8.0	8.3	8.5	8.5	8.6	8.7	8.6	8.8	8.8	8.2
65-070	M	6.5	7.2	7.9	8.6	9.5	9.9	9.8	10.5	11.1	11.8	12.2	12.4	13.4	13.4	13.8	13.0
65-081	F	4.5	4.8	5.2	6.2	6.7	7.2	6.9	7.7	8.1	8.4	8.4	9.0	9.0	9.5	9.5	9.2
65-083	M	4.4	4.5	5.2	5.7	6.3	6.7	6.3	6.9	7.5	8.1	7.8	8.3	8.7	9.1	9.1	8.5
65-086	M	4.2	4.5	5.5	6.1	6.7	7.1	7.0	7.6	8.1	8.3	8.8	9.1	9.1	9.2	9.6	9.2
65-093	F	3.7	3.9	4.1	4.5	4.8	4.9	4.7	5.2	5.3	5.5	5.7	5.7	6.2	6.3	6.7	6.1
<u>100 ppm.:</u>																	
65-072	M	3.9	4.5	5.1	5.3	6.1	6.2	6.3	6.9	7.1	7.8	8.0	8.2	8.5	9.1	9.2	8.7
65-074	M	4.6	5.5	6.1	7.0	7.5	8.0	7.9	8.9	9.3	9.8	10.2	10.5	10.9	11.3	11.5	10.8
65-076	M	5.4	5.9	6.7	7.4	7.9	8.2	8.3	9.1	9.8	10.4	10.9	11.3	11.6	12.0	12.4	11.9
65-077	F	4.5	4.9	5.2	6.1	6.5	7.2	6.9	7.6	8.1	8.6	8.9	8.5	9.2	9.4	10.0	9.4
65-085	F	4.5	4.8	5.5	5.7	6.2	6.4	6.2	6.4	6.8	6.6	6.8	7.4	7.3	7.7	7.5	7.2
65-091	F	5.5	6.0	6.6	7.0	7.8	8.1	7.9	8.6	8.9	9.5	9.7	9.8	9.9	10.2	10.7	9.9
<u>500 ppm. :* </u>																	
65-078	M	4.5	5.0	5.5	6.0	6.7	7.2	7.1	7.9	8.2	8.8	9.2	9.6	9.7	10.1	10.4	9.9
65-079	M	3.5	3.9	4.2	4.7	5.1	5.6	5.4	6.0	6.1	6.3	6.4	6.9	6.9	7.4	7.3	6.9
65-087	M	6.4	7.3	8.1	9.2	9.8	10.5	10.4	11.0	11.4	11.8	12.6	11.5	12.8	13.7	13.9	13.5
65-092	F	3.1	3.4	3.7	4.3	4.5	4.8	4.7	5.1	5.4	5.9	6.2	5.8	6.1	6.5	6.7	6.5
65-094	F	5.5	6.1	6.7	7.3	7.8	8.2	8.3	9.1	9.4	10.0	10.3	10.3	10.9	10.8	11.4	11.0
65-095	F	4.1	4.3	4.7	5.3	5.7	6.1	5.8	6.5	6.8	7.3	7.5	7.4	8.2	8.4	8.5	7.9
<u>2500 ppm. : **</u>																	
65-088	M	3.4	3.5	3.9	4.3	4.7	5.0	4.8	5.4	5.7	6.0	6.2	6.3	6.7	6.6	7.0	6.7
65-090	M	4.7	5.3	6.1	6.7	7.3	7.9	7.9	8.5	9.1	9.6	9.7	10.1	10.7	10.9	11.3	10.6
65-096	F	4.6	5.0	5.5	6.0	6.6	7.0	7.0	7.4	7.9	8.3	8.3	8.5	8.9	9.1	9.1	8.8
65-097	F	5.1	5.5	5.8	6.4	6.9	7.5	7.4	8.2	8.8	9.4	9.5	9.8	10.2	10.7	10.7	10.0
65-098	F	3.5	3.9	4.0	4.9	5.3	5.6	5.5	6.0	6.5	6.8	6.8	7.2	7.2	7.5	7.8	7.2
65-099	M	4.3	4.8	5.4	5.5	6.1	6.5	6.5	6.9	7.4	7.5	7.9	8.0	8.5	8.7	8.7	8.4

* Increased to 1000 ppm. in the 6th week of therapy.

** Increased to 5000 ppm. in the 6th week of therapy.

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(P)
(G)
Ninety-Day Feeding Study in the Dog.

TABLE 2. Average Daily Food Consumption, Grams.

Dog Number	Sex	Control Period			Compound Administration Weeks												
		1	2	3	1	2	3	4	5	6	7	8	9	10	11	12	13
<u>Control:</u>																	
65-038	F	210	229	256	270	234	226	264	193	157	196	196	176	212	216	225	168
65-070	M	446	378	446	407	410	366	400	458	332	182	424	385	394	361	449	304
65-081	F	278	236	315	274	304	340	280	342	289	304	326	208	269	269	344	247
65-083	M	218	204	264	271	290	288	263	294	254	283	273	185	281	284	263	299
65-086	M	307	251	354	304	329	323	287	299	266	247	260	254	286	333	358	210
65-093	F	190	139	191	216	152	215	157	203	177	209	222	163	238	228	174	178
<u>100 ppm.:</u>																	
65-072	M	262	279	282	250	317	334	295	325	225	259	283	235	370	281	318	209
65-074	M	283	240	357	312	328	393	347	401	333	334	342	295	355	355	341	237
65-176	M	299	353	311	339	325	343	370	404	346	381	377	347	398	382	329	353
65-077	F	196	234	248	310	300	338	288	298	286	297	321	254	319	301	266	284
65-085	F	201	206	275	262	245	269	223	279	203	183	219	187	239	223	236	169
65-091	F	344	303	347	305	368	318	314	360	327	350	315	292	335	263	296	300
<u>500 ppm.:</u> *																	
65-078	M	250	231	270	285	339	336	283	342	276	299	325	246	364	314	305	278
65-079	M	299	215	219	222	267	274	233	311	228	223	248	216	240	295	243	177
65-087	M	420	361	417	432	399	424	418	403	302	376	385	149	450	477	395	295
65-092	F	220	181	231	200	205	221	225	231	189	206	229	134	190	214	207	215
65-094	F	336	339	401	394	384	353	353	457	331	372	315	261	348	353	309	341
65-095	F	181	210	225	320	260	244	241	299	254	294	274	205	290	275	257	282
<u>2500 ppm.:</u> **																	
65-088	M	142	139	213	216	213	214	1	245	194	237	236	183	283	229	251	167
65-090	M	242	268	334	324	331	361	340	378	326	390	309	271	395	337	318	208
65-096	F	226	223	276	268	291	288	262	282	217	252	236	216	287	251	248	179
65-097	F	224	224	233	263	284	325	306	323	266	306	292	281	319	347	313	202
65-098	F	230	206	251	238	236	242	2	259	225	238	244	204	266	218	235	176
65-099	M	232	215	280	257	240	284	249	294	242	249	269	225	294	277	245	192

* Increased to 1000 ppm. in the 6th week of therapy.

** Increased to 5000 ppm. in the 6th week of therapy.

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* Increased to 1000 ppm. in the 6th week of therapy.
 ** Increased to 5000 ppm. in the 6th week of therapy.

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 Ninety-Day Feeding Study in the Dog.

TABLE 3. Average Daily Compound Consumption, Mg./Kg./Day.

Animal No. & Group	Sex	Compound Administration Weeks												
		1	2	3	4	5	6	7	8	9	10	11	12	13
<u>100 ppm.:</u>														
65-072	M	4.7	5.2	5.4	4.6	4.7	3.2	3.3	3.5	2.9	4.4	3.1	3.5	2.4
65-074	M	4.5	4.4	4.9	4.4	4.5	3.6	3.4	3.4	2.8	3.3	3.1	3.5	2.2
65-076	M	4.6	4.1	4.2	4.5	4.4	3.5	3.7	3.5	3.1	3.4	3.2	3.0	2.2
65-077	F	5.1	4.6	4.7	4.2	3.9	3.5	3.5	3.6	3.0	3.5	3.2	2.7	3.0
65-085	F	4.6	4.0	4.2	3.6	4.4	3.0	2.8	3.2	2.5	3.3	3.0	3.1	2.3
65-091	F	4.4	4.7	3.9	4.0	4.2	3.7	3.7	3.2	3.0	3.4	2.6	2.8	3.0
<u>500 ppm.:</u> *														
65-078	M	23.8	25.3	23.3	19.9	21.6	33.7	34.0	35.3	25.6	37.5	31.1	29.3	28.1
65-079	M	21.5	26.2	24.5	21.6	25.9	37.4	35.4	38.8	31.3	34.8	39.9	33.3	25.7
65-087	M	23.5	20.4	20.2	20.1	18.3	26.5	31.9	30.6	12.9	35.2	34.8	28.4	21.9
65-092	F	23.3	22.8	23.0	23.9	22.6	35.0	34.9	36.9	23.1	31.1	32.9	30.9	33.1
65-094	F	27.0	24.6	21.5	21.3	25.1	35.2	37.2	30.6	25.3	31.9	33.1	27.1	31.0
65-095	F	30.2	22.8	20.0	20.8	23.0	37.4	40.3	36.5	17.7	35.4	32.7	30.2	35.7
<u>2500 ppm.:</u> **														
65-088	M	125.6	113.3	107.0	104.7	113.4	170.2	197.5	190.3	145.2	211.2	173.5	179.3	124.6
65-090	M	120.9	113.4	114.3	107.6	111.2	179.1	203.1	159.3	134.2	184.6	154.6	140.7	98.1
65-096	F	111.7	110.2	102.2	93.6	95.3	137.3	151.8	142.2	127.1	161.2	137.9	136.3	101.7
65-097	F	102.7	102.9	108.3	103.4	98.5	151.1	162.8	153.7	143.4	156.3	162.1	146.3	101.0
65-098	F	121.4	111.3	108.0	103.6	107.9	173.1	175.0	179.4	141.7	184.7	145.3	150.6	122.2
65-099	M	116.8	98.4	109.2	95.8	107.5	163.5	166.0	170.3	140.6	173.0	159.2	140.8	114.3

* Increased to 1000 ppm. in the 6th week of therapy.

** Increased to 5000 ppm. in the 6th week of therapy.

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(10) Ninety-Day Feeding Study in the Dog.

TABLE 4. Average Daily Water Intake (W.I.), ml.; Urine Output (U.O.), ml.; and Water Intake-to-Urine Output Ratio (W/U).

Time Interval	Control																	
	Dog 65-038 F			Dog 65-070 M			Dog 65-081 F			Dog 65-083 M			Dog 65-086 M			Dog 65-093 F		
	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U
Control Weeks																		
1	520	190	2.7	895	128	7.0	610	90	6.8	915	468	2.0	640	139	4.6	365	110	3.3
2	498	234	2.1	801	168	4.8	603	121	5.0	1005	455	2.2	686	195	3.5	428	288	1.5
3	627	265	2.4	868	298	2.9	607	170	3.6	790	250	3.2	518	173	3.0	327	127	2.6
Compound Administration Weeks																		
1	509	183	2.8	1425	435	3.3	690	109	6.3	1225	753	1.6	1025	380	2.7	350	208	1.7
9	553	198	2.8	1465	505	2.9	830	174	4.8	1248	578	2.2	1005	329	3.1	480	281	1.7
12	495	243	2.0	1213	426	2.8	723	238	3.0	1125	664	1.7	737	297	2.5	460	265	1.7

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59 Ninety-Day Feeding Study in the Dog.

TABLE 4. Continued. Average Daily Water Intake (W.I.), mL.; Urine Output (U.O.), mL.; and Water Intake-to-Urine Output Ratio (W/U).

Time Interval	Dog 65-072 M			Dog 65-074 M			Dog 65-076 M			Dog 65-077 M			Dog 65-085 F			Dog 65-091 F		
	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U
Control Weeks																		
1	580	70	8.3	635	239	2.7	860	213	4.0	660	128	5.2	645	290	2.2	618	173	3.7
2	490	109	4.5	850	295	2.9	808	286	2.8	585	210	2.8	684	319	2.1	773	161	4.8
3	587	130	4.5	900	340	2.6	867	307	2.8	747	233	3.2	807	297	2.7	480	210	2.2
Compound Administration Weeks																		
1	850	286	3.0	1240	460	2.7	1135	343	3.3	773	300	2.6	790	389	2.0	738	176	4.2
9	1038	265	3.9	1488	361	4.1	1150	454	2.5	1280	433	3.0	1015	489	2.1	1060	316	3.4
12	853	319	2.7	1000	563	1.8	1258	390	3.2	975	465	2.1	770	430	1.8	750	259	2.9

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(P) (O)

Ninety-Day Feeding Study in the Dog.

TABLE 4, Continued. Average Daily Water Intake (W.I.), ml.; Urine Output (U.O.), ml.; and Water Intake-to-Urine Output Ratio (W/U).

Time Interval	500 ppm.*																	
	Dog 65-078 M			Dog 65-079 M			Dog 65-087 M			Dog 65-092 F			Dog 65-094 F			Dog 65-095 F		
	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U
Control Weeks																		
1	525	138	3.8	465	90	5.2	765	171	4.5	415	140	3.0	1455	354	4.1	840	120	7.0
2	555	159	3.5	498	108	4.6	1025	243	4.2	558	185	3.0	1378	553	2.5	434	255	1.7
3	647	155	4.2	487	145	3.4	593	180	3.3	460	233	2.0	1450	487	3.0	393	145	2.7
Compound Administration Weeks																		
1	790	230	3.4	483	191	2.5	883	243	3.6	438	232	1.9	760	270	2.8	417	250	1.7
9	875	266	3.3	683	290	2.4	485	144	3.4	270	166	1.6	935	188	5.0	545	271	2.0
12	888	245	3.6	538	240	2.2	1100	403	2.7	380	258	1.5	918	349	2.6	485	217	2.2

* Increased to 1000 ppm. in the 6th week of therapy.

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(A) (b) Ninety-Day Feeding Study in the Dog.

TABLE 4, Continued. Average Daily Water Intake (W.I.), mL.; Urine Output (U.O.), mL.; and Water Intake-to-Urine Output Ratio (W/U).

Time Interval	2500 ppm.*																	
	Dog 65-088 M			Dog 65-090 M			Dog 65-096 F			Dog 65-097 F			Dog 65-098 F			Dog 65-099 M		
	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U
Control Weeks																		
1	480	205	2.3	545	139	3.9	570	103	5.5	505	198	2.5	365	95	3.8	463	149	3.1
2	549	240	2.3	574	195	2.9	573	173	3.3	488	228	2.1	448	156	2.9	558	214	2.6
3	607	263	2.3	587	193	3.0	593	130	4.6	573	273	2.1	580	157	3.7	580	195	3.0
Compound Administration Weeks																		
1	750	430	1.7	704	185	3.8	645	115	5.6	690	414	1.7	513	203	2.5	613	183	3.3
9	785	389	2.0	867	249	3.5	720	188	3.8	780	320	2.4	745	191	3.9	605	268	2.3
12	605	329	1.8	843	280	3.0	648	175	3.7	650	343	1.9	535	225	2.4	387	210	1.8

* Increased to 5000 ppm. in the 6th week of therapy.

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(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 30. Actual (Grams) and Relative (% Body Weight) Organ Weights.

Group & Animal Number	Sex	Terminal Body Wt. Kg.	Spleen		Liver		Adrenals		Kidneys		Ovaries/ Testes	
			Wt.	%	Wt.	%	Wt.	%	Wt.	%	Wt.	%
<u>Control:</u>												
65-070	M	13.0	29.12	0.224	310.87	2.391	0.90	0.007	63.99	0.492	23.08	0.178
65-083	M	8.5	30.70	0.361	242.42	2.852	0.98	0.012	43.25	0.509	14.22	0.167
65-086	M	9.2	28.58	0.311	248.83	2.705	0.98	0.011	49.53	0.538	18.90	0.205
65-038	F	8.2	19.98	0.244	198.81	2.425	1.40	0.017	38.58	0.470	0.67	0.008
65-081	F	9.2	24.32	0.264	250.50	2.723	1.06	0.012	39.62	0.431	0.74	0.008
65-093	F	6.1	13.59	0.223	151.11	2.477	0.78	0.013	29.28	0.480	0.41	0.007
<u>100 ppm.:</u>												
65-072	M	8.7	25.87	0.297	238.89	2.746	0.82	0.009	55.60	0.639	19.78	0.227
65-074	M	10.8	32.31	0.299	285.70	2.645	1.23	0.011	58.12	0.538	13.86	0.128
65-076	M	11.9	25.39	0.213	325.52	2.735	1.02	0.009	50.68	0.426	17.71	0.149
65-077	F	9.4	29.18	0.310	241.79	2.572	1.11	0.012	43.93	0.467	0.55	0.006
65-085	F	7.2	25.31	0.352	177.56	2.466	1.21	0.017	33.08	0.459	0.62	0.009
65-091	F	9.9	23.40	0.236	210.70	2.128	1.16	0.012	52.61	0.531	0.58	0.006
<u>1000 ppm.:</u>												
65-078	M	9.9	23.70	0.239	281.62	2.845	1.00	0.010	61.60	0.622	14.95	0.151
65-079	M	6.9	18.11	0.262	210.71	3.054	0.84	0.012	44.15	0.640	10.10	0.146
65-087	M	13.5	41.42	0.307	443.25	3.283	1.98	0.015	71.48	0.529	21.78	0.161
65-092	F	6.5	18.18	0.280	209.89	3.229	0.98	0.015	29.50	0.454	0.66	0.010
65-094	F	11.0	28.50	0.259	320.71	2.916	1.12	0.010	59.81	0.544	0.71	0.006
65-095	F	7.9	18.73	0.237	228.27	2.889	1.18	0.015	38.31	0.491	0.90	0.011
<u>5000 ppm.:</u>												
65-088	M	6.7	19.79	0.295	301.90	4.506	0.84	0.013	34.61	0.517	9.71	0.145
65-090	M	10.6	19.67	0.186	479.03	4.519	1.41	0.013	55.24	0.521	19.00	0.179
65-099	M	8.4	17.88	0.213	396.70	4.723	0.93	0.011	46.71	0.556	12.76	0.152
65-096	F	8.8	21.99	0.250	339.91	3.863	1.02	0.012	52.03	0.591	0.60	0.007
65-097	F	10.0	24.09	0.241	426.29	4.263	1.00	0.010	53.12	0.531	0.72	0.007
65-098	F	7.2	16.50	0.229	327.31	4.546	0.60	0.008	39.72	0.552	0.54	0.008

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(P)

Ninety-Day Feeding Study in the Dog.

TABLE 4, Continued. Average Daily Water Intake (W.I.), ml.; Urine Output (U.O.), ml.; and Water Intake-to-Urine Output Ratio (W/U).

Time Interval	500 ppm.*																	
	Dog 65-078 M			Dog 65-079 M			Dog 65-087 M			Dog 65-092 F			Dog 65-094 F			Dog 65-095 F		
	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U
Control Weeks																		
1	525	138	3.8	465	90	5.2	765	171	4.5	415	140	3.0	1455	354	4.1	840	120	7.0
2	555	159	3.5	498	108	4.6	1025	243	4.2	558	185	3.0	1378	553	2.5	434	255	1.7
3	647	155	4.2	487	145	3.4	593	180	3.3	460	233	2.0	1450	487	3.0	393	145	2.7
Compound Administration Weeks																		
1	790	230	3.4	483	191	2.5	883	243	3.6	438	232	1.9	760	270	2.8	417	250	1.7
9	875	266	3.3	683	290	2.4	485	144	3.4	270	166	1.6	935	188	5.0	545	271	2.0
12	888	245	3.6	538	240	2.2	1100	403	2.7	380	258	1.5	918	349	2.6	485	217	2.2

* Increased to 1000 ppm, in the 6th week of therapy.

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██████████ (3) Ninety-Day Feeding Study in the Dog.

TABLE 4, Continued. Average Daily Water Intake (W.I.), ml.; Urine Output (U.O.), ml.; and Water Intake-to-Urine Output Ratio (W/U).

Time Interval	2500 ppm.*																	
	Dog 65-088 M			Dog 65-090 M			Dog 65-096 F			Dog 65-097 F			Dog 65-098 F			Dog 65-099 M		
	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.O.	W/U	W.I.	U.C.	W/U	W.I.	U.C.	W/U
Control Weeks																		
1	480	205	2.3	545	137	3.9	570	103	5.5	505	138	2.6	365	95	3.8	463	149	3.1
2	549	240	2.3	574	195	2.9	573	173	3.3	488	228	2.1	448	156	2.9	558	214	2.6
3	607	263	2.3	587	193	3.0	593	130	4.6	573	273	2.1	580	157	3.7	580	195	3.0
Compound Administration Weeks																		
1	750	430	1.7	704	185	3.8	645	115	5.6	690	414	1.7	513	203	2.5	613	183	3.3
9	785	389	2.0	867	249	3.5	720	188	3.8	780	320	2.4	745	191	3.9	605	268	2.3
12	605	329	1.8	843	280	3.0	648	175	3.7	650	343	1.9	535	225	2.4	387	210	1.8

* Increased to 5000 ppm. in the 6th week of therapy.

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(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 7. Results of Hematological, Biochemical and Urinalysis Studies.

Dog No. 65-081, Female Dosage: Control	Control Periods			Compound Administration Months		
	1	2	3 3*	1 1*	2	3
Hematology:						
Total Erythrocytes ($\times 10^6$ /cmm.)	5.21	4.71	3.58	5.32	7.39	6.83
Hemoglobin, gm./100 ml.	11.6	10.3	10.0	10.8	13.8	13.9
Hematocrit, %	36	32	32	35	44	44
Sedimentation Rate, mm./hr.	2	4	1	1	0	0
Total Leucocytes, ($\times 10^3$ /cmm.)	11.65	10.85	11.95	10.09	9.84	13.65
Differential Count:						
Neutrophils, %	52	51	72	41 37	51	66
Seg., %	52	49	71	41 37	51	65
Non-Seg., %	0	2	1	0 0	0	1
Lymphocytes, %	44	44	25	49 58	46	30
Eosinophils, %	1	2	1	7 4	2	3
Monocytes, %	3	3	2	3 1	1	1
Basophils, %	0	0	0	0 0	0	0
Appearance of Erythrocytes	No		No	SH	H	No
Plasma Biochemistry:						
Glucose, mg./100 ml.	125	127	136	131 ^a	121	114
Protein, gm./100 ml.	5.91	5.85	5.00	5.05	5.75	5.65
Albumin, gm./100 ml.	2.58	2.45	2.29	2.73	3.01	2.98
Albumin-to-Globulin Ratio	0.78	0.72	0.85	1.17	1.09	1.11
Urea Nitrogen, mg./100 ml.	10.3	13.8	10.8	11.6	12.8	13.0
Alkaline Phosphatase, units	17	18	19	10	12	12
Cholesterol, mg./100 ml.	161	162	153	149	175	167
Prothrombin Time, sec.	8	8	8	8	7	7
SGOT units/ml. ¹	19	22	30 28	18	23	18
SGPT units/ml. ²	19	19	18 1	19	11	19
Urinalysis:						
Volume, ml.	60	105	195	180	135	330
Color	S-cl	S-cl	S-cl	S-cl	S-cl	LS-cl
pH	6.4	6.2	6.5	6.8	7.2	6.8
Specific Gravity	1.062	1.048	1.035	1.030	1.026	1.022
Albumin	N	N	N	N	N	N
Bilirubin	N	N	N	N	N	N
Glucose	N	N	N	N	N	N
Occult Blood	N	N	N	N	N	N
Microscopic:						
Leucocytes	4-5	3-5			F	
Amorphous Urates	F		F	F		L
Epithelial Cells	F		occ	2-3	occ	
Triple Phosphates	L	M		F		F
Ammonium Urates	M	F	F	F	F	F
Bacteria	M	F	M	M	F	M
Code:	S - Straw	N - Negative	L - Loaded	a - Repeat 132		
	LS - Light Straw	No - Normal	F - Few			
	cl - Cloudy	SH - Slight Hypochromia	M - Many			
		H - Hypochromia	occ - Occasional			
			¹ Serum Glutamic Oxalacetic Transaminase			
			² Serum Glutamic Pyruvic Transaminase			

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(b)(4)

Ninety-Day Feeding Study in the Dog.

TABLE 9. Results of Hematological, Biochemical and Urinalysis Studies.

Dog No. 65-086, Male Dose ¹ : Control	Control Periods			Compound Administration Months		
	1	2	3 3*	1 1*	2	3
Hematology:						
Total Erythrocytes (x10 ⁶ /cmm.)	4.81	4.40	3.70	5.18	6.13	6.09
Hemoglobin, gm./100 ml.	11.0	10.1	9.6	12.8	14.0	15.3
Hematocrit, %	35	32	31	40	43	45
Sedimentation Rate, mm./hr.	2	1	1	1	1	0
Total Leucocytes, (x10 ³ /cmm.)	13.79	12.20	13.57	17.48	10.92	9.11
Differential Count:						
Neutrophils, %	61	51	60	24 32	47	55
Seg., %	60	49	59	24 32	47	52
Non-Seg., %	1	2	1	0 0	0	3
Lymphocytes, %	30	42	35	70 64	51	37
Eosinophils, %	2	0	2	2 1	1	1
Monocytes, %	7	7	2	4 3	1	7
Basophils, %	0	0	1	0 0	0	0
Appearance of Erythrocytes	No	MH	No	MH	No	No
Plasma Biochemistry:						
Glucose, mg./100 ml.	126 ^a	107	104	111	100	102
Protein, gm./100 ml.	5.58	5.41	4.75	4.73	4.96	5.04
Albumin, gm./100 ml.	1.96	2.09	2.09	2.45	2.50	2.70
Albumin-to-Globulin Ratio	0.54	0.63	0.76	1.07	1.02	1.15
Urea Nitrogen, mg./100 ml.	14.8	16.8	12.3	10.7	9.4	10.7
Alkaline Phosphatase, units	16	15	15	9	11	7
Cholesterol, mg./100 ml.	196	174	142	181	203	200
Prothrombin Time, sec.	7	8	7	8	7	8
SGOT units/ml. ¹	18	21	28 25	13	10	13
SGPT units/ml. ²	16	17	10	11	8	13
Urinalysis:						
Volume, ml.	125	165	130	290	130	230
Color	S-cl	LS-cl	S-cl	LS-cl	S-cl	S-cl
pH	6.3	6.8	6.8	7.2	7.0	7.3
Specific Gravity	1.044	1.018	1.060	1.016	1.016	1.022
Albumin	N	N	N	N	N	N
Bilirubin	N	N	N	N	2 ^b	N
Glucose	N	N	N	N	N	N
Occult Blood	N	N	N	N	N	N
Microscopic:						
Leucocytes	4-6	8-10	3-4	1-2	8-10	1-3
Amorphous Urates		F		F		
Epithelial Cells	F				F	occ
Erythrocytes						R
Triple Phosphates	F	F	L	M	ccc	F
Ammonium Urates	M			F	L	
Bacteria	L	M	M	M	L	F
Code: S - Straw N - Negative L - Loaded * - Repeat Determinations						
LS - Light Straw No - Normal F - Few a - Repeat 134						
cl - Cloudy MH - Marked Hypochromia M - Many b - Repeat 1+						
1+ - Trace-to-slight R - Rare						
2+ - Slight-to-moderate occ - Occasional						

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¹Serum Glutamic Oxalacetic Transaminase²Serum Glutamic Pyruvic Transaminase

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(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 10. Results of Hematological, Biochemical and Urinalysis Studies.

Dog No. 65-093, Female Dosage: Control	Control Periods			Compound Administration Months		
	1	2	3 3 ^{1/2}	1	2	3
<u>Hematology:</u>						
Total Erythrocytes ($\times 10^6$ /cmm.)	5.97	4.93	3.77	5.76	6.84	5.94
Hemoglobin, gm./100 ml.	12.6	11.1	10.2	12.6	14.8	14.6
Hematocrit, %	33	33	30	40	46	44
Sedimentation Rate, mm./hr	1	1	14 16	2	0	0
Total Leucocytes, ($\times 10^3$ /cmm.)	15.90	14.53	9.21	17.51	12.34	11.90
<u>Differential Count:</u>						
Neutrophils, %	61	57	53	67	58	67
Seg., %	60	56	53	67	58	66
Non-Seg., %	1	1	0	0	0	1
Lymphocytes, %	37	39	44	29	38	32
Eosinophils, %	1	1	1	1	4	1
Monocytes, %	1	3	2	3	0	0
Basophils, %	0	0	0	0	0	0
Appearance of Erythrocytes	No	SH	SH	SH	No	No
<u>Plasma Biochemistry:</u>						
Glucose, mg./100 ml.	127	125	115	118	112	112
Protein, gm./100 ml.	5.63	5.53	5.38	5.05	5.08	5.11
Albumin, gm./100 ml.	1.89	2.01	2.00	2.08	2.48	2.60
Album n-to-Globulin Ratio	0.51	0.57	0.59	0.70	0.95	1.04
Urea Nitrogen, mg./100 ml.	13.5	13.0	12.0	12.8	13.8	14.6
Alkaline Phosphatase, units	19	18	19	13	13	10
Cholesterol, mg./100 ml.	144	128	147	132	115	124
Prothrombin Time, sec.	7	7	7	7	7	8
SGOT units/ml. ¹	16	17	19	12	15	12
SGPT units/ml. ²	22	22	26	16	18	15
<u>Urinalysis:</u>						
Volume, ml.	50	130	90	80	105	280
Color	S-C	S-C	DS-cl	S-C	S-C	S-cl
pH	7.4	7.0	7.0	7.4	8.0 ^a	7.3
Specific Gravity	1.050	1.022	1.058	1.041	1.027	1.031
Albumin	N	N	N	N	N	N
Bilirubin	N	N	N	N	N	N
Glucose	N	N	N	N	N	N
Occult Blood	N	N	N	N	N	N
<u>Microscopic:</u>						
Leucocytes	F	1-3	1-2		6-8	occ
Amorphous Urates		F				
Epithelial Cells		1-2	1-2	1-2	2-3	1-2
Erythrocytes						occ
Triple Phosphates	F	F	M	F	L	
Ammonium Urates	F				F	F
Bacteria	F	F	F	F	M	F

Code: S - Straw N - Negative L - Loaded * - Repeat Determinations
 DS - Dark Straw No - Normal F - Few a - Repeat 6.8
 cl - Cloudy SH - Slight Hypochromia M - Many

occ - Occasional

¹Serum Glutamic Oxalacetic Transaminase²Serum Glutamic Pyruvic Transaminase

(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 10. Results of Hematological, Biochemical and Urinalysis Studies.

Dog No. 65-093, Female Dose: Control	Control Periods			Compound Administration Months		
	1	2	3 3*	1	2	3
<u>Hematology:</u>						
Total Erythrocytes ($\times 10^6/\text{cmm.}$)	5.97	4.93	3.77	5.76	6.84	5.94
Hemoglobin gm./100 ml.	12.6	11.1	10.2	12.6	14.8	5
Hematocrit, %	40	33	30	40	46	44
Sedimentation Rate, mm./hr	0	1	14 16	2	0	0
Total Leucocytes, ($\times 10^3/\text{cmm.}$)	15.90	14.53	9.21	17.51	12.34	11.90
<u>Differential Counts:</u>						
Neutrophils, %	61	57	53	67	58	67
Seg., %	60	56	53	67	58	66
Non-Seg., %	1	1	0	0	0	1
Lymphocytes, %	37	39	44	29	38	32
Eosinophils, %	1	1	1	1	4	1
Monocytes, %	1	3	2	3	0	0
Basophils, %	0	0	0	0	0	0
Appearance of Erythrocytes	No	SH	SH	SH	No	No
<u>Plasma Biochemistry:</u>						
Glucose, mg./100 ml.	127	125	115	118	112	112
Protein, gm./100 ml.	5.63	5.53	5.38	5.05	5.08	5.11
Albumin, gm./100 ml.	1.89	2.01	2.00	2.08	2.48	2.60
Albumin-to-Globulin Ratio	0.51	0.57	0.59	0.70	0.95	1.04
Urea Nitrogen, mg./100 ml.	13.5	13.0	12.0	12.8	13.8	14.6
Alkaline Phosphatase, units	19	18	19	13	13	10
Cholesterol, mg./100 ml.	144	128	147	132	115	124
Prothrombin Time, sec.	7	7	7	7	7	8
SGOT units/ml. ¹	16	17	19	12	15	12
SGPT units/ml. ²	22	22	26	16	18	15
<u>Urinalysis:</u>						
Volume, ml.	50	130	90	80	105	280
Color	S-C	S-C	DS-cl	S-C	S-C	S-cl
pH	7.4	7.0	7.0	7.4	8.0 ^a	7.3
Specific Gravity	1.050	1.022	1.058	1.041	1.027	1.031
Albumin	N	N	N	N	N	N
Bilirubin	N	N	N	N	N	N
Glucose	N	N	N	N	N	N
Occult Blood	N	N	N	N	N	N
<u>Microscopic:</u>						
Leucocytes	F	1-3	1-2		6-8	occ
Amorphous Urates		F				
Epithelial Cells		1-2	1-2	1-2	2-3	1-2
Erythrocytes						occ
Triple Phosphates	F	F	M	F	L	
Ammonium Urates	F				F	F
Bacteria	F	F	F	F	M	F

Code: S - Straw N - Negative L - Loaded * - Repeat Determinations
 DS - Dark Straw No - Normal F - Few a - Repeat 6.8
 cl - Cloudy SH - Slight Hypochromia M - Many
 occ - Occasional

¹Serum Glutamic Oxalacetic Transaminase
²Serum Glutamic Pyruvic Transaminase

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(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 11. Results of Hematological, Biochemical and Urinalysis Studies.

Dog No. 65-072, Male
 Dose: 100 ppm.

Days	Sign Months	Control Periods			Compound Administration Months			
		1	2	3	1	2	3	
<u>Hematology:</u>								
5.94		Total Erythrocytes (x10 ⁶ /cmm.)	5.44	4.76	4.10	5.61	6.77	6.39
44		Hemoglobin, gm /100 ml.	12.6	10.7	11.8	13.7	16.2	16.4
U		Hematocrit, %	40	34	37	42	46	50
11.90		Sedimentation Rate, mm./hr.	0	1	0	0	0	0
		Total Leucocytes, (x10 ³ /cmm.)	11.96	11.23	11.30	7.47	11.01	10.15
<u>Differential Count:</u>								
67		Neutrophils, %	63	62	70	58	52	64
66		Seg., %	62	60	69	58	52	63
1		Non-Seg., %	1	2	1	0	0	1
32		Lymphocytes, %	31	34	26	36	42	35
1		Eosinophils, %	3	3	2	4	5	1
0		Monocytes, %	3	1	2	2	1	0
0		Basophils, %	0	0	0	0	0	0
10		Appearance of Erythrocytes	No	H	SH	SH	No	No
<u>Plasma Biochemistry:</u>								
12		Glucose, mg./100 ml.	114	111	119	112	113	106
5.11		Protein, gm./100 ml.	5.63	5.13	4.60	4.65	5.45	5.15
2.60		Albumin, gm./100 ml.	2.53	2.22	2.14	2.28	2.53	2.72
1.04		Albumin-to-Globulin Ratio	0.82	0.76	0.87	0.96	0.86	1.12
4.6		Urea Nitrogen, mg./100 ml.	10.2	10.4	11.8	11.0	10.7	9.5
0		Alkaline Phosphatase, units	17	16	17	10	10	8
14		Cholesterol, mg./100 ml.	132	139	120	118	158	163
8		Prothrombin Time, sec.	8	8	8	8	6	7
2		SGOT units/ml. ¹	22	18	19	17	16	20
5		SGPT units/ml. ²	14	14	15	17	8	16
<u>Urinalysis:</u>								
0		Volume, ml.	90	105	90	245	160	235
-cl		Color	S-cl	S-cl	DS-cl	S-cl	S-cl	S-cl
7.3		pH	6.0	6.0	7.1	6.5	6.3	6.5
1.031		Specific Gravity	1.059	1.032	1.055	1.020	1.024	1.023
N		Albumin	N	N	N	N	N	N
N		Bilirubin	N	N	N	N	N	N
N		Glucose	N	N	N	N	N	N
N		Occult Blood	N	N	N	N	2+ ^a	N
<u>Microscopic:</u>								
cc		Calcium Oxalate	M					
		Leucocytes	20-30	F	1-2	1-2	20	occ
		Amorphous Urates	L			M		
-2		Epithelial Cells	2-3			4-5	occ	occ
cc		Triple Phosphates	M	F	M	F	F	
F		Ammonium Urates					M	L
F		Bacteria	L	M	F	M	L	M

Code: S - Straw N - Negative L - Loaded a - Repeat N
 DS - Dark Straw No - Normal F - Few
 cl - Cloudy SH - Slight Hypochromia M - Many
 H - Hypochromia occ - Occasional
¹Serum Glutamic Oxalacetic Transaminase
²Serum Glutamic Pyruvic Transaminase

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(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 13. Results of Hematological, Biochemical and Urinalysis Studies

Dog No. 65-076, Male Dosage: 100 ppm.	Control Periods			Compound Administration Months		
	1 1*	2	3	1	2	3
<u>Hematology</u>						
Total Erythrocytes ($\times 10^6$ /cmm.)	4.39	3.88	3.35	5.02	6.06	5.44
Hemoglobin, gm./100 ml.	9.4	8.0	9.7	11.6	14.1	14.1
Hematocrit, %	28	26	32	36	42	43
Sedimentation Rate, mm./hr	10 11	5	1	1	1	0
Total Leucocytes, ($\times 10^3$ /cmm.)	14.52	17.92	11.97	11.71	11.11	12.71
Differential Count:						
Neutrophils, %	45	69	64	44	44	45
Seg., %	42	69	63	44	44	45
Non-Seg., %	3	0	1	0	0	0
Lymphocytes, %	48	27	32	45	49	46
Eosinophils, %	2	4	2	5	4	6
Monocytes, %	5	0	2	6	3	3
Basophils, %	0	0	0	0	0	0
Appearance of Erythrocytes	No	MH	SH	MH	H	No
<u>Plasma Biochemistry:</u>						
Glucose, mg./100 ml.	125 ^a	135	129	123	119	116
Protein, gm./100 ml.	5.44	5.84	5.01	4.89	5.42	5.25
Albumin, gm./100 ml.	2:00	2.39	2.09	2.35	2.57	2.63
Albumin-to-Globulin Ratio	0.58	0.69	0.72	0.92	0.93	1.00
Urea Nitrogen, mg./100 ml.	13.5	14.2	13.3	12.4	13.6	12.5
Alkaline Phosphatase, units	16	18	17	11	13	10
Cholesterol, mg./100 ml.	159	163	132	168	181	203
Prothrombin Time, sec.	7	7	8	8	7	8
SGOT units/ml. ¹	20	19	19	19	28	15
SGPT ² units/ml. ²	16	12	10	17	19	14
<u>Urinalysis:</u>						
Volume, ml.	220	305	370	360	355	420
Color	S-cl	S-cl	S-cl	LS-cl	S-cl	LS-cl
pH	6.4	7.1	7.0	6.0	7.0	6.0
Specific Gravity	1.027	1.021	1.026	1.021	1.018	1.025
Albumin	N	N	N	N	N	N
Bilirubin	N	N	N	N	N	N
Glucose	N	N	N	N	N	N
Occult Blood	N	N	N	N	N	N
<u>Microscopic:</u>						
Amorphous Urates				F	F	L
Leucocytes	1-2	1-3				F
Epithelial Cells				1-2	occ	3-5
Erythrocytes						occ
Triple Phosphates	F	M	F	F		
Calcium Oxalate	F					
Ammonium Urates	F			F	M	
Bacteria	M	F	H	M	M	L

Code: S - Straw N - Negative L - Loaded a - Repeat 150
 LS - Light Straw No - Normal F - Few
 C - Clear SH - Slight Hypochromia M - Many
 cl - Cloudy MH - Marked Hypochromia Occ - Occasional
 H - Hypochromia

¹ Serum Glutamic Oxaloacetic Transaminase
² Serum Glutamic Pyruvic Transaminase

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ZONY

TABL

Dog

Dosa

Hema

Tota

Hemo

Hema

Sedl

Tota

Diff

N

L

E

M

B

Appe

Plas

Gluc

Prot

Albu

Albu

Urea

Alka

Chol

Prot

SGOT

SGPT

Urin

Volu

Color

pH

Spec

Albu

Bili

Gluc

Occu

Micro

Leuc

Amor

Epith

Trip

Amor

Bacte

Code

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Ninety-Day Feeding Study in the Dog.

TABLE 14. Results of Hematological, Biochemical and Urinalysis Studies.

Months	Dog No. 65-077, Female Dosage: 100 ppm.	Control Periods			Compound Administration Months		
		1 1*	2	3 3*	1	2	3
<u>Hematology:</u>							
.44	Total Erythrocytes (x10 ⁶ /cmm.)	5.13	4.69	3.95	5.31	6.60	6.21
.1	Hemoglobin, mg./100 ml.	11.5	9.9	11.5	12.1	15.4	15.6
	Hematocrit, %	36	31	33	38	46	48
	Sedimentation Rate, mm./hr.	3	2	10 12	1	0	0
.71	Total Leucocytes, (x10 ³ /cmm.)	11.0	11.88	16.81	12.81	10.10	12.48
<u>Differential Count:</u>							
	Neutrophils, %	40 41	54	43 47	61	52	65
	Seg., %	38 40	53	42 46	61	52	63
	Non-Seg., %	2 1	1	1 1	0	0	2
	Lymphocytes, %	58 54	38	52 50	32	41	27
	Eosinophils, %	0 2	2	2 1	3	1	5
	Monocytes, %	2 3	6	3 2	4	6	3
	Basophils, %	0 0	0	0 0	0	0	0
	Appearance of Erythrocytes	No	H	No	MH	No	No
<u>Plasma Biochemistry:</u>							
.25	Glucose, mg./100 ml.	118	121	125	128 ^a	126 ^b	96
.63	Protein, gm./100 ml.	5.63	5.56	5.48	4.99	5.45	5.20
.00	Albumin, gm./100 ml.	2.58	2.55	2.09	2.62	2.88	2.91
.5	Albumin-to-Globulin Ratio	0.85	0.85	0.62	1.10	1.12	1.27
	Urea Nitrogen, mg./100 ml.	11.5	10.5	14.5	12.9	13.0	12.6
	Alkaline Phosphatase, units	20	21	18	12	15	11
	Cholesterol, mg./100 ml.	155	153	188	142	182	169
	Prothrombin Time, sec.	8	8	8	8	7	8
	SGOT units/ml. ¹	26	23	18	16	16	13
	SGPT units/ml. ²	16	17	12	14	11	13
<u>Urinalysis:</u>							
.1	Volume, ml.	105	140	255	260	240	180
0	Color	S-cl	S-cl	S-cl	LS-cl	S-C	S-cl
025	pH	6.5	7.3	7.3	6.8	7.0	7.0
	Specific Gravity	1.043	1.022	1.025	1.020	1.023	1.023
	Albumin	N	N	N	N	N	N
	Bilirubin	N	N	N	N	N	N
	Glucose	N	N	N	N	N	N
	Occult Blood	N	N	N	N	N	N
<u>Microscopic:</u>							
	Leucocytes	3-4			1-2		occ
	Amorphous Urates				F		
5	Epithelial Cells	F		1-2	3-4	F	1-3
c	Triple Phosphates	L	F	F	F	F	occ
	Ammonium Urates	M	F		F	F	
	Bacteria	L	M	F	F	M	M
Code: S - Straw N - Negative L - Loaded a - Repeat 128							
LS - Light Straw No - Normal F - Few b - Repeat 121							
C - Clear MH - Marked Hypochromia M - Many							
ci - Cloudy H - Hypochromia occ - Occasional							
¹ Serum Glutamic Oxalacetic Transaminase							
² Serum Glutamic Pyruvic Transaminase							

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(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 15. Results of Hematological, Biochemical and Urinalysis Studies.						
Dog No. 65-085, Female	Control Periods			Compound Administration Months		
Dosage: 100 ppm.	1	2	3	1	2	3
<u>Hematology:</u>						
Total Erythrocytes (x10 ⁶ /cmm.)	6.17	5.19	4.44	5.58	6.94	6.65
Hemoglobin, gm./100 ml.	14.1	12.1	12.1	14.9	17.7	18.0
Hematocrit, %	44	38	39	47	54	51
Sedimentation Rate, mm./hr.	1	1	1	0	0	0
Total Leucocytes, (x10 ³ /cmm.)	16.47	17.52	13.96	14.45	9.66	10.74
<u>Differential Count:</u>						
Neutrophils, %	49	48	51	53	54	46
Seg., %	47	47	51	53	53	46
Non-Seg., %	2	1	0	0	1	0
Lymphocytes, %	44	44	47	39	40	44
Eosinophils, %	2	4	2	3	2	4
Monocytes, %	5	4	0	5	4	6
Basophils, %	0	0	0	0	0	0
Appearance of Erythrocytes	No	H	No	H	No	No
<u>Plasma Biochemistry:</u>						
Glucose, mg./100 ml.	142 ^a	121	119	122	106	106
Protein, gm./100 ml.	5.58	6.08	5.59	5.39	5.69	5.82
Albumin, gm./100 ml.	2.16	2.20	2.39	2.60	2.82	3.14
Albumin-to-Globulin Ratio	0.63	0.57	0.75	0.92	0.98	1.17
Urea Nitrogen, mg./100 ml.	9.8	13.4	11.8	11.0	11.7	12.1
Alkaline Phosphatase, units	15	15	13	8	11	8
Cholesterol, mg./100 ml.	159	132	148	128	141	161
Prothrombin Time, sec.	8	8	8	8	8	9
SGOT units/ml. ¹	20	22	19	15	16	11
SGPT units/ml. ²	25	19	19	14	17	9
<u>Urinalysis:</u>						
Volume, ml.	140	135	325	335	165	200
Color	S-cl	LS-cl	LS-cl	LS-cl	S-cl	S-cl
pH	7.0	7.0	6.9	6.8	7.0	6.8
Specific Gravity	1.023	1.019	1.027	1.011	1.015	1.018
Albumin	N	N	N	N	N	N
Bilirubin	N	N	N	N	N	N
Glucose	N	N	N	N	N	N
Occult Blood	N	N	N	N	N	N
<u>Microscopic:</u>						
Leucocytes	6-8	4-5				
Amorphous Urates	F		F	F		
Epithelial Cells		F		2-3	F	
Erythrocytes						occ
Triple Phosphates	F	F	F		M	
Ammonium Urates	M			F	L	
Bacteria	L	F	M	M	L	M
Code: S - Straw N - Negative L - Loaded a - Repeat 148						
LS - Light Straw No - Normal F - Few						
C - Clear H - Hypochromia M - Many						
cl - Cloudy occ - Occasional						
¹ Serum Glutamic Oxalacetic Transaminase						
² Serum Glutamic Pyruvic Transaminase						

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(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 16. Results of Hematological, Biochemical and Urinalysis Studies.

Dog No. 65-091, Female Dosage: 100 ppm.	Control Periods			Compound Administration Months		
	1	2	3	1	2 Q*	3
<u>Hematology:</u>						
Total Erythrocytes (x10 ⁶ /cmm.)	5.78	4.86	4.26	5.81	6.13	5.60
Hemoglobin, gm./100 ml.	12.6	11.6	11.6	14.2	15.2	15.3
Hematocrit, %	40	36	38	43	46	48
Sedimentation Rate, mm./hr.	1	1	0	0	0	0
Total Leucocytes, (x10 ³ /cmm.)	10.20	12.39	11.83	11.39	10.18	10.96
<u>Differential Count:</u>						
Neutrophils, %	49	45	46	56	30 40	41
Seg., %	49	43	46	36	30 39	41
Non-Seg., %	0	2	0	0	0 1	0
Lymphocytes, %	42	45	48	36	63 52	53
Eosinophils, %	3	5	3	6	3 0	3
Monocytes, %	6	5	3	2	4 8	3
Basophils, %	0	0	0	0	0 0	0
Appearance of Erythrocytes	No	No	H	H	No	No
<u>Plasma Biochemistry:</u>						
Glucose, mg./100 ml.	112	106	115	119	108	109
Protein, gm./100 ml.	5.58	5.38	4.80	5.01	5.08	5.20
Albumin, gm./100 ml.	1.90	1.95	1.98	2.35	2.56	2.73
Albumin-to-Globulin Ratio	0.52	0.57	0.70	0.88	1.01	1.10
Urea Nitrogen, mg./100 ml.	12.7	17.3	12.4	11.4	12.3	13.0
Alkaline Phosphatase, units	28	25	24	12	19	16
Cholesterol, mg./100 ml.	160	138	149	143	155	149
Prothrombin Time, sec.	8	7	7	8	8	10
SGOT units/ml. ¹	23	22	16	16	19	15
SGPT units/ml. ²	14	18	18	12	8	6
<u>Urinalysis:</u>						
Volume, ml.	150	205	140	120	175	355
Color	S-cl	LS-cl	S-cl	S-cl	S-cl	S-cl
pH	6.1	6.5	6.9	6.1	6.8	7.0
Specific Gravity	1.058	1.021	1.043	1.032	1.023	1.012
Albumin	N	N	N	N	N	N
Bilirubin	N	N	N	N	N	N
Glucose	N	N	N	N	N	N
Occult Blood	N	N	N	N	N	N
<u>Microscopic:</u>						
Leucocytes			3-4	3-4		
Amorphous Urates		F		F	F	F
Epithelial Cells	F		occ			occ
Triple Phosphates	M	F	L	M	M	
Ammonium Urates	M	F	M	M	M	
Bacteria	M	L	L	F	L	F

Code: S - Straw N - Negative L - Loaded
 LS - Light Straw No - Normal F - Few
 cl - Cloudy H - Hypochromia M - Many
 occ - Occasional
¹Serum Glutamic Oxalacetic Transaminase
²Serum Glutamic Pyruvic Transaminase

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(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 17. Results of Hematological, Biochemical and Urinalysis Studies.

Dog No. 65-078, Male Dosage: 500 ppm.	Control Periods			Compound Administration Months				
	1	2	2*	3	1	2	2*	3
<u>Hematology:</u>								
Total Erythrocytes ($\times 10^6$ /cmm.)	4.66	3.63	3.41	4.65	5.69	5.49		
Hemoglobin, gm./100 ml.	12.0	8.0	9.3	11.7	14.5	15.3		
Hematocrit, %	38	25	31	36	43	46		
Sedimentation Rate, mm./hr.	2	16	20	3	1	0		
Total Leucocytes, ($\times 10^3$ /cmm.)	10.95	22.50 ^a	11.66	7.59	9.98	11.61		
<u>Differential Count:</u>								
Neutrophils, %	35	26	27	69	52	41		54
Seg., %	55	26	27	69	51	41		54
Non-Seg., %	0	0	0	0	1	0		0
Lymphocytes, %	40	70	68	30	39	51		41
Eosinophils, %	3	4	3	1	5	4		4
Monocytes, %	2	0	2	0	4	4		1
Basophils, %	0	0	0	0	0	0		0
Appearance of Erythrocytes	No	H	H	No	No	No		
<u>Plasma Biochemistry:</u>								
Glucose, mg./100 ml.	138 ^b	146	134	118	117	113		
Protein, gm./100 ml.	5.82	6.13	4.92	4.74	5.25	5.16		
Albumin, gm./100 ml.	2.68	2.39	2.00	2.42	2.71	2.78		
Albumin-to-Globulin Ratio	0.85	0.64	0.69	1.04	1.06	1.17		
Urea Nitrogen, mg./100 ml.	11.5	10.4	9.9	11.5	11.5	11.1		
Alkaline Phosphatase, units	22	21	25	13	17	16		15
Cholesterol, mg./100 ml.	129	169	132	154	180	203		
Prothrombin Time, sec.	8	8	8	8	7	9		
SGOT units/ml. ¹	20	26	22	19	20	15		
SGPT units/ml. ²	18	13	10	17	10	15		
<u>Urinalysis:</u>								
Volume, ml.	80	175	150	140	140	275		
Color	S-cl	LS-cl	S-cl	S-cl	S-cl	S-cl		
pH	6.7	6.8	7.3	6.5	7.3	6.7		
Specific Gravity	1.045	1.026	1.051	1.033	1.025	1.025		
Albumin	N	N	N	N	N	N		
Bilirubin	N	N	N	N	tr ^c	1+ ^d		
Glucose	N	N	N	N	N	N		
Occult Blood	N	N	N	N	N	N		
<u>Microscopic:</u>								
Leucocytes			occ					R
Amorphous Urates	F	F		F	F			
Epithelial Cells	F	F		3-4	F			
Triple Phosphates	M	M	F	F	F	F		
Ammonium Urates	M				M			
Bacteria	M	M	M	M	M	M		
Code: S - Straw	N - Negative	L - Loaded	a - Repeat 22.65					
LS - Light Straw	No - Normal	F - Few	b - Repeat 140					
cl - Cloudy	H - Hypochromia	M - Many	c - Repeat 1+					
	tr - Trace	R - Rare	d - Repeat 2+					
	1+ - Trace-to-slight	occ - Occasional	* - Repeat Determinations					
	2+ - Slight-to-moderate	¹ Serum Glutamic Oxalacetic Transaminase						
		² Serum Glutamic Pyruvic Transaminase						

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Ninety-Day Feeding Study in the Dog.

TABLE 18. Results of Hematological, Biochemical and Urinalysis Studies.

on Months 3	Dog No. 65-079, Male Dosage: 500 ppm.	Control Periods			Compound Administration Months		
		1 1*	2	3	1	2 2*	3
	<u>Hematology:</u>						
5.49	Total Erythrocytes ($\times 10^6$ /cmm.)	4.72	4.21	4.00	5.15	5.70	5.49
5.3	Hemoglobin, gm./100 ml.	11.3	9.9	10.1	12.1	14.6	15.1
6	Hematocrit, %	35	33	34	38	44	46
0	Sedimentation Rate, mm./hr.	3	1	1	0	0	0
1.61	Total Leucocytes, ($\times 10^3$ /cmm.)	10.08	10.70	9.62	9.85	10.60	10.34
	<u>Differential Count:</u>						
4	Neutrophils, %	42 43	51	56	48	41 32	50
0	Seg., %	40 41	51	55	48	40 32	48
1	Non-Seg., %	2 2	0	1	0	1 0	2
4	Lymphocytes, %	53 55	42	41	46	49 59	47
1	Eo inophils, %	2 0	0	1	2	1 1	0
0	Monocytes, %	3 2	7	2	4	9 8	3
0	Basophils, %	0 0	0	0	0	0 0	0
	Appearance of Erythrocytes	No	MI	H	SH	H	No
	<u>Plasma Biochemistry:</u>						
3	Glucose, mg./100 ml.	142 ^a	140	132	124	120	113
5.16	Protein, gm./100 ml.	6.03	6.00	5.00	4.98	5.38	5.31
2.78	Albumin, gm./100 ml.	2.60	2.61	2.29	2.60	2.80	2.95
1.17	Albumin-to-Globulin Ratio	0.76	0.77	0.85	1.09	1.08	1.25
1.1	Urea Nitrogen, mg./100 ml	16.3	14.9	9.9	13.3	14.8	12.0
5	Alkaline Phosphatase, units	21	24	23	12	16 16	12
3	Cholesterol, mg./100 ml.	161	149	147	135	166	169
3	Prothrombin Time, sec.	7	8	8	8	7	8
5	SGOT units/ml. ¹	34	20	22	18	16	13
5	SGPT units/ml. ²	26	25	19	19	12	15
	<u>Urinalysis:</u>						
-cl	Volume, ml.	50	30	200	75	105	85
5.7	Color	S-cl	S-C	S-cl	S-cl	S-cl	DS-cl
1.025	pH	6.9	6.5	6.9	6.9	7.5	7.3
1	Specific Gravity	1.050	1.050	1.027	1.026	1.033	1.030
d	Albumin	N	N	N	N	N	N
1	Bilirubin	N	N	N	N	1 ⁺ ^b	4 ⁺ ^c
1	Glucose	N	N	N	N	N	N
1	Occult Blood	N	N	N	N	N	N
	<u>Microscopic:</u>						
1	Leucocytes	20-30	5-7	1-2			1-3
	Amorphous Urates				F		
	Epithelial Cells	3-4	F	occ	1-2	F	
	Erythrocytes						occ
	Triple Phosphates	L	M	F	M	L	H
	Ammonium Urates	F			F	F	
	Bacteria	F	M	M	M	L	L
	Flagellates			R			
	Code: S - Straw	N - Negative	L - Loaded	a - Repeat 144			
	DS - Dark Straw	No - Normal	F - Few	b - Repeat 1+			
	C - Clear	SH - Slight Hypochromia	M - Many	c - Repeat 4+			
	cl - Cloudy	H - Hypochromia	R - Rare	* - Repeat Determinations			
		1+ - Trace-to-slight	occ - Occasional				
		4+ - Marked					
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Ninety-Day Feeding Study in the Dog.

TABLE IV. Results of Hematological, Biochemical and Urinalysis Studies.						
Dog No. 65-087, Male	Control Periods			Compound Administration Months		
Dosage: 500 ppm	1 J*	2	3 J ^a	1	2 2*	3
Hematology:						
Total Erythrocytes ($\times 10^6$ /cmm.)	5.29	4.55	4.39	5.64	6.38	6.91
Hemoglobin, gm./100 ml.	12.5	11.0	11.2	13.0	15.1	16.2
Hematocrit, %	40	33	35	40	45	50
Sedimentation Rate, mm./hr.	10 11	5	0	0	11 8	9
Total Leucocytes, ($\times 10^3$ /cmm.)	12.38	9.44	9.92	9.73	10.72	11.54
Differential Count:						
Neutrophils, %	56	46	39 35	35	57	42
Seg., %	55	45	39 34	35	55	41
Non-Seg., %	1	1	0 1	0	2	1
Lymphocytes, %	42	46	59 62	60	37	51
Eosinophils, %	0	4	1 2	2	0	0
Monocytes, %	2	4	1 1	3	6	7
Basophils, %	0	0	0 0	0	0	0
Appearance of Erythrocytes	No	H	H	No	H	No
Plasma Biochemistry:						
Glucose, mg./100 ml.	140 ^a	124	116	116	103	113
Protein, gm./100 ml.	6.37	6.13	5.14	5.30	6.05	6.25
Albumin, gm./100 ml.	2.30	2.32	2.55	2.90	2.72	3.38
Albumin-to-Globulin Ratio	0.57	0.61	0.98	1.20	0.82	1.22
Urea Nitrogen, mg./100 ml.	11.5	11.8	9.6	12.7	12.3	8.0
Alkaline Phosphatase, units	15	13	14	9	19 17	9
Cholesterol, mg./100 ml.	159	171	125	125	250 ^b	214
Prothrombin Time, sec.	8	7	8	8	7	8
SGOT units/ml. ¹	13	15	16	14	15	9
SGPT units/ml. ²	10	18	11	14	10	8
Urinalysis:						
Volume, ml.	125	150	305	150	110	360
Color	S-cl	S-C	S-cl	S-cl	DS-cl	LS-cl
pH	6.3	6.1	6.2	6.2	6.0	6.6
Specific Gravity	1.044	1.031	1.038	1.049	1.058	1.015
Albumin	N	N	N	N	N	N
Bilirubin	N	N	N	N	2+ ^c	N
Glucose	N	N	N	N	N	N
Occult Blood	N	N	N	N	N	N
Microscopic:						
Leucocytes	70-80	3-4	10-12	3-5	8-10	
Amorphous Urates		M	F			
Epithelial Cells	F	1-2	1-3	1-2	8-10	0-3
Triple Phosphates	F			F		
Calcium Oxalate		F				
Ammonium Urates	M			F	M	M
Bacteria	L	M	M	F	F	-M

Code: S - Straw N - Negative L - Loaded a - Repeat 150
 LS - Light Straw No - Normal F - Few b - Repeat 215
 DS - Dark Straw H - Hypochromia M - Many c - Repeat 2+
 cl - Cloudy 2+ - Slight-to-moderate occ - Occasional * - Repeat Determinations

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¹Serum Glutamic Oxalacetic Transaminase
²Serum Glutamic Pyruvic Transaminase

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Ninety-Day Feeding Study in the Dog.

TABLE 20. Results of Hematological, Biochemical and Urinalysis Studies.

n Months	Dog No. 65-092	Control Periods			Compound Administration Months		
		1	2	3	1	2	3
<u>Hematology:</u>							
.91	Total Erythrocytes (x10 ⁶ /cmm.)	5.40	4.76	4.09	5.44	6.38	5.78
.2	Hemoglobin, gm./100 ml	12.2	10.8	10.6	13.2	14.6	15.1
	Hematocrit, %	39	34	35	42	45	46
	Sedimentation Rate, mm./hr.	0	1	1	0	2	0
.54	Total Leucocytes, (x10 ³ /cmm.)	14.71	11.74	11.04	10.69	12.12	21.88
<u>Differential Count:</u>							
	Neutrophils, %	67	73	65	66	80	77
	Seg., %	65	72	65	66	80	73
	Non-Seg., %	2	1	0	0	0	4
	Lymphocytes, %	27	22	33	31	16	20
	Eosinophils, %	1	1	2	1	0	0
	Monocytes, %	5	4	0	2	4	3
	Basophils, %	0	0	0	0	0	0
	Appearance of Erythrocytes	No	H	H	SH	No	No
<u>Plasma Biochemistry:</u>							
.25	Glucose, mg./100 ml.	116	120	118	109	108	107
.38	Protein, gm./100 ml.	5.82	5.48	4.95	4.99	5.86	5.45
.22	Albumin, gm./100 ml.	1.91	1.95	2.13	2.52	2.64	2.83
0	Albumin-to-Globulin Ratio	0.49	0.55	0.76	1.02	0.82	1.08
	Urea Nitrogen, mg./100 ml.	18.0	16.8	19.4	19.0	14.5	11.3
	Alkaline Phosphatase, units	15	18	18	12	17 ^a	13
	Cholesterol, mg./100 ml.	140	122	120	121	191	160
	Prothrombin Time, sec.	8	8	8	9	6	8
	SGOT units/ml. ¹	22	20	25	15	11	13
	SGPT units/ml. ²	28	29	14	18	17	11
<u>Urinalysis:</u>							
1	Volume, ml.	130	145	190	245	105	310
6	Color	S-cl	LS-cl	S-cl	LS-cl	S-C	LS-cl
015	pH	7.1	6.8	7.4	6.5	7.5	7.0
	Specific Gravity	1.039	1.020	1.034	1.013	1.026	1.018
	Albumin	N	N	N	N	N	N
	Bilirubin	N	N	N	N	N	N
	Glucose	N	N	N	N	N	N
	Occult Blood	N	N	N	N	N	N
<u>Microscopic:</u>							
	Leucocytes	8-10	8-10	4-5		12-15	
	Amorphous Urates			F	F		
	Epithelial Cells	F			3-4	3-4	occ
	Triple Phosphates	M	F	F		M	occ
	Ammonium Urates	M	F	F		F	
	Bacteria	F	M	M	M	F	F

Code: S - Straw N - Negative L - Loaded a - Repeat 18
 LS - Light Straw No - Normal F - Few
 C - Clear SH - Slight Hypochromia M - Many
 cl - Cloudy H - Hypochromia occ - Occasional

¹Serum Glutamic Oxalacetic Transaminase
²Serum Glutamic Pyruvic Transaminase

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Ninety-Day Feeding Study in the Dog.

TABLE 21. Results of Hematological, Biochemical and Urinalysis Studies.

Dog No. 65-094, Female Dosage: 500 ppm.	Control Periods			Compound Administration Months		
	1	2	3	1	2 2*	3
Hematology:						
Total Erythrocytes (x10 ⁶ /cmm.)	4.96	4.99	4.14	4.84	6.01	5.10
Hemoglobin, gm./100 ml.	11.6	11.6	10.6	12.4	14.9	15.1
Hematocrit, %	37	36	34	38	46	46
Sedimentation Rate, mgs./hr.	1	4	4	3	0	0
Total Leucocytes, (x10 ³ /cmm.)	18.16	17.17	16.30	13.67	12.60	13.88
Differential Count:						
Neutrophils, %	48	49	55	58	41 29	53
Seg., %	47	48	55	58	41 29	53
Non-Seg., %	1	1	0	0	0 0	0
Lymphocytes, %	48	40	37	38	56 68	45
Eosinophils, %	1	8	2	2	1 0	0
Monocytes, %	3	3	6	2	2 2	2
Basophils, %	0	0	0	0	0 0	0
Appearance of Erythrocytes	No	SH	H	SH	H	No
Plasma Biochemistry:						
Glucose, mg./100 ml.	108	114	122	114	118	113
Protein, gm./100 ml.	5.43	5.80	5.40	5.20	5.78	5.36
Albumin, gm./100 ml.	1.91	2.05	2.12	2.33	2.68	2.70
Albumin-to-Globulin Ratio	0.54	0.55	0.65	0.81	0.87	1.01
Urea Nitrogen, mg./100 ml.	10.1	11.8	10.3	10.5	10.2	10.0
Alkaline Phosphatase, units	23	21	25	15	17 18	15
Cholesterol, mg./100 ml.	128	129	126	141	181	192
Prothrombin Time, sec.	7	8	8	8	6	8
SGOT units/ml. ¹	17	19	19	20	16	17
SGPT units/ml. ²	13	11	13	14	6	14
Urinalysis:						
Volume, ml.	395	500	490	200	110	345
Color	LS-cl	LS-cl	S-cl	S-cl	S-cl	S-cl
pH	7.2	6.0	7.0	6.0	6.8	6.8
Specific Gravity	1.028	1.015	1.020	1.035	1.031	1.026
Albumin	N	N	N	N	N	N
Bilirubin	N	N	N	N	N	N
Glucose	N	N	N	N	N	N
Occult Blood	N	N	N	N	N	N
Microscopic:						
Leucocytes			1-2	1-2		3-5
Amorphous Urates		F				
Epithelial Cells			occ		F	1-3
Triple Phosphates	F		F		M	
Ammonium Urates	L			F	M	
Bacteria	L	M	M	L	L	L
Flagellates		M				
Code: S - Straw N - Negative L - Loaded * - Repeat Determinations						
LS - Light Straw No - Normal F - Few						
cl - Cloudy SH - Slight Hypochromia M - Many						
occ - Occasional						
¹ Serum Glutamic Oxalacetic Transaminase						
² Serum Glutamic Pyruvic Transaminase						

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Ninety-Day Feeding Study in the Dog.

TABLE 22. Results of Hematological, Biochemical and Urinalysis Studies.

Month	Dog No. 65-095, female Dosage: 500 ppm.	Control Periods			Compound Administration Months		
		1	1*	2	3	1	2
Hematology:							
	Total Erythrocytes (x10 ⁶ /cmm.)	5.19	4.34	4.22	5.19	6.18	5.44
	Hemoglobin, gm./100 ml.	11.6	11.9	10.4	12.4	14.9	15.0
	Hematocrit, %	35	35	34	38	45	45
	Sedimentation Rate, mm./hr.	1	1	2	0	0	0
	Total Leucocytes, (x10 ² /cmm.)	10.71	12.48	12.51	10.23	10.78	9.91
Differential Count:							
	Neutrophils, %	28	30	63	37	50	51
	Seg., %	25	30	62	37	50	49
	Non-Seg., %	3	0	1	0	0	2
	Lymphocytes, %	67	65	35	60	47	44
	Eosinophils, %	1	2	0	1	2	2
	Monocytes, %	4	3	2	2	1	3
	Basophils, %	0	0	0	0	0	0
	Appearance of Erythrocytes	No		SH	H	H	No
Plasma Biochemistry:							
	Glucose, mg./100 ml.	108	122	121	110	107	103
	Protein, gm./100 ml.	5.51	5.36	5.01	5.15	5.61	5.60
	Albumin, gm./100 ml.	1.90	2.11	1.99	2.52	2.79	3.09
	Albumin-to-Globulin Rat.	0.53	0.65	0.66	0.95	0.99	1.23
	Urea Nitrogen, mg./100 ml.	12.0	13.3	9.0	11.9	11.8	12.6
	Alkaline Phosphatase, units	16	17	14	10	14	11
	Cholesterol, mg./100 ml.	142	162	154	136	167	204
	Prothrombin Time, sec.	9	8	8	8	7	9
	SGOT units/ml. ¹	19	20	15	14	12	10
	SGPT units/ml. ²	17	22	11	16	14	15
Urinalysis:							
	Volume, ml.	180	130	180	160	130	255
	Color	S-cl	S-cl	S-cl	S-cl	S-C	S-cl
	pH	7.1	7.3	6.1	6.7	8.0 ^a	7.2
	Specific Gravity	1.044	1.016	1.036	1.025	1.022	1.026
	Albumin	N	N	N	N	N	N
	Bilirubin	N	N	N	N	N	N
	Glucose	N	N	N	N	N	N
	Occult Blood	N	N	N	N	N	N
Microscopic:							
	Leucocytes	F	1-2		1-2		
	Amorphous Urates			F			
	Epithelial Cells	2-3	occ			occ	
	Erythrocytes						occ
	Triple Phosphates	F	F	L	F	M	F
	Ammonium Urates	L	F		F	F	
	Bacteria	L	M	F	F	M	M
	Waxy Casts	4-6/LPF					

Code: S - Straw N - Negative L - Loaded a - Repeat 7.0
 cl - Cloudy No - Normal F - Few * - Repeat Determinations
 SH - Slight Hypochromia M - Many LPF - Low Powered Field
 H - Hypochromia occ - Occasional

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¹Serum Glutamic Oxalacetic Transaminase
²Serum Glutamic Pyruvic Transaminase

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Ninety-Day Feeding Study in the Dog.

TABLE 23. Results of Hematological, Biochemical and Urinalysis Studies.						
Dog No. 65-088, Male Dosage: 2500 ppm.	Control Periods			Compound Administration Months		
	1	2	3	1	2	3
<u>Hematology:</u>						
Total Erythrocytes ($\times 10^6$ /cmm.)	5.32	4.70	4.25	5.68	6.16	6.35
Hemoglobin, gm./100 ml.	12.1	11.0	10.7	12.8	15.8	15.9
Hematocrit, %	38	35	35	39	49	49
Sedimentation Rate, mm./hr.	1	1	0	0	0	0
Total Leucocytes, ($\times 10^3$ /cmm.)	16.72	17.69	12.78	12.38	13.25	12.29
<u>Differential Count:</u>						
Neutrophils, %	57	65	55	52	51	51
Seg., %	56	63	55	52	51	50
Non-Seg., %	1	2	0	0	0	1
Lymphocytes, %	42	28	39	44	40	41
Eosinophils, %	1	1	1	1	1	5
Monocytes, %	0	6	5	3	8	3
Basophils, %	0	0	0	0	0	0
Appearance of Erythrocytes	No	MH	H	MH	No	No
<u>Plasma Biochemistry:</u>						
Glucose, mg./100 ml.	128 ^a	119	108	111	104	103
Protein, gm./100 ml.	5.99	5.73	4.85	4.98	5.78	5.58
Albumin, gm./100 ml.	2.53	2.55	2.32	2.60	3.03	3.22
Albumin-to-Globulin Ratio	0.73	0.80	0.92	1.09	1.10	1.36
Urea Nitrogen, mg./100 ml.	10.1	12.5	13.5	11.4	12.8	12.0
Alkaline Phosphatase, units	14	16	14	12	17 ^b	16
Cholesterol, mg./100 ml.	109	119	100	109	185	187
Prothrombin Time, sec.	9	9	8	8	7	9
SGOT units/ml. ¹	17	18	15	14	9	12
SGPT units/ml. ²	29 ^c	31	18	19	16	19
<u>Urinalysis:</u>						
Volume, ml.	140	130	325	280	255	215
Color	S-cl	S-C	LS-cl	LS-cl	LS-cl	LS-cl
pH	6.8	7.5	6.5	6.5	6.4	6.7
Specific Gravity	1.025	1.016	1.016	1.011	1.016	1.021
Albumin	N	N	N	N	N	N
Bilirubin	N	N	N	N	N	N
Glucose	N	N	N	N	N	N
Oculta Blood	N	N	N	N	N	N
<u>Microscopic:</u>						
Leucocytes	55-65	2-3	1-2			
Amorphous Urates		F	F	F		
Epithelial Cells		occ	occ	occ		
Triple Phosphates	F	M		F	occ	
Ammonium Urates	M				M	M
Bacteria	M	F	F	M	L	L
Code: S - Straw N - Negative L - Loaded a - Repeat 139						
LS - Light Straw No - Normal F - Few b - Repeat 18						
C - Clear MH - Marked Hypochromia M - Many c - Repeat 29						
cl - Cloudy H - Hypochromia occ - Occasional						
¹ Serum Glutamic Oxalacetic Transaminase						
² Serum Glutamic Pyruvic Transaminase						

125-017

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125-0

(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 24. Results of Hematological, Biochemical and Urinalysis Studies.

Months	Control Periods			Compound Administration Months			
	1	2	3	1	2	3	
<u>Hematology:</u>							
	Dog No. 65-090, Male						
	Dosage: 2500 ppm.						
	Total Erythrocytes (x10 ¹⁰ /cmm.)	5.47	4.88	4.76	5.25	6.03	6.06
	Hemoglobin, gm./100 ml.	13.0	11.5	11.6	12.5	14.3	14.8
	Hematocrit, %	40	36	36	39	43	45
	Sedimentation Rate, mm./hr.	1	1	0	0	1	0
	Total Leucocytes, (x10 ³ /cmm.)	15.76	15.72	13.47	11.36	14.41	12.60
<u>Differential Count:</u>							
	Neutrophils, %	59	73	61	55	52	53
	Seg., %	59	72	60	54	52	52
	Non-Seg., %	0	1	1	1	0	1
	Lymphocytes, %	34	25	34	42	42	40
	Eosinophils, %	3	0	0	2	5	1
	Monocytes, %	3	2	5	1	1	6
	Basophils, %	1	0	0	0	0	0
	Appearance of Erythrocytes	No	MH	SH	H	No	No
<u>Plasma Biochemistry:</u>							
	Glucose, mg./100 ml.	138 ^a	133	132	124 ^b	121 ^c	120
	Protein, gm./100 ml.	5.63	5.38	4.80	4.90	5.86	5.60
	Albumin, gm./100 ml.	1.93	1.98	2.05	2.20	2.55	2.58
	Albumin-to-Globulin Ratio	0.52	0.58	0.75	0.81	0.78	0.86
	Urea Nitrogen, mg./100 ml.	15.0	15.8	12.9	13.5	13.4	8.7
	Alkaline Phosphatase, units	21	23	24	18	28 ^d	33 ^e
	Cholesterol, mg./100 ml.	163	146	140	195 ^f	208	284
	Prothrombin Time, sec.	7	7	7	7	6	7
	SGOT units/ml. ¹	19	19	18	17	13	15
	SGPT units/ml. ²	16	20	14	16	5	20
<u>Urinalysis:</u>							
	Volume, ml.	155	135	205	120	115	360
	Color	S-cl	S-C	S-cl	S-cl	S-cl	S-cl
	pH	6.8	7.2	7.1	6.8	6.2	7.0
	Specific Gravity	1.036	1.034	1.045	1.033	1.029	1.028
	Albumin	N	F	N	N	N	N
	Bilirubin	N	F	N	N	N	N
	Glucose	N	N	N	N	N	N
	Occult Blood	N	"	H	N	N	N
<u>Microscopic:</u>							
	Leucocytes	F	1-2	2-4	1-2		3-5
	Amorphous Urates		-		F		
	Epithelial Cells	F	occ	occ	3-4		
	Erythrocytes						1-3
	Triple Phosphates	M	M	M	M	M	occ
	Calcium Oxalate	F					F
	Ammonium Urates	M					
	Bacteria	M	F	M	M	M	M

Code: S - Straw N - Negative L - Loaded a - Repeat 146 e - Repeat 122
 C - Clear - Normal F - Few b - Repeat 126 f - Repeat 200
 cl - Cloudy MH - Marked Hypochromia M - Many e - Repeat 118 g - Repeat 221
 SH - Slight Hypochromia occ - Occasional d - Repeat 23
 H - Hypochromia
¹Serum Glutamic Oxalacetic Transaminase
²Serum Glutamic Pyruvic Transaminase 000079

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(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 45. Results of Hematological, Biochemical and Urinalysis Studies.

Dog No. 65-096, Female Dosage: 2500 ppm.	Control Periods			Compound Administration Months		
	1	2	3	1	2	3
<u>Hematology:</u>						
Total Erythrocytes ($\times 10^6$ /cmm.)	5.58	4.55	3.98	5.26	6.03	5.94
Hemoglobin, gm./100 ml.	12.2	11.3	10.5	12.3	12.8	13.1
Hematocrit, %	39	34	34	39	40	41
Sedimentation Rate, mm./hr.	1	1	0	0	0	0
Total Leucocytes, ($\times 10^3$ /cmm.)	11.15	11.96	10.40	12.51	11.82	12.66
<u>Differential Count:</u>						
Neutrophils, %	55	68	63	43	49	51
Seg., %	54	67	63	43	49	48
Non-Seg., %	1	1	0	0	0	3
Lymphocytes, %	43	27	36	55	43	46
Eosinophils, %	0	2	1	0	0	2
Monocytes, %	2	3	0	2	8	1
Basophils, %	0	0	0	0	0	0
Appearance of Erythrocytes	No	H	H	H	H	No
<u>Plasma Biochemistry:</u>						
Glucose, mg./100 ml.	109	130 ^a	121	126 ^b	113	118
Protein, gm./100 ml.	5.78	5.68	4.95	5.39	6.31	5.90
Albumin, gm./100 ml.	2.12	2.10	2.32	2.69	2.95	3.13
Albumin-to-Globulin Ratio	0.58	0.59	0.88	1.00	0.88	1.13
Urea Nitrogen, mg./100 ml.	13.0 ^c	13.5	11.3	12.4	12.0	10.7
Alkaline Phosphatase, units	22	22	22	14	19 ^c	18
Cholesterol, mg./100 ml.	167	158	131	215 ^d	269 ^e	307 ^f
Prothrombin Time, sec.	7	7	8	7	6	8
SCOT units/r.l. ¹	19	20	20	19	15	20
SGPT units/ml. ²	14	11	16	14	11	15
<u>Urinalysis:</u>						
Volume, ml.	110	205	150	125	200	135
Color	S-cl	LS-C	S-cl	S-C	S-cl	S-cl
pH	6.5	7.1	7.1	6.8	6.8	6.8
Specific Gravity	1.057	1.025	1.051	1.048	1.020	1.045
Albumin	N	N	N	N	N	N
Bilirubin	N	N	N	N	N	N
Glucose	N	N	N	N	N	N
Occult Blood	N	N	N	N	N	N
<u>Microscopic:</u>						
Leucocytes	F	6-8		25-30	3-4	occ
Epithelial Cells	F	1-3	1-2	3-4	occ	1-3
Erythrocytes						8-10
Triple Phosphates	F	M	M	F	F	
Ammonium Urates	M				M	
Bacteria	M	F	M	F	M	F
Waxy Casts	2-3/LPF					
Code:	S - Straw	N - Negative	L - Loaded	r - Repeat 141	d - Repeat 210	
	LS - Light Straw	No - Normal	F - Few	h - Repeat 121	e - Repeat 251	
	C - Clear	H - Hypochromia	M - Many	c - Repeat 19	f - Repeat 300	
	cl - Cloudy		occ - Occasional			
			1 - Serum Glutamic Oxalacetic Transaminase			
			2 - Serum Glutamic Pyruvic Transaminase			
			LPF - Low Powered Field			

000380

(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 26. Results of Hematological, Biochemical and Urinalysis Studies.

Dog No. 65-097, Male Dosage: 2500 ppm.	Control Periods			Compound Administration Months		
	1	2	3	1	2	3
<u>Hematology:</u>						
Total Erythrocytes ($\times 10^6/\text{cmm.}$)	5.26	4.49	4.12	4.94	5.70	5.71
Hemoglobin, gm./100 ml.	12.1	10.8	10.2	12.1	13.7	14.5
Hematocrit, %	36	33	33	36	40	46
Sedimentation Rate, mm./hr.	1	6	6	0	0	0
Total Leucocytes, ($\times 10^3/\text{cmm.}$)	10.7	10.44	11.24	11.41	10.99	10.95
<u>Differential Count:</u>						
Neutrophils, %	48	57	49	52	53	52
Seg., %	47	57	49	52	53	52
Non-Seg., %	1	0	0	0	0	0
Lymphocytes, %	45	40	50	45	44	43
Eosinophils, %	5	2	1	1	1	2
Monocytes, %	2	1	0	2	2	3
Basophils, %	0	0	0	0	0	0
Appearance of Erythrocytes	No	MH	H	SH	H	No
<u>Plasma Biochemistry:</u>						
Glucose, mg./100 ml.	133 ^a	122	112	121	110	100
Protein, gm./100 ml.	5.58	5.63	5.38	5.53	5.19	5.90
Albumin, gm./100 ml.	2.08	2.05	2.04	2.53	2.87	3.15
Albumin-to-Globulin Ratio	0.59	0.57	0.61	0.85	1.26	1.14
Urea Nitrogen, mg./100 ml.	10.5	13.1	12.4	15.5	13.8	15.4
Alkaline Phosphatase, units	15	15	14	10	16 ^b	15
Cholesterol, mg./100 ml.	129	133	147	175	233 ^c	274
Prothrombin Time, sec.	9	8	9	8	7	8
SGOT units/ml. ¹	16	18	17	16	13	12
SGPT units/ml. ²	17	19	18	11	12	14
<u>Urinalysis:</u>						
Volume, ml.	105	230	380	325	180	390
Color	S-C	LS-cl	LS-cl	LS-cl	S-cl	S-C
pH	7.8	7.3	7.0	6.9	6.6	6.9
Specific Gravity	1.025	1.018	1.023	1.022	1.027	1.022
Albumin	N	N	N	N	N	N
Bilirubin	N	N	N	N	N	N
Glucose	N	N	N	N	N	N
Occult Blood	N	N	N	N	N	N
<u>Microscopic:</u>						
Leucocytes	6-8		occ			
Amorphous Urates				L		
Epithelial Cells	F			1-2	occ	2-5
Triple Phosphates	F	F	F	F	M	F
Calcium Oxalate		F				
Ammonium Urates	M	F	F		F	
Bacteria	F	F	M	M	M	F

Code: S - Straw N - Negative L - Loaded a - Repeat 138
 LS - Light Straw no - Normal F - Few b - Repeat 17
 C - Clear MH - Marked Hypochromia M - Many c - Repeat 214
 cl - Cloudy SH - Slight Hypochromia-occ - Occasional
 H - Hypochromia

¹Serum Glutamic Oxalacetic Transaminase
²Serum Glutamic Pyruvic Transaminase

125-017

000081

(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 27. Results of Hematological, Biochemical and Urinalysis Studies.

Dog No. 65-098, Female Dosage: 2500 ppm.	Control Periods			Compound Administration Months		
	1 1*	2	3	1	2 2*	3
<u>Hematology:</u>						
Total Erythrocytes ($\times 10^6$ /cmm.)	5.20	4.86	4.49	5.27	6.36	5.70
Hemoglobin, gm./100 ml.	12.6	12.1	11.3	13.7	15.1	15.4
Hematocrit, %	40	37	38	43	45	47
Sedimentation Rate, mm./hr.	0	0	0	0	0	0
Total Leucocytes ($\times 10^3$ /cmm.)	15.10	13.91	15.31	13.41	11.45	12.61
<u>Differential Count:</u>						
Neutrophils, %	39 38	43	72	58	40 59	47
Seg., %	39 38	42	72	58	40 58	45
Non-Seg., %	0 0	1	0	0	0 1	2
Lymphocytes, %	52 53	40	25	41	49 36	44
Eosinophils, %	3 3	2	1	0	2 1	3
Monocytes, %	6 6	5	2	1	9 4	6
Basophils, %	0 0	0	0	0	0 0	0
Appearance of Erythrocytes	No	H	No	No	No No	No
<u>Plasma Biochemistry:</u>						
Glucose, mg./100 ml.	106	112	112	117	112	111
Protein, gm./100 ml.	5.82	5.63	4.95	5.15	5.70	5.70
Albumin, gm./100 ml.	2.40	2.24	2.38	2.60	2.94	3.09
Albumin-to-Globulin Ratio	0.70	0.66	0.93	1.02	1.06	1.18
Urea Nitrogen, mg./100 ml.	14.8	14.3	11.3	11.5	11.7	12.3
Alkaline Phosphatase, units	23	20	25	20 ^a	24 ^a	24
Cholesterol, mg./100 ml.	133	117	120	198 ^b	244 ^c	249
Prothrombin Time, sec.	8	8	8	8	6	8
SGOT units/ml. ¹	19	19	24	19	12	7
SGPT units/ml. ²	21	19	13	20	23 ^d	16
<u>Urinalysis:</u>						
Volume, ml.	80	155	205	135	120	255
Color	S-cl	S-cl	S-cl	S-cl	S-cl	S-C
pH	7.0	7.0	7.1	7.1	8.0 ^e	7.5
Specific Gravity	1.060	1.019	1.032	1.031	1.024	1.039
Bilirubin	N	N	N	N	N	N
Glucose	N	N	N	N	N	N
Occult Blood	N	N	N	N	N	N
<u>Microscopic:</u>						
Leucocytes	F	6-8	1-2	1-2	3-4	
Epithelial Cells	F	1-2		2-3	occ	
Erythrocytes						ccc
Triple Phosphates	F	M	F	F	M	
Ammonium urates	M			F	F	F
Bacteria	M	F	F	F	L	F

Code: S - Straw N - Negative L - Loaded a - Repeat 22 e - Repeat 6.5
 C - Clear No - Normal F - Few b - Repeat 20
 cl - Cloudy H - Hypochromia M - Many c - Repeat 21
 occ - Occasional d - Repeat 28

¹Serum Glutamic Oxalacetic Transaminase²Serum Glutamic Pyruvic Transaminase

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000082

(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 28. Results of Hematological, Biochemical and Urinalysis Studies.

Dog No. 65-099, Male Dosage: 2500 ppm.	Control Periods			Compound Administration Months		
	1	2 2*	3	1	2	3
Hematology:						
Total Erythrocytes (x10 ⁶ /cmm.)	5.55	5.15	4.41	5.82	6.40	6.19
Hemoglobin, gm./100 ml.	12.8	12.1	11.3	13.7	14.9	15.3
Hematocrit, %	40	36	36	41	45	45
Sedimentation Rate, mm./hr.	1	0	0	0	0	0
Total Leucocytes, (x10 ³ /cmm.)	15.36	13.16	11.67	10.62	13.74	11.71
Differential Count:						
Neutrophils, %	60	72 64	60	59	68	57
Seg., %	58	68 64	60	57	68	54
Non-Seg., %	2	4 0	0	2	0	3
Lymphocytes, %	32	16 22	33	36	26	35
Eosinophils, %	5	8 11	3	2	0	5
Monocytes, %	3	4 3	4	3	6	3
Basophils, %	0	0 0	0	0	0	0
Appearance of Erythrocytes	No	MH	No	H	H	No
Plasma Biochemistry:						
Glucose, mg./100 ml.	119	134 ^a	120	128 ^b	121 ^c	118
Protein, gm./100 ml.	5.67	5.24	4.60	5.05	5.82	5.21
Albumin, gm./100 ml.	2.23	1.90	2.04	2.40	2.50	2.70
Albumin-to-Globulin Ratio	0.65	0.57	0.80	0.91	0.75	1.07
Urea Nitrogen, mg./100 ml.	13.0	12.6	10.5	9.8	8.2	11.5
Alkaline Phosphatase, units	17	20	17	15	28 ^d	33 ^e
Cholesterol, mg./100 ml.	182	150	120	170 ^f	2338	270
Prothrombin Time, sec.	7	7	8	8	6	8
SGOT units/ml. ¹	23	19	18	12	11	11
SGPT units/ml. ²	16	15	22	17	13	18
Urinalysis:						
Volume, ml.	105	145	80	150	200	210
Color	S-C	LS-C	DS-cl	S-cl	S-cl	S-cl
pH	6.8	7.0	6.1	6.9	7.3	7.4
Specific Gravity	1.057	1.017	1.060	1.028	1.025	1.036
Albumin	N	N	N	N	N	N
Bilirubin	N	N	N	N	N	N
Glucose	N	N	N	N	N	N
Occult Blood	N	N	N	N	N	N
Microscopic:						
Leucocytes	F					
Amorphous Urates		F	M	F		
Epithelial Cells	F	occ		1-2		occ
Triple Phosphates	F		F	F	M	M
Ammonium Urates	M	F		F	M	
Bacteria	M	F	F	M	L	F
Code: S - Straw N - Negative L - Loaded a - Repeat 125 e - Repeat 30						
LS - Light Straw No - Normal F - Few b - Repeat 126 f - Repeat 179						
DS - Dark Straw MH - Marked Hypochromia M - Many c - Repeat 114 g - Repeat 209						
C - Clear H - Hypochromia occ - Occasional d - Repeat 24						
cl - Cloudy						
¹ Serum Glutamic Oxalacetic Transaminase						
² Serum Glutamic Pyruvic Transaminase						

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000083

(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 28-A. Total Cholesterol Values, Mg. per 100 ml. Plasma.

Dietary Level	Sex	Control Period			Compound Admin. Months		
		1	2	3	1	2	3
<u>Control:</u>							
65-038	F	196	212	211	200	178	184
65-070	M	176	186	140	175	195	198
65-081	F	161	162	153	149	175	167
65-083	M	116	138	122	123	142	157
65-086	M	196	174	142	181	203	200
65-093	F	144	128	147	132	115	124
<u>100 ppm.:</u>							
65-072	M	132	139	120	118	158	163
65-074	M	131	144	147	123	158	172
65-076	M	159	163	132	163	181	203
65-077	F	155	153	188	142	182	169
65-085	F	159	132	148	128	141	161
65-091	F	160	138	149	143	155	149
<u>500 ppm.:</u>							
65-078	M	129	169	132	154	180	203
65-079	M	161	149	147	135	166	169
65-087	M	159	171	125	125	215	214
65-092	F	140	122	120	121	191	160
65-094	F	128	129	126	141	181	192
65-095	F	142	162	154	136	167	204
<u>2500 ppm.:</u>							
65-088	M	109	119	100	109	185	187
65-090	M	163	146	140	195	208	284
65-036	F	167	158	131	215	269	307
65-097	F	129	133	147	175	233	274
65-098	F	133	117	120	198	244	249
65-099	M	182	117	120	170	233	270

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000084

(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 29. Necropsy Observations.

Animal Number	Sex	Organ	Comment
<u>Control:</u>			
65-070	M	small intestine ileocolic junction cecum, colon	Few hookworms present. Mild mucosal congestion. Few 2 to 3 mm. hemorrhages.
65-083	M	small intestine	Ascarid.
65-086	M	ileocolic junction cecum urinary bladder heart	Mild mucosal congestion. Several 2 to 3 mm. mucosal hemorrhages. Few petechial hemorrhages. Tricuspid valve, 2 mm. hematoma.
65-038	F	cecum	Few petechia in the mucosa.
65-081	F	ileocolic junction colon	Mild mucosal congestion. Several mucosal petechiae.
65-093	F	small intestine	Few petechial hemorrhages at the gastroduodenal junction, fecal material was present in the stomach.
<u>100 ppm.:</u>			
65-072	M	ileocolic junction urinary bladder	Mucosal congestion. Petechial hemorrhages at the neck.
65-074	M	small intestine ileocolic junction	Few hookworms present. Mild mucosal congestion.
65-076	M	urinary bladder	Area of hyperemia at neck.
65-077	F	small intestine	Areas of hyperemia at ileocolic orifice.
65-085	F	small intestine cecum, colon	3 mm. raised firm area in the duodenum; terminal portion of the ileum had mild mucosal hemorrhage at the ileocolic junction. Mild mucosal hemorrhage.
65-091	F	stomach ileocolic junction cecum, colon	Fecal material present in the stomach. Mild mucosal congestion. Several 2 mm. areas of hemorrhage in the mucosa.

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000085

(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 29, Continued. Necropsy Observations.

Animal Number	Sex	Organ	Comment
<u>1000 ppm.:</u>			
65-078	M	duodenum	Few petechial hemorrhages at pylorus.
		small intestine	Moderate mucosal congestion throughout the anterior half.
		ileocolic junction	Mild mucosal congestion.
65-079	M	small intestine	Several 1 to 2 mm. hemorrhages at the gastroduodenal junction.
		ileocolic junction	Mild mucosal congestion.
65-087	M	urinary bladder	Few petechial hemorrhages at the neck.
65-092	F	urinary bladder	Few petechial hemorrhages at the neck.
65-094	F	stomach	Many scattered gray raised areas less than 1 mm. in diameter in pyloric region.
		cecum	Few 2 mm. hemorrhages scattered in the mucosa.
65-095	F	stomach	Few petechial hemorrhages in the pyloric region.
		small intestine	Petechial hemorrhages at the gastroduodenal junction, several ascarids.
		ileocolic junction	Mild mucosal congestion.
		cecum	Few mucosal petechiae.
<u>5000 ppm.:</u>			
65-088	M	small intestine	Few mucosal petechiae scattered throughout the middle third of the intestine.
65-090	M	small intestine	Few 1 mm. hemorrhages at the gastroduodenal junction.
65-099	M	small intestine	Ascarid
		cecum	Few 1 to 2 mm. mucosal hemorrhages.
65-096	F	cecum	Several 2 mm. mucosal hemorrhages.
65-097	F	cecum	Several mucosal petechiae.
		small intestine	Several mucosal petechiae at the terminal portion of the ileum.
		urinary bladder	Several circumscribed dark areas with light centers approximately 1 mm. in diameter scattered throughout the mucosa.

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000086

(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 29, Continued. Necropsy Observations.

Animal Number	Sex	Organ	Comment
5000 ppm., Cont'd.:			
65-098	F	heart	10 mm. white streak in the left ventricular wall.

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000087

(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 30. Actual (Grams) and Relative (% Body Weight) Organ Weights.

Group & Animal Number	Sex	Terminal Body Wt. Kg.	Spleen		Liver		Adrenals		Kidneys		Ovaries/ Testes	
			Wt.	%	Wt.	%	Wt.	%	Wt.	%	Wt.	%
<u>Control:</u>												
65-070	M	13.0	29.12	0.224	310.87	2.391	0.90	0.007	63.99	0.492	23.08	0.178
65-083	M	8.5	30.70	0.361	242.42	2.852	0.98	0.012	43.25	0.509	14.22	0.167
65-086	M	9.2	28.58	0.311	248.83	2.705	0.98	0.011	49.53	0.538	18.90	0.205
65-038	F	8.2	19.98	0.244	198.81	2.425	1.40	0.017	38.58	0.470	0.67	0.008
65-081	F	9.2	24.32	0.264	250.50	2.723	1.06	0.012	39.62	0.431	0.74	0.006
65-093	F	6.1	13.59	0.223	151.11	2.477	0.78	0.013	29.28	0.480	0.41	0.007
<u>100 ppm.:</u>												
65-072	M	8.7	25.87	0.297	238.89	2.746	0.82	0.009	55.60	0.639	19.78	0.227
65-074	M	10.8	32.31	0.299	285.70	2.645	1.23	0.011	58.12	0.538	13.86	0.128
65-076	M	11.9	25.39	0.213	325.52	2.735	1.02	0.009	50.68	0.426	17.71	0.149
65-077	F	9.4	29.18	0.310	241.79	2.572	1.11	0.012	43.93	0.467	0.55	0.006
65-085	F	7.2	25.31	0.352	177.56	2.466	1.21	0.017	33.08	0.459	0.62	0.009
65-091	F	9.9	23.40	0.236	210.70	2.128	1.16	0.012	52.61	0.531	0.58	0.006
<u>1000 ppm.:</u>												
65-078	M	9.9	23.70	0.239	281.62	2.845	1.00	0.010	61.60	0.622	14.95	0.151
65-079	M	6.9	18.11	0.262	210.71	3.054	0.84	0.012	44.15	0.640	10.10	0.146
65-087	M	13.5	41.42	0.307	443.25	3.283	1.98	0.015	71.48	0.529	21.78	0.161
65-092	F	6.5	18.18	0.280	209.89	3.229	0.98	0.015	29.50	0.454	0.66	0.010
65-094	F	11.0	28.50	0.259	320.71	2.916	1.12	0.010	59.81	0.544	0.71	0.006
65-095	F	7.9	18.73	0.237	228.27	2.889	1.18	0.015	38.31	0.491	0.90	0.011
<u>5000 ppm.:</u>												
65-088	M	6.7	19.79	0.295	301.90	4.506	0.84	0.013	34.61	0.517	9.71	0.145
65-090	M	10.6	19.67	0.186	479.03	4.519	1.41	0.013	55.24	0.521	19.00	0.179
65-099	M	8.4	17.88	0.213	396.70	4.723	0.93	0.011	46.71	0.556	12.76	0.152
65-096	F	8.8	21.99	0.250	339.91	3.863	1.02	0.012	52.03	0.591	0.60	0.007
65-097	F	10.0	24.09	0.241	426.29	4.263	1.00	0.010	53.12	0.531	0.72	0.007
65-098	F	7.2	16.50	0.229	327.31	4.546	0.60	0.008	39.72	0.552	0.54	0.008

Thymus		Heart		Lung		Thyroid		Brain		Pituitary	
Wt.	%	Wt.	%	Wt.	%	Wt.	%	Wt.	%	Wt.	%
38.20	0.294	115.72	0.890	115.40	0.888	1.37	0.011	84.27	0.648	0.069	0.0005
16.13	0.190	62.81	0.739	85.70	1.008	0.59	0.007	78.86	0.928	0.059	0.0007
22.71	0.247	76.21	0.828	90.44	0.983	0.93	0.010	82.02	0.892	0.072	0.0008
10.08	0.123	68.12	0.831	67.13	0.819	0.79	0.010	69.42	0.847	0.049	0.0006
15.53	0.169	77.50	0.842	74.62	0.811	0.73	0.008	83.24	0.905	0.065	0.0007
16.61	0.272	53.34	0.874	60.60	0.993	0.52	0.009	70.79	1.160	0.039	0.0006
21.59	0.248	80.53	0.926	87.30	1.003	0.72	0.008	78.35	0.901	0.072	0.0008
20.81	0.193	79.67	0.738	102.91	0.953	0.90	0.008	77.45	0.717	0.071	0.0007
21.01	0.177	84.59	0.711	102.98	0.865	0.82	0.007	92.08	0.774	0.071	0.0006
21.13	0.225	76.89	0.818	91.10	0.969	0.74	0.008	86.68	0.922	0.066	0.0007
18.00	0.250	55.00	0.764	72.12	1.002	0.86	0.012	68.21	0.947	0.064	0.0009
16.51	0.167	87.09	0.880	90.40	0.913	0.72	0.007	73.05	0.738	0.078	0.0008
20.29	0.205	72.22	0.729	75.96	0.767	0.73	0.007	37.77	0.887	0.060	0.0006
19.77	0.287	59.67	0.865	65.18	0.945	-	-	78.20	1.133	0.091	0.0013
37.81	0.280	89.63	0.664	119.10	0.882	1.35	0.010	84.98	0.629	0.031	0.0002
13.69	0.211	47.00	0.723	64.39	0.991	0.42	0.006	67.48	1.038	0.055	0.0008
20.10	0.183	81.71	0.743	95.25	0.866	0.88	0.008	78.13	0.710	0.086	0.0008
14.75	0.187	63.85	0.808	76.72	0.971	0.75	0.009	63.71	0.806	0.07	0.0009
16.55	0.247	44.20	0.660	60.50	0.903	0.53	0.008	70.70	1.055	0.052	0.0008
24.43	0.230	64.29	0.607	73.78	0.696	1.32	0.012	79.51	0.750	0.076	0.0007
24.51	0.292	58.48	0.696	70.01	0.833	0.58	0.007	80.91	0.963	0.059	0.0007
19.39	0.220	62.55	0.711	63.91	0.726	0.62	0.007	78.35	0.890	0.072	0.0008
24.90	0.249	75.79	0.758	69.43	0.694	0.83	0.008	73.31	0.753	0.077	0.0008
12.53	0.174	51.61	0.717	60.50	0.840	0.97	0.013	68.41	0.950	0.064	0.0009

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(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 31. Histopathologic Observations.

Animal No and Group	Sex	Tissue	Comment
<u>Control:</u>			
65-070	M	all tissues	No lesion.
65-083	M	all tissues	No lesion.
65-086	M	all tissues	No lesion.
65-038	F	skin	Folliculitis with lymphocyte and plasma cell infiltrate in corium.
		kidney	Moderate subacute pyelonephritis.
65-081	F	all tissues	No lesions.
65-093	F	kidney	Moderate subacute pyelonephritis.
<u>100 ppm. (Liver Only):</u>			
65-072	M		No lesion.
65-074	M		No lesion.
65-076	M		No lesion.
65-077	F		No lesion.
65-085	F		No lesion.
65-091	F		No lesion.
<u>1000 ppm. (Liver Only):</u>			
65-078	M		No lesion.
65-079	M		No lesion.
65-087	M		No lesion.
65-092	F		No lesion.
65-094	F		No lesion.
65-095	F		No lesion.

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(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 31, Continued. Histopathologic Observations.

Animal No. and Group	Sex	Issue	Comment
<u>5000 ppm.:</u>			
65-088	M	liver	Hepatocytes appeared hypertrophied as compared to controls with less coarse granularity to their cytoplasm.
65-090	M	kidney liver	Moderate subacute pyelonephritis. Hepatocytes slightly hypertrophied with cytoplasm less coarsely granular than control.
65-099	M	liver	Hepatocytes slightly hypertrophied with less coarse granularity of cytoplasm than control.
65-096	F	all tissues	No lesion.
65-097	F	liver	Slight portal lymphocytic infiltrate.
65-098	F	heart	Small areas of calcification of myocardial fibers.
		liver	Hepatocytes hypertrophied as compared to controls with less coarse granularity of cytoplasm.

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(b) (4)

Ninety-Day Feeding Study in the Dog.

BLE 32. Summary of Incidence of Histopathologic Lesions.

Tissue and Lesion	Control		100 ppm.		1000 ppm.		5000 ppm.	
	Male	Female	Male	Female	Male	Female	Male	Female
brain - no lesion	3/3	3/3					3/3	3/3
spinal cord - no lesion	3/3	3/3					3/3	3/3
peripheral nerve - no lesion	3/3	3/3					3/3	3/3
eye - no lesion	3/3	3/3					3/3	3/3
pituitary - no lesion	3/3	3/3					3/3	3/3
thyroid - no lesion	3/3	3/3					3/3	3/3
parathyroid - no lesion	1/1	2/2					2/2	1/1
adrenal - no lesion	3/3	3/3					3/3	3/3
trachea - no lesion	3/3	3/3					3/3	3/3
lung - no lesion	3/3	3/3					3/3	3/3
heart - no lesion	3/3	3/3					3/3	2/3
- myocardial calcification								1/3
aorta - no lesion	3/3	2/2					3/3	3/3
spleen - no lesion	3/3	3/3					3/3	3/3
lymph node - no lesion	3/3	3/3					2/2	3/3
thymus - no lesion	3/3	3/3					3/3	3/3
bone marrow - no lesion	3/3	3/3					3/3	3/3
salivary gland - no lesion	3/3	3/3					3/3	3/3
esophagus - no lesion	3/3	3/3					3/3	3/3
stomach - no lesion	3/3	3/3					3/3	3/3
small intestine - no lesion	3/3	3/3					3/3	3/3
large intestine - no lesion	3/3	3/3					3/3	3/3
pancreas - no lesion	3/3	3/3					2/2	3/3

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(b) (4)

Ninety-Day Feeding Study in the Dog.

TABLE 32, Continued. Summary of Incidence of Histopathologic Lesions.

Tissue and Lesion	Control		100 ppm.		1000 ppm.		5000 ppm.	
	Male	Female	Male	Female	Male	Female	Male	Female
liver - no lesion	3/3		3/3	3/3	3/3	3/3		1/3
- hepatocyte hypertrophy							3/3	1/3
- portal infiltrate								1/3
gall bladder - no lesion	3/3	3/3					3/3	3/3
kidney - no lesion	3/3	3/3					2/3	3/3
- subacute pyelonephritis		2/3					1/3	
urinary bladder - no lesion	3/3	3/3					3/3	3/2
testis or ovary - no lesion	3/3	3/3					3/3	3/3
prostate or uterus - no lesion	3/3	3/3					3/3	3/3
skeletal muscle - no lesion	3/3	3/3					3/3	2/2
skin - no lesion	3/3	2/3					3/3	2/3
- folliculitis		1/3						
bone - no lesion	3	3/3					3/3	3/3

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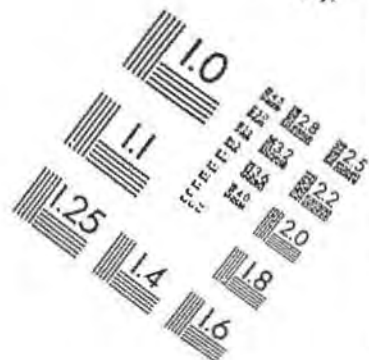
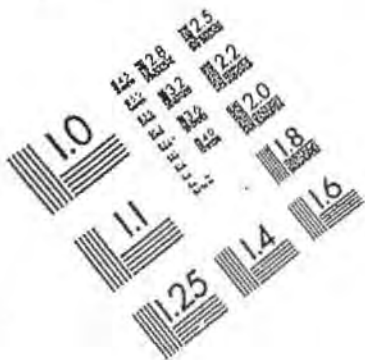
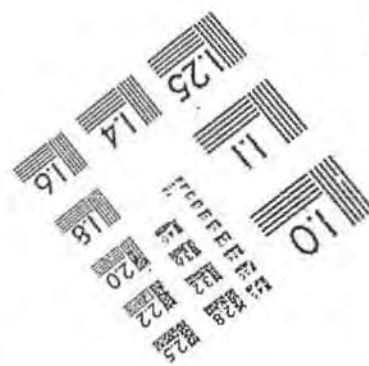
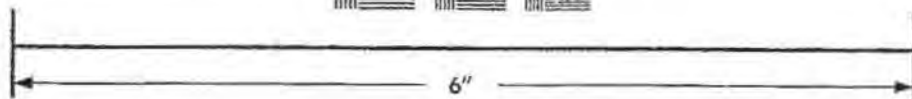
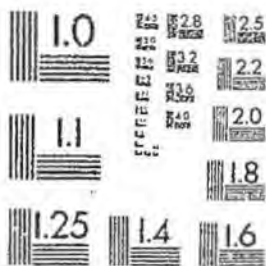


IMAGE EVALUATION
TEST TARGET (MT-3)



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International Research and Development Corporation

SPONSOR: E. I. duPont de Nemours and Company

MATERIAL: (b) (4)

SUBJECT: Ninety-Day Feeding Study in the Rat.



Francis X. Wazeter, Ph.D.
Director of Research
International Research and
Development Corporation

Collaborators:

R. H. Buller, Ph.D., Director of Pharmacology
R. G. Geil, D.V.M., Director of Pathology

Date: November 30, 1965

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I. SYNOPSIS

In a 90-day feeding study, male and female albino rats were fed diets containing [REDACTED] at levels of 100, 500 or 2500 ppm. After 35 days of continuous feeding, the 500 and 2500 ppm. dietary levels were increased to 1000 and 5000 ppm., respectively for the remainder of the study. After the prescribed 90-day period of compound administration, representative animals were placed on a withdrawal study.

All rats appeared essentially normal with respect to behavior and appearance throughout the study.

No adverse effect on body weight gain was found at any dietary level employed in this study, both in the active compound administration phase and in the withdrawal period.

Average total weekly food consumption measured in grams/rat/week in those groups fed 100 and 500 - 1000 ppm. of (b) (4) in the diet compared favorably with the control rats throughout the study. At the 2500 - 5000 ppm. dietary level, food consumption of the male rats ranged from 1.1 to 8.7 per cent less than control male rats, and food consumption of the female rats ranged from 5.2 to 16.4 per cent less than the female control rats. These differences were first noted in the 8th week for males and in the 4th week for females and continued throughout the treatment period.

No meaningful differences in food consumption were reflected by the treated groups of rats in comparison to the control group on the basis of grams of food consumed per day per kilogram of body weight.

No compound-related hematologic or biochemical changes were found

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at the 100 and 500 - 1000 ppm. dietary levels of (b) (4). However, slightly decreased values for erythrocyte counts, hematocrits and hemoglobin concentrations were found for males and females at the 2500 - 5000 ppm. level, particularly at the terminal (90-day) clinicopathology examination. Urinalyses were normal at all times.

Compound-related changes observed at the 90-day necropsy examination consisted of increased liver and kidney weight at the 1000 and 5000 ppm. dosage levels and pale yellowish livers in some male rats from the 500 - 1000 and 2500 - 5000 ppm. dosage levels. In histologic section, only livers from the 2500 - 5000 ppm. dosage level showed any change and this consisted of a slight hypertrophy of centrilobular hepatocytes. The increase in liver and kidney weights and centrilobular hepatocyte hypertrophy persisted with diminished magnitude through 21 days of compound withdrawal. Similar organ weight and histologic changes were observed at the 30 and 60-day interim sacrifices.

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II. COMPOUND

The test compound was received from E. I. duPont de Nemours and Company, Wilmington, Delaware, on June 19, 1965. It was a brown amorphous solid in containers bearing the label "MPD-3110A - (b) (4) Active Ingredient, Haskell No. 4212."

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III. CLINICAL STUDIES:

A. METHODS:

1. General Procedure:

Eighty male (weighing from 45 to 64 grams) and eighty female (weighing from 47 to 63 grams) albino rats of the Charles River strain were used for this study.

The rats were housed individually in cages suspended above the droppings in an air-conditioned room throughout the study and were fed a diet of Purina Laboratory Chow for rats ad libitum. Water also was available at all times.

The animals were divided into one control group and three treated groups of 20 male and 20 female rats each.

The rats in each sex group were selected so that the average body weight of each group was similar to that of the other groups of the same sex.

2. Compound Administration:

(b) (4) was incorporated into the standard powdered laboratory diet of Purina Laboratory Chow and offered to the treated groups of rats ad libitum. The test diet was freshly prepared each week and the compound-in-diet levels mixed so that the rats received (b) (4) at dietary levels of 100, 500, or 2500 ppm. In the sixth week of compound administration those groups receiving 500 or 2500 ppm. were increased in concentration to dietary levels of 1000 or 5000 ppm., respectively. Those animals receiving 100 ppm. of (b) (4) in the diet continued to receive this level throughout the 13-week study period.

The control groups of rats received the powdered diet of Purina Laboratory Chow, but without (b) (4)

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Following 13 weeks of compound administration rats in all groups were sacrificed and subjected to necropsy examination with the exception of certain selected animals from the control group and from the treated groups at the 1000 and 5000 ppm. dietary levels which were continued on study in a compound withdrawal phase. The withdrawal phase of this study will be reported in its entirety in a subsequent and separate report.

3. Observations:

The control and test animals were observed daily for mortality, alteration in general appearance and behavior, and signs of pharmacodynamic and/or toxic effects.

Body weights, food consumption, and food efficiency values were recorded for each rat weekly throughout the study.

4. Laboratory Tests:

a. Hematology:

Hematologic examination consisted of erythrocyte counts, total¹ and differential leucocyte counts, hematocrits², and hemoglobin³ concentrations. These studies were performed individually on 6 male and 6 female rats randomly selected in the control and each test group during the control period and again at 30, 60, and 90 days.

b. Urinalysis:

Urine samples were obtained from the same animals at the same time intervals used to obtain blood for hematology. Urinalysis

¹ Coulter Particle Size Counter, Model A., Coulter Electronics, 590 W. 20th Street, Hialeah, Florida.

² Miller, S., Microcapillary Method, Textbook of Clinical Pathology, 1960, Williams and Wilkins Company, Philadelphia, Pa., p. 43.

³ Miller, S., Cyanmethemoglobin Method, Textbook of Clinical Pathology, 1960, Williams and Wilkins Company, Philadelphia, Pa., p. 35.

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consisted of qualitative tests for glucose,^{4,5,6} bilirubin⁷, occult blood,^{8,9,10} and albumin,^{4,11,12,13} measurements of volume, pH¹⁴ and specific gravity, and microscopic examination of the urinary sediments.

c. Biochemistry:

Biochemical examinations were conducted at the same intervals as for hematology. Serum transaminase (SGOT and SGPT)¹⁵ and plasma alkaline phosphatase determinations¹⁶ were performed on 6 male

-
- 4 "Combistix" (Ames Reagent Strips).
5 "Clinistix" (Ames Reagent Strips).
6 "Clinitest" (Ames Reagent Tablets).
7 "Ictotest" (Ames Reagent Tablets).
8 "Hemastix" (Ames Reagent Strips).
9 "Hematest" (Ames Reagent Tablets).
10 "Occultest" (Ames Reagent Tablets).
11 "Albustix" (Ames Reagent Strips).
12 "Rumintest" (Ames Reagent Tablets).
13 Heller's Ring Test, Practical Physiologic Chemistry, Hawk, Oser and Summerson, 13th Ed., p. 830.
14 Beckman Expanded Scale pH Meter, Model No. 76.
15 Reitman, S., and Frankel, S., Colorimetric Method for the Determination of Serum Transaminase Activity, Am. J. of Clin. Path., 28: 56, 1957.
16 Marsh, W., Modified King-Armstrong Method, Clin. Chem. 5: 119, 1959.

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and 6 female rats randomly selected from the control and treated groups. The animals chosen for hematology values were not used for these biochemical determinations.

B. RESULTS:

1. General Behavior and Appearance:

No adverse changes in behavior or appearance were encountered that could be related to the administration of (b) (4)

Animals in the control and all treated groups appeared essentially normal each day with the exception of an occasional rat in each group that exhibited slight nasal and/or ocular porphyrin discharge.

Other incidental findings, unrelated to compound administration, included one treated female animal (Rat #14374) at the 5000 ppm. dietary level which exhibited a swollen nose in the 13th week of study, one treated male (Rat #14298) at this dietary level which exhibited a mass on the flank from the 16th week (withdrawal period) until terminal necropsy examination, and one treated male (Rat #14324) at this same dietary level which exhibited destruction of the right eye, from the 15th week to the terminal (in the withdrawal period) necropsy examination.

2. Body Weights (Tables 1-8 and Figures 1 and 2):

a. Control:

The control animals maintained body weight curves which were consistent with those curves exhibited by control animals of the same age and strain maintained in these laboratories from time-to-time.

b. 100 and 500 ppm.*:

Male and female rats at these dietary levels maintained body weights which paralleled closely those of their respective control groups.

* 500 ppm. dietary level increased to 1000 ppm. in the 6th week of study.

c. 2500 ppm.**:

No marked body weight changes occurred among male and female rats at this dietary level during the course of compound administration. Male animals in the 9th week exhibited a body weight gain 8.8 per cent less than control males. This difference in body weight gain persisted for the duration of the study period. During the withdrawal phase of this study the greatest decrease in body weight gain occurred. Even then, however, this difference was only about 10 per cent less than that of the male control animals.

Female treated animals in this group in the 7th week of study exhibited a weight gain which was 11.5 per cent less than that of the control female animals. This difference in body weight gain persisted for the duration of the treatment period. The greatest difference in body weight gain of the female group was noted in the 12th week of study at which time a difference of only 11.7 per cent occurred.

3. Food Consumption (Tables 10 and 11):

a. Grams/Rat/Week:

Average total weekly food consumption for male and female rats in those groups receiving 100 ppm. and 500 ppm,* compared favorably with similar measurements obtained from the control group.

Treated rats receiving 2500 ppm.** showed food consumption values less than those of control animals beginning in the 4th week for treated females and in the 8th week for treated males. This decrease in food consumption continued throughout the study period and ranged from 1.1 to 8.7 per cent for the males and 5.2 to 16.4 per cent for the females in this group. The decreased food consumption in this

* 500 ppm. dietary level increased to 1000 ppm. in the 6th week of study.

** 2500 ppm. dietary level increased to 5000 ppm. in the 6th week of study.

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group continued in both sexes for the duration of the treatment period.

b. Grams/Kg./Day:

No biologically meaningful differences were observed on food consumption in the treated groups of rats when compared with the control group on a basis of grams/kg./day food consumed.

4. Survival (Table 9.):

Other than for those animals subjected to interim necropsy examination at 30 and 60 days, all control and treated animals survived the course of study with two exceptions. One control female (Rat #14160) succumbed in the terminal (13th) week of study and one treated male (Rat #14212) at the 100 ppm. level of (b) (4) succumbed in the 11th week of study.

5. Laboratory Tests:

a. Hematology:

No alterations in the hematologic parameters measured were observed which were considered to be related to treatment with (b) (4)

Group average values are summarized for male rats in Table 12 and for female rats in Table 13. Individual values for all male and female rats appear in Tables 14 through 17).

b. Plasma Biochemistry:

No compound-related changes were found at any period of examination with respect to serum alkaline phosphatase activity or serum glutamic pyruvic transaminase (SGPT) or serum glutamic oxalacetic transaminase (SGOT) activities.

Values obtained in these studies appear in Table 18 through 21.

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c. Urinalysis:

Urinalysis examinations failed to reveal changes which were considered to be related to treatment with the test compound. Results of these measurements appear in Tables 22 through 25).

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IV. PATHOLOGICAL STUDIES

A. METHODS:

1. Gross Examination:

After 30 and 60 days of compound administration, 3 male and 3 female rats from the control and each treated group were sacrificed by exsanguination and subjected to necropsy examination. After 90 days of compound administration, 10 male and 10 female rats from the control, 1000, and 5000 ppm. dietary level groups and all surviving rats from the 100 ppm. group were sacrificed by exsanguination and subjected to necropsy examination. Three male and 3 female rats from the control, 1000 and 5000 ppm. groups were sacrificed and subjected to necropsy examination after a 21-day compound withdrawal period. (Other rats that remained on withdrawal beyond 21 days will be reported on in a separate report.)

At necropsy major organs were weighed and representative tissues from each rat were collected into 10 per cent neutral buffered formalin for subsequent histologic processing. At the 90-day sacrifice, specimens of brain, liver, kidneys, muscle, fat, spleen, testes and blood were pooled by sex and dietary group, frozen and forwarded to the sponsor. Specimens of liver from the interim and withdrawal sacrifice were also pooled by sex and dietary group, frozen and shipped to the sponsor.

Rats which died on study were also subjected to necropsy examination unless this was precluded by advanced autolysis.

2. Microscopic Examination:

The following tissues from each of 3 male and 3 female rats from the control and high dosage groups from the 30 and 60-day interim and 21-day withdrawal sacrifices and from each of 10 male and 10

female control and high dietary group rats from the 90-day terminal sacrifice were paraffin-embedded, sectioned, stained with hematoxylin and eosin and examined microscopically:

brain	heart	pancreas
spinal cord	spleen	liver
peripheral nerve	lymph node	kidneys
eye	thymus	urinary bladder
pituitary	bone marrow	testes or ovaries
thyroid	salivary gland	prostate or uterus
parathyroid	stomach	skeletal muscle
adrenal	small intestine	skin
lung	large intestine	bone

Sections of liver from 10 male and 10 female rats from the 1000 ppm. level - 90-day sacrifice rats were also processed as above and examined.

B. RESULTS:

1. Gross Pathology (Table 26) and Organ Weights (Tables 27 and 28):

Compound related gross changes observed at necropsy were limited to male rats from the 1000 and 5000 ppm. dietary level groups and consisted of pale, yellowish livers in some but not all male rats from the 5000 ppm. dietary level group and in a few rats from the 1000 ppm. dietary level group.

None of the rats dying on study died of compound related causes. Rat #14160 (Control) died of pneumonia. Autolysis precluded diagnostic necropsy of Rat #14212 (100 ppm.).

Compound related variations in organ weights were limited to the liver and kidneys of treated rats. At the 90-day sacrifice there was a moderate increase in actual and relative liver weights of the 1000 and 5000 ppm. dietary level rats. This increase was also seen in the 5000 ppm. dietary level rats at the 60-day interim

sacrifice and in the 2500 ppm. dietary level rats at the 30-day interim sacrifice. After 21 days of compound withdrawal, a slight increase in liver weight persisted at the 5000 ppm. dietary level.

Mean actual and relative kidney weights were slightly in the 1000 and 5000 ppm. dietary level rats at the 90-day sacrifice. Kidney weights were also slightly increased in the 1000 and 5000 ppm. level rats at the 60-day interim sacrifice and 21-day withdrawal sacrifice and in the 500 and 2500 ppm. level at the 30-day interim sacrifice. Although the values from the interim and withdrawal sacrifices represent only 3 rats per sex group, these variations in kidney weights always had a dietary-level relationship.

2. Histopathology (Tables 29 and 30):

Compound related histopathologic changes were found only in the livers of rats from the highest (2500-5000 ppm.) dietary level and consisted of slight hypertrophy of centrilobular hepatocytes. Affected liver cells had cytoplasm which was less coarsely granular and more homogeneous than the unaffected cells at the periphery of the liver lobules and in the livers of rats in the control and lower dietary levels. This change, to a slight degree was seen after 30 days at the 2500 ppm. level. After this group was raised to 5000 ppm., the change was more marked at the 60 and 90-day sacrifices. A very slight change persisted in the 5000 ppm. level male rats sacrificed after a 21-day compound withdrawal period. This liver change was always more marked in male rats and was seen only at the highest (2500-5000 ppm.) dietary level.

No lesions in other organs were considered to have been of compound related origin. No histologic basis was found for the slight increase in kidney weights in treated rats.

Ninety-Day Feeding Study in the Rat.

TABLE 1. Individual Weekly Body Weights, Grams.

Rat Number	Control Period		Compound Administration Weeks										
	1	2	1	2	3	4	5	6	7	8	9	10	
Control - Female:													
14142	55	93	129	149	175	185	195	Sacrificed					
14143	54	68	95	123	136	144	155	169	191	198	Sacrificed		
14144	56	99	134	163	187	207	249	260	285	296	306	314	
14145	56	83	107	130	142	159	166	Sacrificed					
14146	56	94	136	61	184	196	217	Sacrificed					
14147	55	91	123	141	160	179	184	191	231	218	221	236	
14148	57	88	124	149	170	178	197	214	249	241	252	268	
14149	60	101	135	162	177	199	215	230	261	265	Sacrificed		
14150	55	72	103	126	149	164	191	213	243	243	252	271	
14151	58	83	116	137	158	181	189	202	237	224	224	234	
14152	56	67	114	133	154	171	189	203	235	226	Sacrificed		
14153	50	52	93	122	138	143	166	183	231	207	215	248	
14154	57	63	82	117	141	156	172	195	237	225	233	246	
14155	57	71	116	142	160	170	192	203	239	223	244	258	
14156	51	67	115	139	161	161	196	210	243	241	250	261	
14157	58	64	105	121	134	154	153	166	165	174	178	185	
14158	57	73	106	132	153	149	172	190	232	244	215	236	
14159	58	54	99	146	156	181	199	219	240	232	250	264	
14160	50	76	124	147	162	157	189	206	221	215	239	256	
14161	54	48	91	128	148	144	178	192	231	214	226	236	
Mean	55	75	112	138	157	169	188	203	234	229	236	251	

00108

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(b) (4)
Ninety-Day Feeding Study in the Rat.

TABLE 1. Continued. Individual Weekly Body Weights, Grams.

Rat Number	Compound Administration Weeks								
	11	12	13	14*	15	16	17	18	19
<u>Control - Female:</u>									
14144	32	326	332						
14147	244	252	332						
14148	271	285	267						
14150	285	288	233						
14151	241	251	242						
14153	260	248	244						
14154	256	263	241						
14155	265	271	238						
14156	275	283	259						
14157	200	200	191						
14158	245	253	231	250	264	266	Sacrificed		
14159	277	281	282	289	299	310	Sacrificed		
14160	265	271	Died						
14161	241	251	257	261	268	276	Sacrificed		
14313				242	249	251	256	255	254
Mean	260	266	258	251	270	276	256	255	254

* Initiation of withdrawal period (14th week).

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000109

(b) (4)
Ninety-Day Feeding Study in the Rat.

TABLE 2. Individual Weekly Body Weights, Grams.

Rat Number	Control Period		Compound Administration Weeks									
	1	2	1	2	3	4	5	6	7	8	9	10
<u>Control - Male:</u>												
14162	54	99	143	185	230	244	263	Sacrificed				
14163	52	97	151	207	256	294	309	338	354	388	402	412
14164	60	100	89	169	229	288	324	366	388	446	461	480
14165	59	94	157	214	251	309	346	Sacrificed				
14166	55	92	133	175	211	248	274	300	321	344	360	379
14167	50	67	103	145	187	231	260	290	311	308	Sacrificed	
14168	61	98	147	189	243	276	308	Sacrificed				
14169	65	74	113	143	224	274	307	337	365	395	413	433
14170	58	95	136	185	231	265	285	317	348	380	Sacrificed	
14171	51	83	119	158	191	260	257	287	310	349	364	390
14172	60	83	152	205	263	307	300	336	371	417	441	467
14173	52	55	105	153	199	242	263	291	306	334	346	370
14174	51	64	113	155	204	238	273	318	341	373	382	412
14175	54	76	137	185	234	251	293	317	370	422	449	469
14176	57	76	136	180	222	264	294	328	354	390	393	420
14177	54	71	123	167	209	241	271	300	318	336	341	358
14178	62	64	117	153	200	234	250	283	311	340	Sacrificed	
14179	52	66	130	181	231	238	261	322	347	380	395	420
14180	53	67	120	172	224	272	300	334	360	388	398	423
14181	55	67	128	177	234	241	300	344	373	401	409	441
Mean	55	79	128	175	224	261	287	318	344	376	397	420

(4) Ninety-Day Feeding Study in the Rat.

TABLE 2. Continued. Individual Weekly Body Weights, Grams.

Rat Number	Compound Administration Weeks								
	11	12	13	14*	15	16	17	18	19
<u>Control - Male:</u>									
14163	406	391	375						
14164	505	505	495						
14166	398	409	383						
14169	446	453	431						
14171	412	423	385						
14172	488	483	478						
14173	389	405	376						
14174	427	440	401						
14175	498	496	506						
14176	442	452	425						
14177	365	374	357	396	402	414	Sacrificed		
14179	435	455	461	479	489	500	Sacrificed		
14180	415	463	461	489	472	514	Sacrificed		
14181	451	463	472	476	466	497	506	515	522
14314				538	518	556	574	571	585
14315				512	503	523	539	544	559
Mean	434	444	429	482	475	501	540	543	555

* Initiation or withdrawal period (14th week).

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000111

(b) (4)
Ninety-Day Feeding Study in the Rat.

TABLE 3. Individual Weekly Body Weight, Grams.

Rat Number	Control Period		Compound Administration Weeks									
	1	2	1	2	3	4	5	6	7	8	9	10
100 ppm. - Female:												
14182	56	86	112	131	151	167	175	Sacrificed				
14183	51	77	123	153	171	203	210	231	250	262	273	285
14184	59	82	113	126	145	165	182	194	211	218	Sacrificed	
14185	55	87	110	135	154	174	186	Sacrificed				
14186	57	101	144	176	210	252	251	275	290	303	307	331
14187	55	76	109	134	155	175	194	206	230	245	252	269
14188	55	80	111	124	139	149	162	Sacrificed				
14189	55	63	91	119	150	168	177	198	216	230	245	257
14190	55	88	116	137	154	176	180	200	211	225	225	242
14191	53	84	122	153	177	187	208	223	241	258	269	286
14192	34	60	106	127	141	172	174	185	193	207	215	234
14193	53	67	113	141	158	181	199	210	222	238	Sacrificed	
14194	61	73	90	124	148	160	179	203	221	234	Sacrificed	
14195	59	69	107	133	157	175	190	211	231	245	243	265
14196	57	65	105	147	159	179	183	199	213	227	236	267
14197	50	58	98	121	146	157	179	197	207	227	238	258
14198	62	76	123	141	167	195	202	220	237	253	259	270
14199	51	60	102	125	141	144	180	197	215	236	241	256
14200	53	70	123	147	165	184	197	212	224	244	246	264
14201	59	65	115	152	179	183	208	235	245	263	271	275
Mean	56	74	112	137	158	177	191	212	227	242	251	269

000112

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(b) (4)
Ninety-Day Feeding Study in the Rat.

TABLE 3. Continued. Individual Weekly Body Weights, Grams.

Rat Number	Compound Administration Weeks								
	11	12	13	14	15	16	17	18	19
100 ppm. - Female:									
14183	290	306	283						
14186	345	353	333						
14187	271	285	258						
14189	272	274	252						
14190	248	255	227						
14191	287	303	283						
14192	236	248	221						
14195	280	286	261						
14196	277	276	247						
14197	251	262	244						
14198	283	296	278						
14199	261	269	273						
14200	273	278	285						
14201	298	301	308						
Mean	277	285	268						

000113

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(b) (4)
Ninety-Day Feeding Study in the Rat.

TABLE 4. Individual Weekly Body Weight, Grams.

Rat Number	Control Period		Compound Administration Weeks										
	1	2	1	2	3	4	5	6	7	8	9	10	
100 ppm. - Male:													
14202	58	79	119	168	214	246	270	Sacrificed					
14203	51	76	116	157	201	224	261	296	328	356	376	400	
14204	62	87	149	203	256	310	343	371	407	448	467	495	
14205	55	86	139	189	242	275	286	Sacrificed					
14206	63	103	160	215	255	298	320	346	373	403	405	434	
14207	54	85	124	165	209	248	282	306	338	363	378	402	
14208	55	81	120	159	199	211	228	Sacrificed					
14209	55	88	128	166	209	244	254	269	301	327	347	372	
14210	60	86	142	197	252	303	330	354	388	398	417	454	
14211	54	87	134	173	217	251	284	312	339	369	385	410	
14212	50	60	108	122	130	168	211	250	256	296	317	300	
14213	53	81	116	161	195	238	243	271	290	305	308	335	
14214	61	83	149	205	267	284	326	352	377	399	407	441	
14215	63	83	136	171	210	250	259	267	289	320	349	375	
14216	53	70	126	164	217	271	308	247	377	407	420	457	
14217	49	58	97	135	168	186	219	260	286	316	Sacrificed		
14218	58	64	100	142	199	247	286	330	369	398	321	454	
14219	55	73	121	155	207	216	275	310	333	358	364	393	
14220	61	68	110	136	196	213	264	287	307	329	Sacrificed		
14221	60	74	135	176	227	255	281	308	331	357	Sacrificed		
Mean	57	79	127	168	214	252	277	308	335	362	376	409	

000114

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(b)(4) Ninety-Day Feeding Study in the Rat.

TABLE 4. Continued. Individual Weekly Body Weight, Grams.

Rat Number	Compound Administration Weeks								
	11	12	13	14	15	16	17	18	19
100 ppm. - Male:									
14203	411	440	427						
14204	521	527	515						
14206	450	468	432						
14207	423	436	410						
14209	385	398	363						
14210	462	477	481						
14211	432	456	432						
14212	died								
14213	353	368	348						
14214	445	456	448						
14215	385	405	383						
14216	482	501	500						
14218	473	496	507						
14219	406	421	430						
Mean	433	450	437						

000115

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(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 5. Individual Weekly Body Weight, Grams.

Rat Number	Control Period		Compound Administration Weeks										
	1	2	1	2	3	4	5	6	7	8	9	10	
500 ppm. - Female:*													
14222	55	88	126	153	177	190	204	Sacrificed					
14223	60	83	116	134	154	172	181	195	202	213	Sacrificed		
14224	58	92	111	127	141	163	185	200	212	238	273	260	
14225	48	59	91	115	136	141	154	Sacrificed					
14226	57	73	115	140	161	182	188	204	215	223	235	247	
14227	57	92	130	157	178	201	210	230	244	256	264	276	
14228	55	86	130	154	166	178	197	Sacrificed					
14229	55	78	113	140	160	174	184	202	215	237	254	261	
14230	55	90	119	134	147	158	175	190	202	215	Sacrificed		
14231	52	76	114	153	184	195	219	237	254	272	287	303	
14232	50	57	100	134	147	174	186	204	216	234	241	253	
14233	52	64	105	125	130	148	160	170	181	191	201	204	
14234	59	73	110	129	140	140	164	176	187	195	Sacrificed		
14235	58	68	119	148	175	201	214	255	249	266	279	297	
14236	56	76	117	150	171	193	213	216	236	242	248	253	
14237	52	52	86	123	145	146	168	188	200	212	221	223	
14238	50	77	119	150	171	195	199	211	222	227	236	243	
14239	57	74	129	146	163	183	198	206	221	234	242	253	
14240	55	75	117	138	154	157	188	197	214	224	230	245	
14241	55	72	100	128	144	143	180	188	200	206	215	236	
Mean	55	75	113	139	157	172	188	204	216	229	243	255	

* Dosage level increased in the 5th week of study to 1000 ppm.

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(014)
Ninety-Day Feeding Study in the Rat.

TABLE 5. Continued. Individual Weekly Body Weights, Grams.

Rat Number	Compound Administration Weeks								
	11	12	13	14*	15	16	17	18	19
500 ppm. - Female:									
14224	267	279	263						
14226	246	257	239						
14227	244	282	269						
14229	265	277	270						
14231	310	314	268						
14232	255	269	251						
14233	212	216	207						
14235	304	312	299						
14236	262	272	254						
14237	232	244	234						
14238	253	256	242	263	276	278	Sacrificed		
14239	259	266	261	262	272	279	Sacrificed		
14240	256	263	259	274	278	280	Sacrificed		
14241	235	245	246	254	269	267	269	282	276
14306				254	266	270	272	284	284
14308				249	258	266	265	273	283
14320				234	236	241	246	250	253
Mean	257	268	254	256	265	269	263	272	274

* Initiation of withdrawal period (14th week).

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(b)
(4)

Ninety-Day Feeding Study in the Rat.

TABLE 6. Individual Weekly Body Weight, Grams.

Rat Number	Control Period		Compound Administration Weeks										
	1	2	1	2	3	4	5	6	7	8	9	10	
500 ppm. - Male:*													
14242	58	85	124	155	185	201	228	Sacrificed					
14243	57	92	136	178	226	269	297	325	351	374	387	410	
14244	56	78	134	196	249	295	314	371	412	443	465	485	
14245	63	96	136	172	213	251	265	Sacrificed					
14246	56	63	91	133	172	210	234	268	292	320	Sacrificed		
14247	58	72	120	162	209	266	305	342	365	386	407	430	
14248	55	83	114	149	183	208	234	Sacrificed					
14249	62	90	134	176	224	270	291	325	356	381	378	415	
14250	58	85	130	192	236	276	300	321	334	359	379	397	
14251	52	75	124	165	207	239	272	297	328	357	Sacrificed		
14252	63	89	147	195	249	293	321	355	326	391	399	445	
14253	62	78	144	189	230	238	299	327	355	379	Sacrificed		
14254	55	75	134	187	235	258	297	317	348	381	396	423	
14255	57	70	123	162	188	221	250	281	305	329	345	368	
14256	55	67	102	140	182	221	258	280	300	328	334	351	
14257	53	81	117	154	192	219	258	306	339	369	365	390	
14258	56	98	151	189	235	285	328	359	385	412	425	453	
14259	52	63	105	145	191	225	249	274	303	330	346	372	
14260	58	69	124	169	220	229	289	324	352	372	385	398	
14261	59	79	151	203	271	285	324	377	408	436	446	467	
Mean	57	79	127	170	215	248	281	321	345	373	390	415	

* Dosage level increased in the 5th week of study to 1000 ppm.

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(b) (4)
Ninety-Day Feeding Study in the Rat.

TABLE 6. Continued. Individual Weekly Body Weights, Grams.

Rat Number	Compound Administration Weeks								
	11	12	13	14*	15	16	17	18	19
500 ppm. - Male:									
14243	445	435	422						
14244	509	525	499						
14247	449	471	447						
14249	434	451	441						
14250	412	431	411						
14252	453	463	431						
14254	452	437	428						
14255	382	396	380						
14256	369	377	348						
14257	408	415	390						
14258	478	499	477	517	496	545	Sacrificed		
14259	384	404	419	435	446	465	Sacrificed		
14260	400	417	434	452	458	476	Sacrificed		
14261	500	520	548	568	542	563	582	612	632
14321				507	487	532	538	559	544
14322				516	497	531	545	550	549
14325				549	525	562	569	586	577
Mean	434	446	434	506	493	525	559	577	576

* Initiation of withdrawal period (14th week).

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Ninety-Day Feeding Study in the Rat.

TABLE 7. Individual Weekly Body Weights, Grams.

Rat Number	Control Period		Compound Administration Weeks									
	1	2	1	2	3	4	5	6	7	8	9	10
* 2500 ppm. - Female												
14262	52	87	120	138	164	174	181*	Sacrificed				
14263	53	79	119	145	166	182	200	230	246	264	Sacrificed	
14264	53	71	107	124	140	149	160	169	180	195	194	207
14265	55	72	104	127	143	154	165	Sacrificed				
14266	50	63	78	109	133	153	171	181	195	203	222	228
14267	55	76	113	134	147	163	175	188	202	216	223	232
14268	63	85	114	132	137	135	158	Sacrificed				
14269	56	86	115	130	148	163	173	182	192	200	202	216
14270	56	85	116	136	151	161	171	174	184	193	Sacrificed	
14271	60	95	134	161	180	187	212	225	240	246	256	260
14272	58	74	117	134	148	158	173	186	193	200	207	213
14273	51	66	116	140	161	169	185	197	202	210	220	226
14274	47	61	99	133	151	171	182	195	206	219	215	225
14275	57	75	122	144	168	174	198	207	222	233	Sacrificed	
14276	52	63	107	135	148	162	179	191	209	226	231	243
14277	52	66	106	134	152	151	168	188	196	208	205	223
14278	47	55	85	115	141	149	174	189	198	216	221	230
14279	61	76	123	144	160	155	185	206	211	222	230	236
14280	56	75	126	154	178	173	204	221	233	244	256	265
14281	53	66	108	132	146	142	171	180	189	193	207	207
Mean	55	75	113	136	154	161	179	196	207	218	221	229

* Dosage level increased in the 5th week of study to 5000 ppm.

000120

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(b) (4)
Ninety-Day Feeding Study in the Rat.

TABLE 7. Continued. Individual Weekly Body Weights, Grams.

Rat Number	Compound Administration Weeks								
	11	12	13	14*	15	16	17	18	19
2500 ppm. - Female:									
14264	205	216	201						
14266	226	228	213						
14267	234	244	213						
14269	214	217	208						
14271	261	264	244						
14272	207	210	204						
14273	226	233	223						
14274	226	218	212						
14276	262	260	263						
14277	228	232	212						
14278	229	241	231	249	259	270	Sacrificed		
14279	236	239	237	257	254	269	Sacrificed		
14280	274	276	276	278	284	285	Sacrificed		
14281	214	216	218	222	239	245	252	258	257
14311				233	246	253	260	278	278
14326				233	236	239	246	258	261
14329				198	202	209	207	220	218
Mean	232	235	225	239	246	253	241	254	254

* Initiation of withdrawal period. (14th week)

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(4)

Ninety-Day Feeding Study in the Rat.

TABLE 8. Individual Weekly Body Weights, Grams.

Rat Number	Control Period		Compound Administration Weeks										
	1	2	1	2	3	4	5	6	7	8	9	10	
* 2500 ppm. - Male													
14282	60	80	117	141	184	225	246	Sacrificed					
14283	53	84	124	151	193	237	268	299	321	343	354	374	
14284	55	76	129	182	219	277	310	351	382	416	440	454	
14285	55	84	133	178	226	267	283	Sacrificed					
14286	32	65	92	125	147	171	203	222	245	270	291	302	
14287	55	84	133	181	227	262	289	308	332	357	371	388	
14288	46	71	193	171	227	265	274	Sacrificed					
14289	60	98	151	194	249	298	322	373	404	437	Sacrificed		
14290	56	84	115	154	193	234	275	314	335	366	387	399	
14291	57	60	107	163	206	228	271	306	332	354	370	381	
14292	32	69	72	104	138	181	203	239	273	297	315	334	
14293	57	82	143	184	228	261	285	312	339	364	Sacrificed		
14294	58	82	133	165	207	231	266	291	315	337	339	355	
14295	64	92	149	189	228	265	294	341	378	416	Sacrificed		
14296	61	84	144	189	231	272	295	321	345	363	365	385	
14297	58	75	133	196	247	281	323	363	396	385	422	446	
14298	52	82	107	140	178	214	236	258	284	306	312	331	
14299	63	89	143	190	241	290	325	351	378	406	411	435	
14300	55	78	114	135	197	215	272	303	325	342	345	370	
14301	52	76	132	169	205	240	271	292	312	332	345	370	
Mean	56	80	129	165	209	245	276	308	335	358	362	380	

* Dosage level increased in the 5th week of study to 5000 ppm.

(b)
(4)

Ninety-Day Feeding Study in the Rat.

TABLE 8. Continued. Individual Weekly Body Weights, Grams.

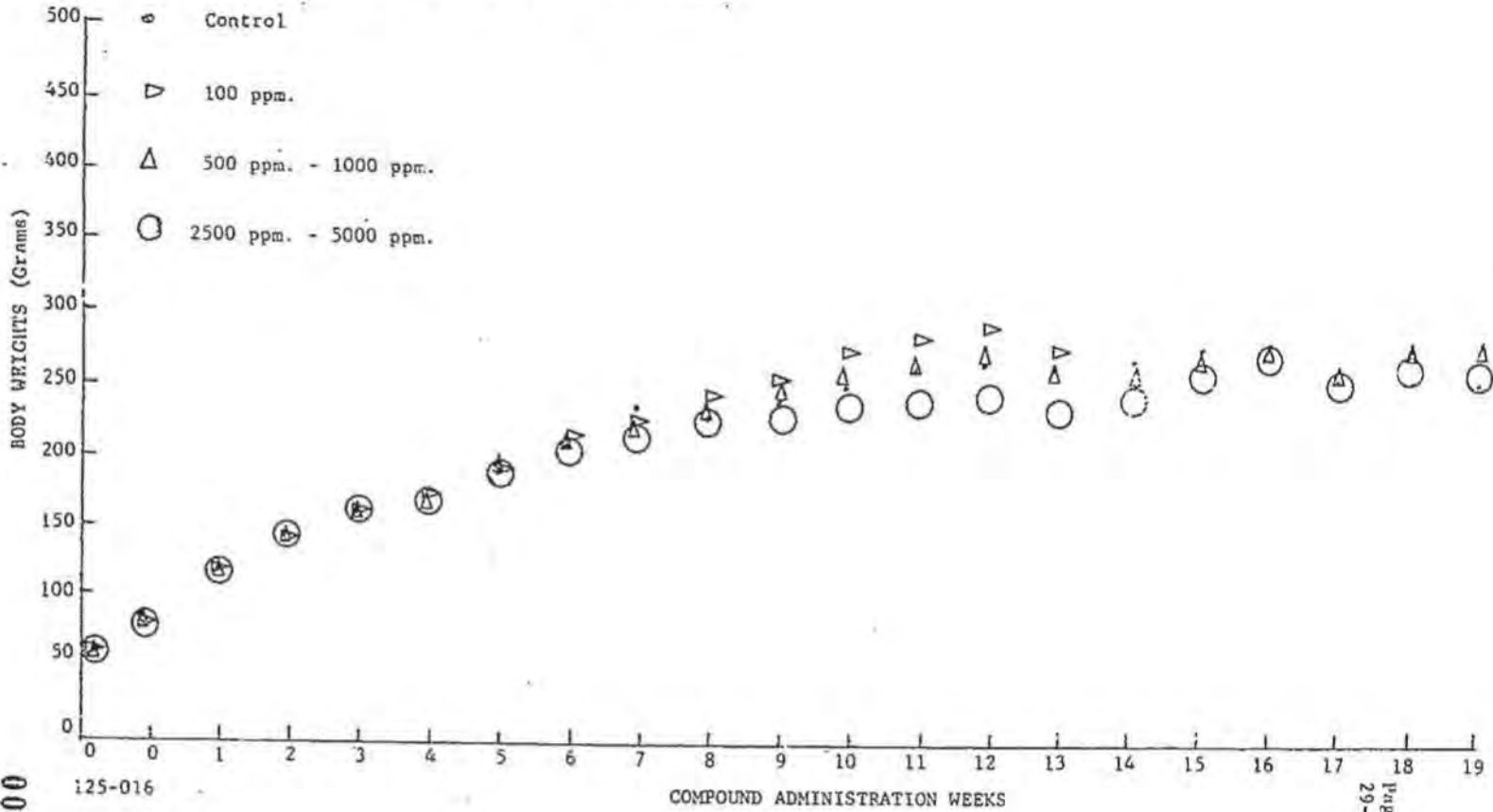
Rat Number	Compound Administration Weeks								
	11	12	13	14*	15	16	17	18	19
2500 ppm. - Male:									
14283	394	410	393						
14284	478	507	497						
14286	318	328	316						
14287	400	414	401						
14290	415	425	413						
14291	401	410	385						
14292	344	373	357						
14294	367	388	364						
14296	405	418	412						
14297	468	480	456						
14298	349	465	327	341	339	342	Sacrificed		
14299	453	463	476	472	473	512	Sacrificed		
14300	381	395	407	416	429	442	Sacrificed		
14301	382	398	414	431	447	448	466	486	508
14327				362	377	390	497	427	433
14328				492	500	517	537	550	556
14324				461	478	489	500	516	531
Mean	397	420	401	425	435	449	500	495	507

* Initiation of withdrawal period. (14th week)

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FIGURE 1. Group Mean Body Weights. Female Rats

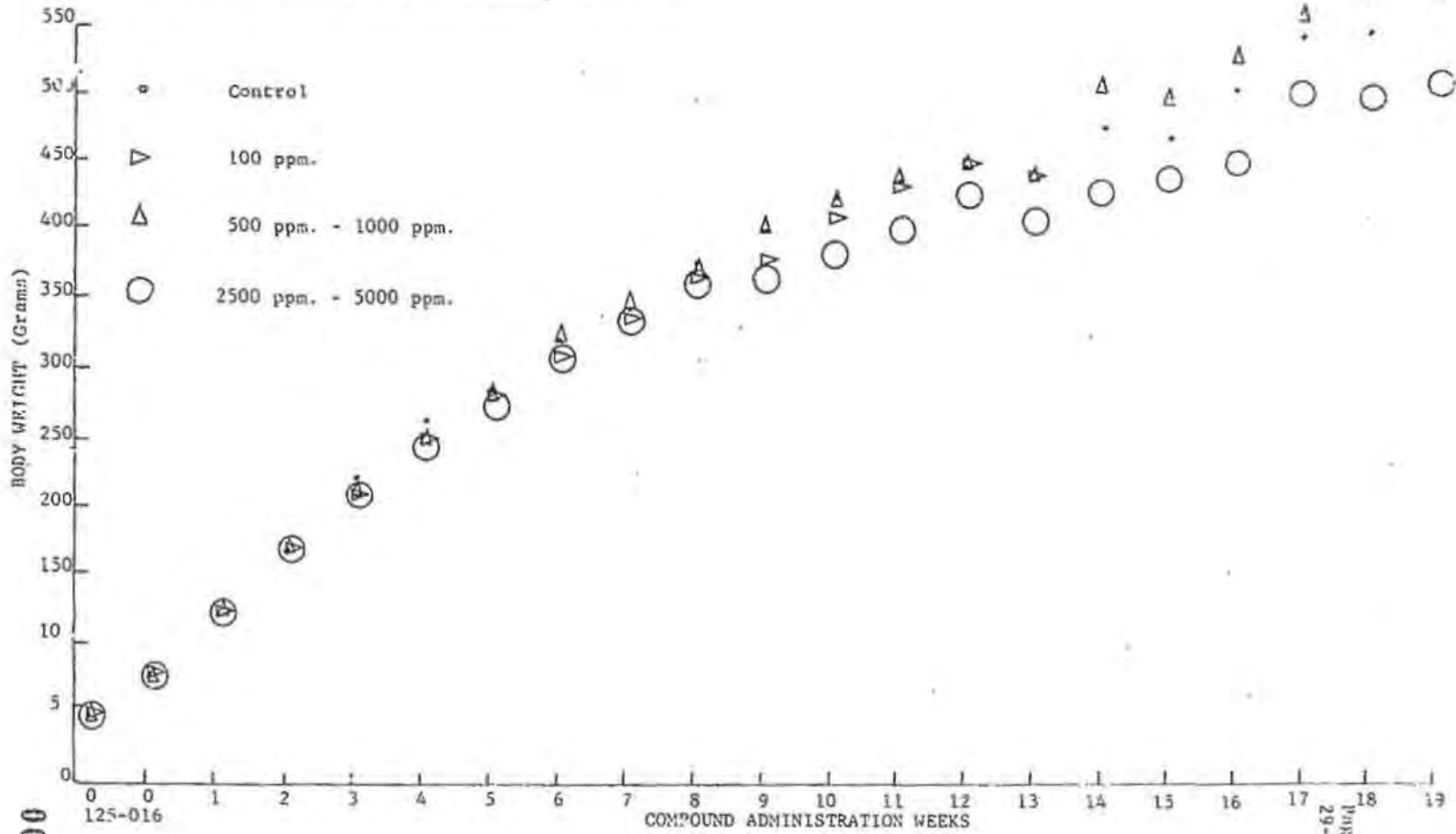


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FIGURE 2. Group Mean Body Weights. Male Rats.



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(b) (4)
Ninety-Day Feeding Study in the Rat.

TABLE 9. Mean Body Weights, Grams; Weight Ranges, Grams; and Survival: FEMALE RATS.

Compound Administration Weeks	Control			100 ppm.			500 ppm.*			2500 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
0	55	50-60	20/20	56	51-62	20/20	55	48-60	20/20	55	47-63	20/20
0	75	48-101	20/20	74	58-101	20/20	75	52-92	20/20	75	55-95	20/20
1	112	82-136	20/20	112	91-144	20/20	113	86-130	20/20	113	78-134	20/20
2	138	117-183	20/20	137	119-176	20/20	139	115-157	20/20	136	109-161	20/20
3	157	134-187	20/20	158	139-210	20/20	157	130-184	20/20	154	133-180	20/20
4	169	143-207	20/20	177	144-252	20/20	172	140-201	20/20	161	135-187	20/20
5	188	153-249	17/20	191	174-251	17/20	188	154-219	17/20	179	160-212	17/20
6	203	166-260	17/20	212	185-275	17/20	204	170-237	17/20	196	169-230	17/20
7	234	155-285	17/20	227	193-290	17/20	216	181-254	17/20	207	180-246	17/20
8	229	174-296	17/20	242	207-303	17/20	229	191-272	17/20	218	193-264	17/20
9	236	178-306	14/20	251	215-307	14/20	243	201-287	14/20	221	194-256	14/20
10	251	185-314	14/20	269	234-331	14/20	255	204-303	14/20	229	207-265	14/20
11	260	200-320	14/20	277	236-345	14/20	257	212-310	14/20	232	207-274	14/20
12	266	200-326	14/20	285	248-353	14/20	268	216-314	14/20	255	210-276	14/20
13	258	191-332	13/20	268	221-333	14/20	254	207-299	14/20	225	201-276	14/20
14	267	250-289	3/20			0/20	259	249-274	6/22	248	222-278	5/22
15	277	264-299	3/20				270	258-278	6/22	256	239-284	5/22
16	284	266-310	3/20				273	266-280	6/22	264	253-285	5/22
17			0/20				269	265-272	3/22	256	252-260	2/22
18							280	273-284	3/22	268	258-278	2/22
19							281	276-284	3/22	243	228-257	2/22

NOTE - Withdrawal period was initiated following 13-weeks of compound administration. Selected animals were continued into the period of withdrawal which continues at the writing of this report.

* Dosage level in this group increased to 1000 ppm. in the 5th week of study.

** Dosage level in this group increased to 5000 ppm. in the 5th week of study.

(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 9. Continued. Mean Body Weights, Grams; Weight Ranges, Grams; and Survival: MALE RATS.

Compound Administration Weeks	Control			100 ppm.			500 ppm.*			2500 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
0	55	45-64	20/20	57	49-63	20/20	58	52-63	20/20	56	45- 4	20/20
0	79	55-100	20/20	79	58-103	20/20	80	63-98	20/20	80	60-98	20/20
1	128	89-157	20/20	127	97-160	20/20	127	91-151	20/20	129	72-193	20/20
2	175	143-214	20/20	168	122-215	20/20	169	125-203	20/20	165	104-196	20/20
3	224	187-263	20/20	214	130-267	20/20	215	172-271	20/20	209	138-249	20/20
4	261	231-309	20/20	252	168-310	20/20	248	201-293	20/20	245	173-298	20/20
5	287	250-346	17/20	277	211-343	17/20	281	234-324	17/20	276	203-325	17/20
6	318	283-366	17/20	308	250-371	17/20	321	268-377	17/20	308	222-373	17/20
7	344	306-388	17/20	335	256-407	17/20	345	292-412	17/20	335	245-404	17/20
8	376	308-446	17/20	362	296-448	17/20	373	320-443	17/20	358	270-437	17/20
9	397	341-461	14/20	376	317-467	14/20	390	334-465	14/20	362	291-440	14/20
10	420	358-480	14/20	409	300-495	14/20	415	351-485	14/20	380	302-454	14/20
11	434	365-505	14/20	429	353-521	13/20	434	369-509	14/20	397	318-478	14/20
12	444	374-505	14/20	446	368-527	13/20	446	377-525	14/20	420	328-507	14/20
13	429	357-506	14/20	437	363-515	13/20	434	348-548	14/20	401	316-497	14/20
14	447	242-538	7/23			0/20	472	234-568	8/24	378	198-492	9/25
15	443	249-518	7/23				461	236-542	8/24	387	202-500	9/25
16	465	251-556	7/23				489	241-563	8/24	399	209-517	9/25
17	469	256-574	4/23				496	246-582	5/24	394	207-537	6/25
18	471	255-571	4/23				511	250-612	5/24	410	220-550	6/25
19	480	254-585	4/23				511	253-631	5/24	418	218-556	6/25

NOTE - Withdrawal period was initiated following 13-weeks of compound administration. Selected animals were continued into the period of withdrawal which continues at the writing of this report.

* Dosage level in this group increased to 1000 ppm. in the 5th week of study.

** Dosage level in this group increased to 5000 ppm. in the 5th week of study.

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Ninety-Day Feeding Study in the Rat.

TABLE 10. FEMALE RATS: Mean Food Consumption, Grams/Rat/Week and Grams/Kilogram/Day; Compound Consumption as Milligrams/Kilograms/Day and Food Efficiency.

Compound Administration week	CONTROL			100 ppm.			500 ppm. *			2500 ppm. **					
	FOOD	CPD.	Eff.	FOOD	CPD.	Eff.	FOOD	CPD.	Eff.	FOOD	CPD.	Eff.			
	g/r/wk	g/kg/d		g/r/wk	g/kg/d		g/r/wk	g/kg/d		g/r/wk	g/kg/d				
0															
1	96.1	122.3		99.6	126.8		12.7	98.9	124.8		62.4	91.4	115.9	289.8	
2	110.5	114.5	0.24	119.7	115.3	0.23	11.5	111.9	115.1	0.23	57.6	107.0	112.5	0.21	304.0
3	110.8	100.6	0.17	116.6	105.7	0.18	10.6	117.9	107.0	0.15	53.5	108.9	101.3	0.17	253.3
4	104.4	88.1	0.11	113.7	91.5	0.17	9.2	108.1	89.5	0.14	44.8	95.4	94.5	0.07	211.3
5	113.8	86.7	0.17	113.1	84.8	0.12	8.5	110.2	83.5	0.15	41.8	107.6	86.0	0.17	215.0
6	105.7	74.4	0.14	110.8	74.5	0.13	7.5	105.5	74.0	0.15	74.0	100.2	73.0	0.17	365.0
7	111.5	67.9	0.28	115.4	72.7	0.13	7.3	110.5	73.1	0.11	73.1	102.7	71.0	0.11	355.0
8	113.2	70.7	-0.04	117.7	69.4	0.13	6.9	111.7	69.9	0.12	69.9	103.5	67.9	0.10	339.5
9	108.1	65.3	0.07	112.8	64.1	0.08	6.4	112.2	65.8	0.12	65.8	93.6	60.6	0.03	303.0
10	102.4	58.2	0.15	121.4	64.3	0.15	6.4	123.9	69.4	0.10	55.9	107.8	67.2	0.07	336.0
11	112.6	61.6	0.09	129.4	66.8	0.06	6.7	116.7	65.0	0.02	65.0	98.0	60.3	0.03	301.5
12	116.2	62.4	0.05	124.0	62.1	0.06	6.2	116.8	62.3	0.09	62.3	97.2	59.1	0.03	295.5
13	123.9	68.6	-0.05	128.1	68.3	-0.13	6.8	128.8	72.4	-0.11	72.4	112.0	71.1	-0.09	355.5
14	***58.0	54.3	+0.09					***59.7	57.5	+0.05		***66.8	63.7	+0.20	
15	110.7	57.0	+0.09					113.7	60.0	+0.10		118.0	66.0	+0.07	
16	114.0	57.	+0.06					111.0	58.2	+0.03		115.2	61.4	+0.07	
17								109.3	58.0	-0.04		121.0	67.6	-0.07	
18								111.0	56.8	+0.01		119.5	63.8	+0.10	
19								110.7	56.2	+0.01		111.5	65.4	-0.22	

NOTE - Withdrawal period was initiated following 13-weeks of compound administration. Selected animals were continued into the period of withdrawal which continues at the writing of this report.

* Dosage level increased to 1000 ppm. in the 5th week of study.

** Dosage level increased to 5000 ppm. in the 5th week of study.

*** Grams/rat/4 days.

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(b) (4)
Ninety-Day Feeding Study in the Rat.

TABLE II. MALE RATS: Mean Food Consumption, Grams/Rat/Week and Grams/Kilograms/Day; Compound Consumption Mg./Kg./Day and Food Efficiency.

Compound Administration week	CONTROL			100 ppm.			500 ppm.*				2500 ppm.**				
	FOOD			FOOD			CPD.	FOOD			CPD.	FOOD			CPD.
	g/r/wk	g/kg/d	Eff.	g/r/wk	g/kg/d	Eff.	mg/kg/d	g/r/wk	g/kg/d	Eff.	mg/kg/d	g/r/wk	g/kg/d	Eff.	mg/kg/d
0															
1	108.8	121.1		99.6	118.3		11.8	100.4	112.6		56.3	112.2	124.0		310.0
2	135.5	110.9		126.3	107.1	0.33	10.7	128.8	108.9	0.33	54.5	121.6	105.5	0.30	263.8
3	150.3	96.0		141.9	94.9	0.32	9.5	144.9	96.3	0.31	48.2	140.5	95.7	0.31	239.3
4	151.7	83.1		151.1	85.7	0.25	8.6	145.3	83.9	0.23	42.0	145.0	84.5	0.25	211.3
5	151.0	75.3	0.11	152.8	78.7	0.20	7.9	154.9	78.6	0.21	39.3	151.9	78.6	0.20	196.5
6	146.6	65.7	0.21	148.0	68.5	0.21	6.9	150.0	66.7	0.26	66.7	149.9	69.5	0.21	347.5
7	155.1	64.5	0.17	157.1	66.9	0.18	6.7	151.6	62.9	0.16	62.9	152.3	65.1	0.18	325.5
8	165.2	62.8	0.19	158.2	62.4	0.17	6.2	161.8	61.9	0.17	61.9	154.1	61.5	0.15	307.5
9	154.1	55.4	0.14	154.1	58.5	0.09	5.9	148.6	54.4	0.11	54.4	140.7	55.5	0.03	277.5
10	159.9	54.3	0.14	166.6	58.2	0.20	5.8	162.5	55.9	0.15	55.9	146.8	38.7	0.12	293.5
11	158.1	52.1	0.09	175.2	58.3	0.11	5.8	164.4	54.1	0.12	54.1	156.4	56.2	0.03	281.0
12	162.8	52.5	0.06	170.9	54.7	0.10	5.5	159.6	51.1	0.08	51.1	150.6	51.2	0.03	256.0
13	184.8	61.5	-0.08	186.2	60.9	-0.07	6.1	181.3	59.7	-0.07	59.7	173.5	63.6	-0.11	318.0
14	***80.4	45.0	+0.13					***89.3	47.2	+0.24		***79.6	52.6	-0.17	
15	145.1	46.7	-0.03					150.3	46.6	-0.07		138.8	51.2	-0.06	
16	159.0	48.8	+0.14					169.0	49.3	+0.17		138.4	49.6	+0.09	
17	162.0	49.3	+0.02					167.4	48.2	+0.04		138.3	50.3	-0.04	
18	149.3	45.2	+0.01					145.0	40.5	+0.10		143.5	50.0	+0.11	
19	149.5	44.6	+0.06					161.8	45.2	0		145.5	49.8	+0.05	

NOTE - Withdrawal period was initiated following 13-weeks of compound administration. Selected animals were continued into the period of withdrawal which continues at the writing of this report.

* Dosage level increased to 1000 ppm. in the 5th week of study.

** Dosage level increased to 5000 ppm. in the 5th week of study.

*** Grams/rat/4 days.

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(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 12. Summary of Hematologic Values for Male Rats.

Hematology	Compound Administration Month	Control	100 ppm.	500 ppm.*	2500 ppm.**
Hematocrit, %	0	47	45	45	44
	1	48	46	47	43
	2	48	45	45	38
	3	48	47	45	38
Hemoglobin gms./100 ml.	0	12.7	12.7	12.3	12.4
	1	14.6	14.1	14.5	13.3
	2	15.9	15.2	15.3	13.2
	3	15.7	15.0	14.7	12.0
Erythrocytes, $\times 10^6$ /cmm.	0	6.38	6.04	6.21	6.04
	1	6.60	6.74	6.43	6.31
	2	7.21	7.55	7.35	6.29
	3	7.16	7.05	7.06	5.90
Leucocytes, $\times 10^3$ /cmm.	0	10.75	9.90	12.48	11.30
	1	11.79	11.21	8.83	8.62
	2	11.22	9.40	11.24	11.93
	3	15.25	10.28	11.15	11.55
Neutrophils, % Seg., %	0	15	15	15	12
	1	7	17	14	11
	2	14	13	14	11
	3	17	20	16	8
Non-Seg., %	0	1	1	0	1
	1	0	0	0	0
	2	0	0	0	0
	3	0	0	0	0
Lymphocytes, %	0	83	82	83	85
	1	90	82	85	87
	2	83	84	84	87
	3	80	78	82	89
Monocytes, %	0	1	1	1	1
	1	2	0	1	1
	2	3	2	1	1
	3	2	0	1	1
Eosinophils, %	0	0	1	1	1
	1	1	1	0	1
	2	0	1	1	1
	3	1	2	1	2
Basophils, %	0	0	0	0	0
	1	0	0	0	0
	2	0	0	0	0
	3	0	0	0	0

* Dosage level in this group increased to 1000 ppm. in the 5th week of study.

** Dosage level in this group increased to 5000 ppm. in the 5th week of study.

Ninety-Day Feeding Study in the Rat.

TABLE 13. Summary of Hematologic Values for Female Rats.

Hematology	Compound Administration Month	Control	100 ppm.	500 ppm.*	2500 ppm.**
Hematocrit, %	0	49	45	46	46
	1	49	46	45	43
	2	46	44	41	33
	3	45	47	40	33
Hemoglobin gms./100 ml.	0	13.3	12.3	12.4	12.9
	1	15.1	14.4	14.4	13.5
	2	15.8	14.8	14.3	11.7
	3	15.6	14.9	13.6	10.6
Erythrocytes, $\times 10^6$ /cmm.	0	6.63	6.38	6.23	6.51
	1	7.13	6.82	6.51	6.30
	2	6.74	6.81	6.57	5.44
	3	6.64	6.82	6.21	5.54
Leucocytes, $\times 10^3$ /cmm.	0	12.64	13.72	11.73	11.72
	1	9.41	7.40	9.08	11.53
	2	11.76	9.27	8.76	8.67
	3	10.96	9.04	10.14	11.38
Neutrophils, % Seg., %	0	14	11	14	11
	1	15	17	14	15
	2	15	13	17	12
	3	11	20	11	8
Non-Seg., %	0	0	0	0	0
	1	0	0	0	0
	2	0	0	0	0
	3	1	0	0	0
Lymphocytes, %	0	83	87	84	88
	1	81	81	84	84
	2	82	83	79	87
	3	85	77	88	90
Monocytes, %	0	1	2	1	1
	1	2	1	1	1
	2	2	2	2	1
	3	2	2	0	1
Eosinophils, %	0	1	0	1	0
	1	2	1	1	0
	2	1	2	2	0
	3	1	1	1	1
Basophils, %	0	0	0	0	0
	1	0	0	0	0
	2	0	0	0	0
	3	0	0	0	0

* Dosage level in this group increased to 1000 ppm. in the 5th week of study.

** Dosage level in this group increased to 5000 ppm. in the 5th week of study.

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Ninety-Day Feeding Study in the Rat.

TABLE 14. Individual Rat Hematologic Values during Control Period.

Rat No. & Sex	Hematocrit %	Hemoglobin gms./100 ml.	Erythrocytes ($\times 10^6$ /cmm.)	Total Leucocytes ($\times 10^3$ /cmm.)	Neutrophils		Differential			
					Seg.%	Non-Seg.%	Lymphocytes %	Monocytes %	Eosinophils %	Basophils %
<u>Control:</u>										
14163M	46	12.6	6.09	7.29	7	1	92	0	0	0
14167M	50	14.0	6.90	14.00	13	0	84	3	0	0
14173M	45	12.3	6.42	12.82	31	0	69	0	0	0
14175M	46	12.7	6.01	10.32	9	2	85	4	0	0
14178M	48	12.6	6.94	11.52	21	1	78	0	0	0
14181M	45	12.0	5.91	8.57	9	0	91	0	0	0
Mean	47	12.7	6.38	10.75	15	1	83	1	0	0
14143F	48	13.2	6.14	16.18	9	0	90	1	0	0
14146F	48	12.5	6.14	12.34	19	0	80	1	0	0
14150F	48	13.2	6.89	14.18	20	0	75	3	2	0
14154F	50	13.9	6.98	13.03	8	0	91	1	0	0
14157F	49	13.1	6.40	9.74	7	0	92	0	1	0
14160F	49	13.6	7.22	10.38	21	0	78	0	1	0
Mean	49	13.3	6.63	12.64	14	0	84	1	1	0
<u>100 ppm.:</u>										
14204M	49	13.4	6.50	9.65	16	0	78	4	0	0
14208M	43	13.4	5.40	8.63	15	0	84	1	0	0
14210M	44	12.1	6.20	12.96	16	2	81	0	1	0
14205M	43	12.2	5.81	7.36	19	1	78	1	1	0
14216M	45	12.0	6.10	6.44	13	0	87	0	0	0
14220M	46	12.9	6.23	14.36	8	0	90	1	1	0
Mean	45	12.7	6.04	9.90	15	1	82	1	1	0
14184F	46	12.1	6.02	25.67	15	0	81	4	0	0
14189F	41	11.1	5.55	14.31	14	0	84	1	1	0
14191F	45	12.0	6.07	10.55	6	0	92	2	0	0
14194F	46	12.6	6.25	10.63	5	0	95	0	0	0
14198F	45	11.7	6.02	9.78	11	0	85	3	1	0
14201F	49	14.1	8.36	11.40	14	0	84	2	0	0
Mean	45	12.3	6.38	13.72	11	0	87	2	0	0

Ninety-Day Feeding Study in the Rat.

TABLE 14. Continued. Individual Rat Hematologic Values during Control Period.

Rat No. & Sex	Hematocrit %	Hemoglobin gms./100 ml.	Erythrocytes ($\times 10^6$ /cmm.)	Total Leucocytes ($\times 10^3$ /cmm.)	Neutrophils		Differential			
					Seg. %	Non-Seg. %	Lymphocytes %	Monocytes %	Eosinophils %	Basophils %
<u>500 ppm.:</u>										
14244M	45	11.5	6.33	10.25	22	0	77	0	1	0
14247M	44	12.3	6.66	13.42	21	0	78	1	0	0
14249M	45	12.3	6.02	12.58	5	0	94	0	1	0
14251M	47	13.0	6.22	10.76	15	0	82	3	0	0
14255M	43	12.1	6.04	10.19	16	0	81	2	1	0
14257M	46	12.6	5.99	17.68	10	0	88	1	1	0
Mean	45	12.3	6.21	12.48	15	0	83	1	1	0
14225F	48	13.3	6.74	23.52	24	0	75	1	0	0
14227F	47	11.3	5.83	9.47	10	0	88	1	1	0
14231F	44	12.8	6.51	10.19	10	0	89	1	0	0
14233F	45	12.5	6.15	10.35	8	0	90	2	0	0
14236F	45	12.4	6.13	8.58	19	0	79	0	2	0
14241F	45	12.0	6.01	8.26	15	0	82	2	1	0
Mean	46	12.4	6.23	11.73	14	0	84	1	1	0
<u>2500 ppm.:</u>										
14284M	44	12.5	6.03	15.14	18	1	79	2	0	0
14288M	46	12.9	6.48	10.32	12	0	88	0	0	0
14290M	44	12.4	6.01	13.88	10	1	87	1	1	0
14295M	43	12.3	5.72	8.92	11	0	86	2	1	0
14298M	42	12.0	6.22	10.30	13	1	85	0	1	0
14301M	44	12.0	5.77	9.21	8	0	90	2	0	0
Mean	44	12.4	6.04	11.30	12	1	85	-	1	0
14264F	46	13.0	6.25	11.62	13	1	85	1	0	0
14267F	46	12.9	6.58	11.10	7	0	91	2	0	0
14269F	45	12.2	6.13	8.96	11	0	87	1	1	0
14276F	31	13.7	6.76	11.35	9	1	89	0	1	0
14278F	43	12.2	7.16	17.47	8	0	90	2	0	0
14281F	45	13.4	6.20	9.84	18	0	81	1	0	0
Mean	46	12.9	6.51	11.72	11	0	88	1	0	0

00133

(b) (4)
Ninety-Day Feeding Study in the Rat.

TABLE 15. Individual Rat Hematologic Values at One Month.

Rat No. & Sex	Hematocrit %	Hemoglobin gms./100 ml.	Erythrocytes ($\times 10^6/\text{cmm.}$)	Total Leucocytes ($\times 10^3/\text{cmm.}$)	Differential					
					Neutrophils		Lymphocytes	Monocytes	Eosinophils	Basophils
					Seg. %	Non-Seg. %	%	%	%	%
<u>Control:</u>										
14162M	50	15.4	7.18	14.40	8	0	86	5	1	0
14165M	46	13.9	6.66	14.75	6	0	91	3	0	0
14168M	47	14.8	6.80	9.27	6	0	90	3	1	0
14171M	47	14.5	6.22	14.34	5	0	94	1	0	0
14174M	48	14.4	6.44	10.88	7	0	92	1	0	0
14177M	47	14.5	6.30	7.08	10	0	88	1	1	0
Mean	48	14.6	6.60	11.79	7	0	90	2	1	0
14142F	48	14.7	6.87	7.82	14	0	82	1	3	0
14144F	48	15.2	7.04	8.80	19	0	77	1	3	0
14146F	50	15.5	8.12	11.60	18	0	77	3	2	0
14148F	51	15.2	7.27	10.53	17	0	80	1	1	1
14150F	47	14.3	6.61	7.00	14	0	80	3	3	0
14153F	49	15.4	6.89	10.72	9	0	89	1	1	0
Mean	49	15.1	7.13	9.41	15	0	81	2	2	0
<u>100 ppm:</u>										
14202M	44	13.6	6.32	19.70	7	0	90	1	2	0
14205M	48	14.8	6.73	7.10	25	0	74	0	1	0
14208M	47	14.6	7.08	8.22	30	0	69	0	1	0
14211M	45	13.7	6.54	6.78	9	0	88	1	2	0
14214M	49	13.8	7.03	11.69	23	0	76	0	1	0
14217M	45	14.1	6.72	13.77	7	0	92	1	0	0
Mean	46	14.1	6.74	11.21	17	0	82	0	1	0
14182F	47	14.2	6.69	9.15	6	0	91	1	2	0
14185F	44	13.6	6.68	3.97	46	3	49	1	1	0
14188F	46	14.3	6.91	8.64	11	0	87	0	2	0
14191F	48	14.8	7.10	6.98	18	0	81	1	0	0
14194F	45	13.9	7.28	6.53	11	0	86	2	1	0
14197F	46	14.4	6.30	9.15	8	0	91	1	0	0
Mean	46	14.4	6.82	7.40	17	0	81	1	1	0

(b) (4)
Ninety-Day Feeding Study in the Rat.

TABLE 3. Continued. Individual Rat Hematologic Values at One Month.

Rat No. & Sex	Hematocrit %	Hemoglobin gms./100 ml.	Erythrocytes ($\times 10^6/\text{cmm.}$)	Total Leucocytes ($\times 10^3/\text{cmm.}$)	Neutrophils		Differential			
					Seg. %	Non-Seg. %	Lymphocytes %	Monocytes %	Eosinophils %	Basophils %
<u>500 ppm.:</u>										
14242M	51	15.9	7.07	7.48	17	0	82	0	1	0
14245M	45	13.6	6.03	7.84	14	1	84	1	0	0
14248M	47	14.6	6.77	9.75	9	0	90	1	0	0
14251M	46	13.9	6.17	11.62	12	0	87	1	0	0
14254M	47	14.7	5.99	8.16	10	0	90	0	0	0
14257M	48	14.5	6.55	8.13	20	0	79	0	1	0
Mean	47	14.5	6.43	8.83	14	0	85	1	0	0
14222F	45	14.4	6.55	11.49	8	0	90	2	0	0
14225F	46	14.3	6.83	9.65	10	0	89	1	0	0
14228F	45	14.4	6.20	7.68	11	0	87	0	2	0
14231F	45	14.2	6.42	9.95	21	1	77	1	0	0
14234F	46	14.4	6.69	5.79	20	0	79	1	0	0
14237F	45	14.5	6.35	9.90	14	0	83	1	2	0
Mean	45	14.4	6.51	9.08	14	0	84	1	1	0
<u>2500 ppm.:</u>										
14282M	42	13.2	6.02	9.79	8	0	91	0	1	0
14285M	44	13.9	6.57	11.49	11	0	88	1	0	0
14288M	42	12.6	5.93	8.82	9	0	90	1	0	0
14291M	45	13.7	6.68	6.71	18	0	82	0	0	0
14294M	41	12.5	6.14	6.54	11	0	85	3	1	0
14297M	45	13.9	6.50	8.34	10	0	89	0	1	0
Mean	43	13.3	6.31	8.62	11	0	87	1	1	0
14262F	44	13.6	6.12	19.29	9	0	88	3	0	0
14265F	42	13.3	6.07	9.08	16	0	83	1	0	0
14268F	46	14.6	7.19	6.28	14	0	85	0	1	0
14271F	41	13.0	5.96	13.43	18	0	80	1	1	0
14274F	40	12.9	5.95	8.84	16	0	83	1	0	0
14277F	44	13.8	6.53	12.23	16	1	81	2	0	0
Mean	43	13.5	6.30	11.53	15	0	84	1	0	0

000133



Ninety-Day Feeding Study in the Rat.

TABLE 16. Individual Rat Hematologic Values at Two Months.

Rat No. & Sex	Hematocrit %	Hemoglobin gms./100 ml.	Erythrocytes (x10 ⁶ /cmm.)	Total Leucocytes (x10 ³ /cmm.)	Neutrophils		Differential			
					Seg. %	Non-Seg. %	Lymphocytes %	Monocytes %	Eosinophils %	Basophils %
Control:										
14164M	47	15.4	7.02	11.44	7	0	90	2	1	0
14167M	49	16.5	7.43	13.95	12	0	83	5	0	0
14170M	52	16.6	7.47	11.11	5	0	93	1	1	0
14174M	47	15.6	7.07	9.73	31	0	64	5	0	0
14178M	47	16.0	7.00	11.22	19	0	81	0	0	0
14181M	48	15.4	7.24	9.88	8	0	90	2	0	0
Mean	48	15.9	7.21	11.22	14	0	83	3	0	0
14143F	47	15.4	6.67	11.86	32	0	67	1	0	0
14147F	48	16.2	6.78	15.15	9	0	87	3	1	0
14149F	49	16.4	7.26	10.64	9	0	88	1	2	0
14152F	41	15.2	6.36	10.92	22	0	76	0	0	0
14154F	50	15.8	7.03	12.83	7	0	90	3	0	0
14158F	42	16.0	6.31	9.16	8	0	90	2	0	0
Mean	46	15.8	6.74	11.76	15	0	82	2	1	0
100 ppm:										
14204M	50	16.0	7.84	10.75	19	0	75	3	3	0
14210M	44	14.9	7.55	9.29	8	0	90	1	1	0
14213M	41	14.8	7.87	12.15	14	0	84	1	1	0
14217M	42	14.9	6.84	7.30	8	0	91	1	0	0
14220M	50	15.8	8.02	9.37	15	0	82	2	1	0
14221M	40	14.5	7.20	7.56	12	0	85	3	0	0
Mean	45	15.2	7.55	9.40	13	0	84	2	1	0
14184F	45	15.2	6.85	10.00	7	0	90	1	2	0
14190F	45	15.0	6.74	6.42	22	2	69	4	3	0
14193F	41	13.6	6.12	7.11	10	0	87	2	1	0
14194F	44	15.1	6.71	6.23	12	0	83	3	2	0
14196F	43	15.1	6.98	13.75	14	0	85	0	1	0
14200F	43	14.5	7.47	12.12	10	0	90	0	0	0
Mean	44	14.8	6.81	9.27	13	0	83	2	2	0

000136

(4) (9)
Ninety-Day Feeding Study in the Rat.

TABLE 16. Continued. Individual Rat Hematologic Values at Two Months.

Rat No. & Sex	Hematocrit %	Hemoglobin gms./100 ml.	Erythrocytes ($\times 10^6$ /cmm.)	Total Leucocytes ($\times 10^3$ /cmm.)	Neutrophils		Differential			
					Seg. %	Non-Seg. %	Lymphocytes %	Monocytes %	Eosinophils %	Basophils %
<u>1000 ppm.:</u>										
14243M	42	15.4	7.71	9.97	23	0	75	1	1	0
14246M	46	15.2	7.11	12.04	13	0	84	1	2	0
14251M	47	15.4	7.42	12.47	11	0	87	1	1	0
14253M	46	14.8	6.94	8.86	15	1	82	1	1	0
14257M	46	15.9	8.03	10.67	6	0	93	0	1	0
14261M	42	15.1	6.89	13.43	13	1	82	2	2	0
Mean	45	15.3	7.35	11.24	14	0	84	1	1	0
14223F	42	15.5	7.28	8.34	16	1	81	0	2	0
14226F	43	14.2	6.63	6.64	18	0	72	5	5	0
14230F	41	14.3	6.28	10.28	8	0	92	0	0	0
14234F	37	13.6	6.63	6.17	24	0	74	1	1	0
14237F	43	15.8	6.85	13.43	28	0	62	8	2	0
14240F	38	12.4	5.77	7.68	6	0	94	0	0	0
Mean	41	14.3	6.57	8.76	17	0	79	2	2	0
<u>5000 ppm.:</u>										
14283M	42	13.3	6.33	11.96	7	0	92	0	1	0
14289M	34	12.0	6.12	17.50	23	0	76	1	0	0
14293M	35	12.3	6.09	11.20	17	0	81	1	1	0
14295M	36	12.7	6.13	6.97	8	0	91	0	1	0
14297M	28	13.6	6.08	14.49	4	0	94	1	1	0
14300M	44	15.0	6.96	9.46	9	1	87	3	0	0
Mean	38	13.2	6.29	11.53	11	0	87	1	1	0
14263F	37	13.0	5.60	11.57	10	1	87	2	0	0
14270F	29	11.2	5.31	5.16	14	0	84	2	0	0
14273F	35	12.1	5.64	9.55	8	0	91	1	0	0
14275F	33	11.8	5.47	8.90	8	0	92	0	0	0
14279F	30	10.4	4.93	6.78	17	0	81	1	1	0
14281F	33	11.7	5.68	10.07	17	0	82	0	1	0
Mean	33	11.7	5.44	8.67	12	0	87	1	0	0

000137

(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 17. Individual Rat Hematologic Values at Three Months.

Rat No. & Sex	Hematocrit %	Hemoglobin gms./100 ml.	Erythrocytes (x10 ⁶ /cmm.)	Total Leucocytes (x10 ³ /cmm.)	Differential					
					Neutrophils		Lymphocytes	Monocytes	Eosinophils	Basophils
					Seg.%	Non-Seg.%	%	%	%	%
<u>Control:</u>										
14164M	53	16.1	7.52	17.93	15	0	82	3	0	0
14169M	46	16.0	6.68	21.59	6		94	0	0	0
14172M	47	15.6	7.14	14.62	23	0	70	5	2	0
14176M	48	15.6	6.79	13.86	15	0	84	1	0	0
14179M	47	15.2	7.53	10.06	17	0	80	1	2	0
14181M	50	15.6	7.10	13.45	24	0	74	2	1	0
Mean	48	15.7	7.16	15.23	17	0	80	2	1	0
14147 ^c	46	16.9	6.64	13.71	7	1	89	2	1	0
14151F	43	15.1	6.52	7.16	18	2	80	0	0	0
14154F	45	15.2	6.66	12.03	15	1	79	1	4	0
14156F	41	15.1	6.33	7.12	9	1	88	1	1	0
14158F	47	16.0	7.02	11.53	5	0	91	2	2	0
14161F	45	15.2	6.69	14.18	13	0	84	2	1	0
Mean	45	15.6	6.64	10.96	11	1	85	1	2	0
<u>100 ppm.:</u>										
14203M	45	14.5	6.60	13.85	40	1	58	1	0	0
14206M	50	15.2	7.47	10.73	24	0	73	0	3	0
14210M	47	14.8	6.91	9.58	7	0	91	0	2	0
14215M	45	15.1	6.80	7.47	20	1	78	0	1	0
14218M	46	14.6	6.90	12.35	16	0	82	0	2	0
14219M	50	15.6	7.60	7.71	12	0	87	0	1	0
Mean	47	15.0	7.05	10.28	20	0	78	0	2	0
14183F	49	15.6	6.89	12.16	13	0	85	2	0	0
14186F	50	15.3	7.26	10.83	29	0	69	1	0	1
14190F	38	12.0	6.09	6.65	28	3	63	3	2	1
14195F	49	15.9	6.89	5.57	11	0	87	1	1	0
14197F	50	16.0	6.77	11.79	15	0	85	0	0	0
14200F	46	14.8	7.03	7.25	26	0	73	1	0	0
Mean	47	14.9	6.82	9.04	20	0	77	2	1	0

000138

Ninety-Day Feeding Study in the Rat.

TABLE 17. Continued. Individual Rat Hematologic Values at Three Months.

Rat No. & Sex	Hematocrit %	Hemoglobin gms./100 ml.	Erythrocytes ($\times 10^6$ /cmm.)	Total Leucocytes ($\times 10^3$ /cmm.)	Neutrophils		Differential			
					Seg. %	Non-Seg. %	Lymphocytes %	Monocytes %	Eosinophils %	Basophils %
<u>500 ppm.:</u>										
14244M	48	15.6	7.59	8.18	7	0	92	0	1	0
14247M	45	14.4	6.91	10.44	23	0	74	0	3	0
14252M	47	15.1	7.28	8.53	9	0	90	0	1	0
14255M	44	13.9	6.48	11.35	12	0	86	0	2	0
14257M	46	15.0	7.27	12.50	31	0	68	1	0	0
14260M	43	14.0	6.82	15.89	13	0	84	2	1	0
Mean	45	14.7	7.06	11.15	16	0	82	1	1	0
14224F	43	14.2	6.14	9.40	6	0	93	0	1	0
14227F	36	12.7	6.07	12.13	18	0	82	0	0	0
14232F	41	14.6	6.52	12.63	16	0	84	0	0	0
14236F	45	14.6	6.39	7.02	13	0	87	0	0	0
14238F	39	12.8	6.22	9.94	6	0	94	0	0	0
14240F	38	12.6	5.90	9.70	8	0	89	1	2	0
Mean	40	13.6	6.21	10.14	11	0	88	0	1	0
<u>2500 ppm.:</u>										
14283M	38	12.1	6.20	13.87	6	0	93	1	0	0
14287M	35	11.8	5.29	8.41	8	0	91	0	1	0
14291M	37	11.9	5.82	10.18	7	0	92	1	0	0
14294M	35	11.0	5.15	12.18	11	1	84	0	4	0
14297M	41	11.8	6.19	13.55	4	0	94	1	1	0
14300M	41	13.4	6.73	11.12	13	1	79	4	3	0
Mean	38	12.0	5.90	11.55	8	0	89	1	2	0
14265F	31	9.7	5.25	13.37	8	0	91	0	1	0
14269F	34	10.5	5.04	13.63	8	1	89	2	0	0
14272F	36	11.6	6.38	8.95	10	0	88	2	0	0
14276F	34	10.5	5.54	9.45	8	1	89	1	1	0
14278F	30	9.5	5.42	14.55	2	0	95	2	1	0
14281F	36	12.0	5.63	8.35	10	0	88	1	1	0
Mean	33	10.6	5.54	11.38	8	0	90	1	1	0

000139

(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 18. Individual and Mean Results of Biochemical Studies During Control Period

Group	Rat No.	Alkaline Phosphatase	SGOT ¹	SGPT ²
Control, Female	14142	78		
	14145	78		
	14149	75		
	14153	105		
	14156	93		
	14154	45		
	14144		34	24
	14147		27	24
	14152		29	23
	14155		28	23
	14158		28	23
	14160		30	25
	Mean		79	29
Control, Male	14162	99		
	14164	93		
	14166	57		
	14172	93		
	14177	93		
	14179	99		
	14170		29	23
	14168		30	22
	14174		31	24
	14176		27	22
	14180		32	23
	14171		29	26
	Mean		89	30
100 ppm., Female	14183	36		
	14188	48		
	14192	39		
	14199	48		
	14182	90		
	14196	45		
	14185		26	22
	14190		29	23
	14193		29	22
	14200		29	25
	14197		29	24
	14195		29	24
	Mean		51	29

¹ Serum Glutamic Oxalacetic Transaminase² Serum Glutamic Pyruvic Transaminase

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000140

(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 18. Continued. Individual and Mean Results of Biochemical Studies During Control Period.

Group	Rat No.	Alkaline Phosphatase	SGOT ¹	SGPT ²
100 ppm., Male	14202	57		
	14209	87		
	14211	63		
	14219	93		
	14214	96		
	14221	36		
	14203		29	23
	14206		27	23
	14212		30	23
	14215		29	23
	14218		26	24
	14217		30	26
	Mean		72	29
500 ppm., Female	14230	90		
	14224	87		
	14222	84		
	14240	96		
	14235	99		
	14232	90		
	14229		29	24
	14228		25	22
	14223		29	22
	14239		30	22
	14237		28	25
	14234		27	22
	Mean		91	28
500 ppm., Male	14242	51		
	14245	57		
	14248	54		
	14252	93		
	14254	39		
	14258	87		
	14243		27	22
	14246		29	22
	14250		26	24
	14253		29	22
	14256		27	22
	14259		25	23
	Mean		64	27

¹ Serum Glutamic Oxalacetic Transaminase² Serum Glutamic Pyruvic Transaminase

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000141

(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 18. Continued. Individual and Mean Results of Biochemical Studies During Control Period

Group	Rat No.	Alkaline Phosphatase	SGOT ¹	SGPT ²	
2500 ppm., Female	14271	39			
	14266	75			
	14262	57			
	14273	99			
	14274	78			
	14277	69			
	14268		27	22	
	14265		32	24	
	14263		28	21	
	14272		31	24	
	14275		28	23	
	14280		29	23	
	Mean		70	29	23
	2500 ppm., Male	14282	90		
14286		90			
14296		51			
14283		51			
14289		93			
14297		48			
14287			32	27	
14291			27	25	
14300			26	24	
14285			29	22	
14292			29	23	
14299			27	21	
Mean			71	28	24

¹ Serum Glutamic Oxalacetic Transaminase² Serum Glutamic Pyruvic Transaminase

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(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 19. Individual and Mean Results of Biochemical Studies at One Month.

Group	Rat No.	Alkaline Phosphatase	SGOT ¹	SGPT ²
Control, Female	14143	60	26	24
	14145	84	28	25
	14147	90	25	23
	14149	78	26	25
	14151	96	24	23
	14154	72	28	25
	Mean		80	26
Control, Male	14163	72	25	24
	14166	53	24	21
	14169	129	25	24
	14172	63	28	23
	14175	114	27	24
	14178	129	24	24
	Mean		93	26
100 ppm., Female	14182	85	26	23
	14186	73	26	24
	14189	117	25	24
	14192	54	25	22
	14195	108	25	23
	14198	114	25	24
	Mean		86	25
100 ppm., Male	14203	84	25	24
	14206	129	27	25
	14209	132	27	24
	14212	105	26	23
	14215	105	26	24
	14218	126	25	23
	Mean		114	26
500 ppm., Female	14223	52	28	25
	14226	99	28	25
	14229	84	26	23
	14232	117	27	23
	14235	123	28	26
	14238	102	26	25
	Mean		96	27

¹ Serum Glutamic Oxalacetic Transaminase² Serum Glutamic Pyruvic Transaminase

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(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 19. Continued. Individual and Mean Results of Biochemical Studies at One Month.

Group	Rat No.	Alkaline Phosphatase	SGOT ¹	SGPT ²
500 ppm., Male	14243	72	27	23
	14246	132	27	25
	14249	132	26	24
	14252	96	26	24
	14255	87	25	23
	14258	132	25	25
Mean		109	26	24
2500 ppm., Female	14263	84	28	24
	14266	51	27	24
	14269	60	26	23
	14272	72	28	24
	14275	84	28	24
	14278	45	28	25
Mean		66	28	24
2500 ppm., Male	14283	72	28	23
	14286	117	27	24
	14289	117	24	23
	14292	69	25	23
	14295	105	26	23
	14298	81	25	24
Mean		94	26	24

¹ Serum Glutamic Oxalacetic Transaminase² Serum Glutamic Pyruvic Transaminase

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(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 20. Individual and Mean Results of Biochemical Studies at Two Months.

Group	Rat No.	Alkaline Phosphatase	SGOT ¹	SGPT ²
Control, Female	14144	60	27	21
	14148	73	26	24
	14150	59	25	22
	14151	56	19	22
	14153	67	25	22
	14155	57	26	22
Mean		64	25	22
Control, Male	14163	54	28	20
	14166	38	28	23
	14169	79	26	23
	14171	98	27	24
	14172	78	24	24
	14173	78	25	22
Mean		71	26	23
100 ppm., Female	14183	31	24	21
	14186	47	23	23
	14187	58	25	22
	14192	39	24	21
	14195	36	30	22
	14198	37	29	22
Mean		41	26	22
100 ppm., Male	14203	56	25	24
	14206	36	28	21
	14209	111	27	22
	14211	64	27	22
	14216	33	29	24
	14219	46	29	23
Mean		58	28	23
1000 ppm., Female	14224	62	26	21
	14227	58	27	22
	14229	64	29	24
	14232	63	26	22
	14235	46	31	22
	14236	27	25	21
Mean		53	27	22

¹ Serum Glutamic Oxalacetic Transaminase² Serum Glutamic Pyruvic Transaminase

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(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 20. Continued. Individual and Mean Results of Biochemical Studies at Two Months.

Group	Rat No.	Alkaline Phosphatase	SGOT ¹	SGPT ²
1000 ppm., Male	14242	39	26	23
	14247	45	27	22
	14249	53	29	21
	14254	41	26	23
	14256	38	29	21
	14259	70	28	22
Mean		48	28	22
5000 ppm., Female	14264	64	27	20
	14267	32	27	21
	14269	32	26	21
	14271	36	27	21
	14274	28	29	21
	14277	37	28	22
Mean		40	27	21
5000 ppm., Male	14284	47	26	23
	14289	49	27	21
	14292	82	27	21
	14294	27	27	20
	14296	50	29	24
	14298	88	28	23
Mean		57	27	22

¹ Serum Glutamic Oxalacetic Transaminase

² Serum Glutamic Pyruvic Transaminase

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(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 21. Individual and Mean Results of Biochemical Studies at Three Months.

Group	Rat No.	Alkaline Phosphatase	SGOT ¹	SGPT ²
Control, Female	14144	26	30	23
	14248	59	23	24
	14155	21	26	22
	14157	20	28	22
	14159	31	27	23
	14160	28	28	26
Mean		31	27	23
Control, Male	14174	24	25	21
	14171	30	25	23
	14173	32	27	22
	14175	79	25	25
	14177	77	27	24
	14180	107	28	27
Mean		58	27	24
100 ppm., Female	14187	22	25	22
	14189	29	26	23
	14192	18	25	21
	14196	14	27	21
	14198	68	23	22
	14199	32	24	21
Mean		31	24	22
100 ppm., Male	14204	16	24	22
	14207	25	23	21
	14209	47	26	20
	14211	25	25	21
	14213	35	24	21
	14216	41	22	22
Mean		32	24	21
1000 ppm., Female	14226	39	23	24
	14229	53	26	24
	14233	73	25	23
	14235	55	25	25
	14237	50	25	22
	14239	22	23	20
Mean		49	25	23

¹ Serum Glutamic Oxalacetic Transaminase² Serum Glutamic Pyruvic Transaminase

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000147

(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 2]. Continued. Individual and Mean Results of Biochemical Studies at Three Months.

Group	Rat No.	Alkaline Phosphatase	SGOT ¹	SGPT ²
1000 ppm., Male	14243	41	29	27
	14250	43	25	22
	14254	15	26	19
	14256	26	23	20
	14259	87	23	23
	14261	34	22	22
Mean		41	25	22
5000 ppm., Female	14264	26	25	22
	14277	19	25	21
	14271	18	25	20
	14274	18	26	22
	14280	26	28	22
	14279	16	25	19
Mean		21	26	21
5000 ppm., Male	14284	49	27	24
	14286	66	25	24
	14290	37	24	21
	14292	75	24	22
	14296	45	24	22
	14298	33	24	21
Mean		51	25	22

¹ Serum Glutamic Oxaloacetic Transaminase² Serum Glutamic Pyruvic Transaminase

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(b) (4)
Ninety-Day Feeding Study in the Rat.

TABLE 22. Urinalysis Values for Male and Female Rats during Control Period.

Rat No.	Sex	Volume (ml.)	Appearance	pH	Specific Gravity	Albu- min	Bili- rubin	Glu- cose	Occ. Blood	Microscopic										
										WBC	RBC	Epi. Cells	Amor. Urates	Amm. Urates	Triple Phos.	Cal- cium Ox.	Bact- eria	Blad- der Worms		
<u>Control:</u>																				
14143	F	5	S;C	7.0	1.028	N	N	N	N	occ										
14146	F	12	LS;cl	6.9	1.030	N	N	N	N					F						F
14150	F	3	S;cl	6.3	1.032	N	N	N	N			F								M
14154	F	5	S;C	6.8	1.032	N	N	N	N				F							F
14157	F	6	S;C	7.0	1.032	N	N	N	N											M
14160	F	6	S;C	7.2	1.030	N	N	N	N					F						F
14163	M	21	LS;C	6.5	1.030	N	N	N	N			occ		F						F
14167	M	1	Am;C	6.4	1.063	3+	N	N	N	occ		1-3								F
14173	M	1	LAm;C	6.2	1.065	N	N	N	N				F							F
14175	M	4	S;cl	6.8	1.040	N	N	N	N	occ										F
14178	M	2	S;cl	6.4	1.045	N	N	N	N											M
14181	M	12	LS;C	9.0	1.030	N	N	N	N											M
<u>100 ppm.:</u>																				
14184	F	6	LS;cl	6.8	1.030	N	N	N	N	occ				F						F
14189	F	7	LS;cl	8.8	1.030	N	N	N	N					F						F
14191	F	4	S;C	6.5	1.030	N	N	N	N	occ		F								F
14194	F	3	S;cl	8.8	1.040	N	N	N	N			occ								M
14198	F	13	LS;C	9.0	1.030	N	N	N	N			occ		M						F
14201	F	3	LAm;C	6.8	1.045	N	N	N	N					F						F
14204	M	6	LS;cl	8.5	1.030	N	N	N	N			occ								M
14208	M	3	S;C	6.2	1.055	N	N	N	N					F						F
14210	M	2	S;C	6.5	1.042	N	N	N	N											F
14205	M	4	S;cl	6.8	1.330	N	N	N	N			occ		M						F
14216	M	4	LS;C	7.0	1.032	N	N	N	N											F
14220	M	9	LS;cl	9.0	1.030	N	N	N	N					F						F

Code: S - Straw C - Clear N - Negative F - Few
 LS - Light Straw cl - Cloudy 1+ - Trace-to-Slight M - Many
 Am - Amber 2+ - Slight-to-Moderate occ - Occasional
 LAm - Light Amber 3+ - Moderate
 4+ - Marked

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LS - Light Straw cl - Cloudy 1+ - Trace-to-Slight M - Many
 Am - Amber 2+ - Slight-to-Moderate occ - Occasional
 LAm - Light Amber 3+ - Moderate
 4+ - Marked

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Ninety-Day Feeding Study in the Rat.

TABLE 22. Continued. Urinalysis Values for Male and Female Rats during Control Period.

Rat No.	Sex	Volume (ml.)	Appearance	pH	Specific Gravity	Albu- min	Bili- rubin	Glu- cose	Occ. Blood	Microscopic					Cal- cium Ox.	Bact- eria	Blad- der Worms
										WBC	RBC	Epi. Cells	Amor. Urates	Amn. Urates			
<u>500 ppm.:</u>																	
14225	F	1	S;C	6.3	1.045	N	N	N	N	occ			F		M		F
14227	F	3	S;cl	8.8	1.042	N	N	N	N						F		M
14231	F	3	S;C	6.3	1.045	N	N	N	N			1-2			F		F
14233	F	3	S;cl	8.0	1.040	N	N	N	N				F	F	M		M
14236	F	7	LS;cl	6.5	1.030	N	N	N	N				F				F
14241	F	3	LAm;C	6.0	1.045	N	N	N	N					F	F		F
14244*	M	4	S;C	6.2	1.040	N	N	N	N					F	F		F
14247	M	4	S;cl	9.0	1.035	N	N	N	N				F	M	F		M
14249	M	5	S;cl	8.3	1.032	N	N	N	N			occ		F	M		M
14251	M	4	S;cl	6.7	1.045	N	N	N	N				F	F	occ		M
14255	M	6	LS;cl	6.7	1.030	N	N	N	N					occ	occ		M
14257	M	4	S;cl	6.5	1.042	N	N	N	N				occ	M	F		M
<u>2500 ppm.:</u>																	
14264	F	1	Am;C	6.5	1.065	N	N	N	N				F	M	M		F
14267	F	6	S;cl	6.9	1.030	N	N	N	N	occ				F	occ		M
14269	F	21	LS;C	7.0	1.030	N	N	N	N				F	occ	occ		F
14276	F	4	S;cl	7.3	1.030	N	N	N	N		occ			M	occ		M
14278	F	4	S;C	7.4	1.033	N	N	N	N			occ		M	M		F
14281	F	2	DS;C	9.0	1.042	N	N	N	N			F		F	F		F
14284	M	2	S;C	7.0	1.048	N	N	N	N				F	N	occ		M
14288	M	2	S;cl	9.0	1.053	N	N	N	N			occ		M			M
14290	M	5	S;cl	9.0	1.037	N	N	N	N					M			F
14295	M	10	LS;cl	9.0	1.030	N	N	N	N	occ				F	M		M
14298	M	12	S;cl	6.9	1.030	N	N	N	N			occ		M	M		L
14301	M	1	Am;C	6.2	1.055	N	N	N	N	occ		2-3		F	F		F

Code: S - Straw C - Clear N - Negative F - Few * Occasional uric acid
 LS - Light Straw cl - Cloudy 1+ - Trace-to-Slight M - Many
 DS - Dark Straw 2+ - Slight-to-Moderate L - Loaded
 Am - Amber 3+ - Moderate occ - Occasional
 LAm - Light Amber 4+ - Marked

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Ninety-Day Feeding Study in the Rat.

TABLE 23. Urinalysis Values for Male and Female Rats at One Month.

Rat No.	Sex	Volume (ml.)	Appearance	pH	Specific Gravity	Albumin	Bilirubin	Glucose	Occ. Blood	Microscopic					Calcium Ox.	Bacteria	Blood-der. Worms
										WBC	RBC	Epi. Cells	Amor. Urates	Amor. Urates			
<u>Control:</u>																	
14162	M	12	LS;cl	8.5	1.013	N	N	N	N			1-2			F		F
14165	M	12	LS;cl	7.9	1.016	N	N	N	N			occ		F		M	occ
14168	M	17	LS;cl	8.9	1.014	N	N	N	N			1-2				M	
14171	M	4	LS;cl	7.2	1.048	N	N	N	N						F		F
14174	M	15	LS;cl	7.0	1.013	N	N	N	N			occ		F		F	
14177	M	9	LS;cl	6.9	1.020	N	N	N	N			1-2		F		F	F
14142	F	10	LS;cl	6.5	1.017	N	N	N	N					F			M
14145	F	7	S;cl	9.0	1.041	N	N	N	N						F		F
14146	F	15	LS;cl	7.1	1.012	N	N	N	N					F		F	F
14148	F	6	DAm;C	8.9	1.031	N	N	N	N			1-2		F		F	F
14150	F	12	LS;cl	6.2	1.011	N	N	N	N			occ				F	M
14153	F	7	S;cl	6.9	1.035	N	N	N	N					F		F	M
<u>100 ppm.:</u>																	
14202	M	7	S;cl	7.0	1.044	N	N	N	N					F		F	
14205	M	26	LS;cl	7.3	1.008	N	N	N	N					F		F	
14208	M	10	S;cl	6.9	1.021	N	N	N	N							F	
14211	M	16	LS;cl	9.0	1.009	N	N	N	N			occ				M	occ
14214	M	14	S;cl	6.5	1.013	N	N	N	N			1-2				F	occ
14217	M	10	S;cl	6.3	1.021	N	N	N	N			occ		F		F	occ
14182	F	4	S;ci	7.0	1.042	N	N	N	N					F		L	
14185	F	13	LS;cl	7.1	1.011	N	N	N	N			occ				F	
14188	F	14	LS;C	9.0	1.007	N	N	N	N					F		F	
14191	F	12	LS;cl	6.8	1.016	N	N	N	N					F		F	
14194	F	7	S;cl	9.0	1.019	N	N	N	N			occ		F		M	F
14197	F	9	S;cl	6.5	1.017	N	N	N	N			occ		F		F	M

Code: S - Straw C - Clear N - Negative F - Few
 LS - Light Straw cl - Cloudy 1+ - Trace-to-Slight M - Many
 DAm - Dark Amber 2+ - Slight-to-Moderate L - Loaded
 3+ - Moderate occ - Occasional
 4+ - Marked

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(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 23. Continued. Urinalysis Values for Male and Female Rats at One Month.

Rat No.	Sex	Volume (ml.)	Appearance	pH	Specific Gravity	Albumin	Bilirubin	Glucose	Occ. Blood	Microscopic						Bladder Worms
										WBC	RBC	Epi. Cells	Amor. Urates	Amm. Urates	Triple Phos.	
<u>500 ppm.:</u>																
14242	M	12	LS;cl	7.1	1.012	N	N	N	N						F	F
14245	M	10	LS;cl	9.0	1.023	N	N	N	N			1-2		F	M	F
14248	M	12	LS;cl	9.0	1.011	N	N	N	N						F	M
14251	M	13	LS;cl	6.1	1.015	N	N	N	N			1-2		F	F	M
14254	M	16	LS;cl	6.8	1.011	N	N	N	N				F		F	M
14257	M	17	LS;cl	8.9	1.012	N	N	N	N					F	M	M
14222	F	8	S;cl	6.5	1.024	N	N	N	N					F	F	M
14225	F	4	S;cl	6.5	1.048	N	N	N	N			occ			F	F
14228	F	6	S;cl	6.6	1.034	N	N	N	N	1-2					F	F
14231	F	14	S;cl	7.2	1.012	N	N	N	N			occ		F	M	F
14234	F	3	DS;cl	6.1	1.050	N	N	N	N	occ			F		F	F
14237	F	16	LS;cl	8.8	1.010	N	N	N	N					F	L	F
<u>2500 ppm.:</u>																
14282	M	14	LS;C	7.1	1.023	N	N	N	N					F	M	F
14285	M	7	LS;cl	7.3	1.035	N	N	N	N			1-2		F	F	F
14288	M	17	LS;cl	8.8	1.015	N	N	N	N						L	F
14291	M	14	LS;cl	9.0	1.012	N	N	N	N					F	F	F
14294	M	4	DS;cl	8.9	1.042	N	N	N	N			occ			M	F
14297	M	17	S;cl	6.9	1.014	N	N	N	N				F		F	F
14262	F	4	S;cl	7.0	1.044	N	N	N	N			occ	F			F
14265	F	4	S;cl	6.1	1.040	N	N	N	N	2-3					F	M
14268	F	6	S;cl	6.5	1.025	N	N	N	N					F	F	F
14271	F	15	LS;cl	7.0	1.011	N	N	N	N				F		F	M
14274	F	14	S;cl	6.7	1.013	N	N	N	N			occ			F	M
14277	F	8	S;cl	7.1	1.017	N	N	N	N			occ		F	M	M

Code: S - Straw C - Clear N - Negative F - Few
 LS - Light Straw cl - Cloudy 1+ - Trace-to-Slight M - Many
 DS - Dark Straw 2+ - Slight-to-Moderate L - Loaded
 3+ - Moderate occ - Occasional
 4+ - Marked

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(b)
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Ninety-Day Feeding Study in the Rat.

TABLE 24. Continued. Urinaysis Values for Male and Female Rats at Two Months.

Rat No.	Sex	Volume (ml.)	Appear- ance	pH	Specific Gravity	Albu- min	Bili- rubin	Glu- cose	Occ. Blood	Microscopic									
										WBC	RBC	Epi- Cells	Amor. Urates	Amm. Urates	Tripla Phos.	Cal- cium Ox.	Bact- eria	Blad- der Norms	
1000 ppm.:																			
14243	M	24	LS;cl	9.0	1.013	N	N	N	N				F	F	F		F		
14246	M	16	LS;cl	6.8	1.017	N	N	N	N					F	M		F		
14251	M	12	LS;cl	6.0	1.026	N	N	N	N	occ	F			F	F		F	F	
14253	M	30	LS;C	7.8	1.010	N	N	N	1+					F	F		M		
14257	M	26	LS;cl	7.2	1.013	N	N	N	N					F	F		M		
14261	M	23	LS;cl	7.2	1.015	N	N	N	N					F	F		F		
14223	F	11	S;cl	7.2	1.013	N	N	N	N				F	M	occ		M		
14226	F	10	S;cl	9.0	1.030	N	N	N	N					F	M		F		
14230	F	12	LS;cl	8.8	1.016	N	N	N	N				F	F	F		M		
14234	F	7	S;cl	6.4	1.023	N	N	N	N			F		F	F		M		
14237	F	14	LS;C	7.5	1.010	N	N	N	N					F	F		F		
14240	F	15	LS;cl	7.8	1.009	N	N	N	N					F	M		M		
5000 ppm.:																			
14283	M	14	LS;cl	9.0	1.021	N	N	N	N					M	F		F	F	
14289	M	27	LS;cl	9.0	1.013	N	N	N	N					F	F		F	F	
14293	M	10	S;cl	9.0	1.034	N	N	N	N			occ		F	F		F	F	
14295	M	40	LS;cl	9.0	1.006	N	N	N	N					F	F		F	M	
14297	M	27	LS;cl	9.0	1.012	N	N	N	N					F	F		F	F	
14300	M	23	LS;cl	6.7	1.010	N	N	N	N					F	M		F	F	
14263	F	12	S;cl	7.0	1.020	N	N	N	N					F	F		F		
14270	F	10	S;cl	7.2	1.017	N	N	N	N				occ	F	F		F		
14273	F	14	LS;cl	9.0	1.013	N	N	N	N					F	M		F		
14275	F	5	Am;cl	8.5	1.024	N	N	N	N			F		M	M		M		
14279	F	8	S;C	6.0	1.026	N	N	N	N					F	F		F		
14281	F	4	S;C	8.2	1.028	N	N	N	N				F		F		F		

Code: S - Straw

C - Clear

N - Negative

F - Few

LS - Light Straw

cl - Cloudy

1+ - Trace-to-Slight

M - Many

Am - Amber

2+ - Slight-to-Moderate

L - Loaded

3+ - Moderate

occ - Occasional

4+ - Marked

125-016

000154

(b)(4)

Ninety-Day Feeding Study in the Rat.

TABLE 24. Urinalysis Values for Male and Female Rats at Two Months.

Rat No.	Sex	Volume (ml.)	Appearance	pH	Specific Gravity	Albumin	Bilirubin	Glucose	Occ. Blood	Microscopic					Calcium Ox.	Bacteria	Bladder Worms		
										WBC	RBC	Epi. Cells	Amor. Urates	Amn. Urates				Triple Phos.	
<u>Control:</u>																			
14164	M	28	LS;cl	7.0	1.015	N	N	N	N					M	M		M	F	
14167	M	16	LS;cl	7.1	1.022	N	N	N	N					M	F		M		
14170	M	12	LS;cl	7.0	1.028	N	N	N	N					M	F		M	F	
14174	M	25	LS;cl	9.0	1.014	N	N	N	N					F			F		
14178	M	24	LS;cl	7.5	1.012	N	N	N	N		occ			M	F		M		
14181	M	30	LS;cl	8.0	1.009	N	N	N	N				F		F		M	F	
14143	F	6	LS;cl	7.5	1.030	N	N	N	N			occ			F	F		M	
14147	F	13	LS;C	7.7	1.022	N	N	N	N					F	M		M		
14149	F	6	S;cl	9.0	1.030	N	N	N	N					F	M		F		
14152	F	11	LS;cl	9.0	1.024	N	N	N	N					F	L		F		
14154	F	3	S;C	6.2	1.065	N	N	N	N		F			occ	M		F		
14158	F	4	S;C	6.0	1.047	N	N	N	N		F			F	F		F		
<u>100 ppm.:</u>																			
14204	M	30	LS;C	7.8	1.016	N	N	N	N						M	M		F	F
14210	M	18	LS;cl	8.8	1.022	N	N	N	N			occ		F	F	F		M	F
14213	M	21	LS;cl	9.0	1.016	N	N	N	N					F	F	F		F	F
14217	M	17	S;cl	9.0	1.015	N	N	N	N					F	F	F		F	F
14220	M	30	LS;cl	8.0	1.008	N	N	N	N		occ				F	F		M	F
14221	M	23	LS;cl	9.0	1.011	N	N	N	N						F	F		F	
14184	F	4	S;cl	7.5	1.044	N	N	N	N		occ				M	M		F	
14190	F	20	LS;cl	8.4	1.008	N	N	N	N						F	M		F	
14193	F	24	LS;cl	6.4	1.006	N	N	N	N						M	occ		M	
14194	F	6	S;cl	9.0	1.028	N	N	N	N						M	F		M	
14196	F	5	S;cl	6.8	1.028	N	N	N	N						F	F		M	
14200	F	8	S;cl	6.2	1.030	N	N	N	N						F	F		F	

Code: S - Straw C - Clear N - Negative F - Few
 LS - Light Straw cl - Cloudy 1+ - Trace-to-Slight M - Many
 2+ - Slight-to-Moderate L - Loaded
 3+ - Moderate occ - Occasional
 4+ - Marked

000153

EE Ninety-Day Feeding Study in the Rat.

TABLE 24. Continued. Urinaysis Values for Male and Female Rats at Two Months.

Rat No.	Sex	Volume (ml.)	Appearance	pH	Specific Gravity	Albu- min	Bili- rubin	Glu- cose	Occ. Blood	Microscopic				Cal- cium Ox.	Bact- eria	Blad- der Worms	
										WBC	RBC	Epi- Cells	Amor. Urates				Amm. Urates
<u>1000 ppm.:</u>																	
14243	M	24	LS;cl	9.0	1.013	N	N	N	N								
14246	M	16	LS;cl	6.8	1.017	N	N	N	N				F	F			
14251	M	12	LS;cl	6.0	1.026	N	N	N	N	occ	F			F		F	
14253	M	30	LS;C	7.8	1.010	N	N	N	1+					F			
14257	M	26	LS;cl	7.2	1.013	N	N	N	N					F		M	
14261	M	23	LS;cl	7.2	1.015	N	N	N	N					F		M	
14223	F	11	S;cl	7.2	1.013	N	N	N	N					F		M	
14226	F	10	S;cl	9.0	1.030	N	N	N	N				F	M	occ	M	
14230	F	12	LS;cl	8.8	1.016	N	N	N	N				F	F	M	F	
14234	F	7	S;cl	6.4	1.023	N	N	N	N			F		F		M	
14237	F	14	LS;C	7.5	1.010	N	N	N	N			F		F		M	
14240	F	15	LS;cl	7.8	1.009	N	N	N	N					F		M	
<u>5000 ppm.:</u>																	
14283	M	14	LS;cl	9.0	1.021	N	N	N	N					M	F		F
14289	M	27	LS;cl	9.0	1.013	N	N	N	N					F			F
14293	M	10	S;cl	9.0	1.034	N	N	N	N			occ		F	F		F
14295	M	40	LS;cl	9.0	1.006	N	N	N	N					F	F		F
14297	M	27	LS;cl	9.0	1.012	N	N	N	N					F	F		M
14300	M	23	LS;cl	6.7	1.010	N	N	N	N					F	F		F
14263	F	12	S;cl	7.0	1.020	N	N	N	N					F	F		P
14270	F	10	S;cl	7.2	1.017	N	N	N	N					F	F		P
14273	F	14	LS;cl	9.0	1.013	N	N	N	N				occ	F	F		P
14275	F	5	Am;cl	8.5	1.024	N	N	N	N			F		M	M		F
14279	F	8	S;C	6.0	1.026	N	N	N	N					M	M		M
14281	F	4	S;C	8.2	1.028	N	N	N	N				F	F	F		F

Code: S - Straw C - Clear N - Negative F - Few
 LS - Light Straw cl - Cloudy 1+ - Trace-to-Slight M - Many
 Am - Amber 2+ - Slight-to-Moderate L - Loaded
 3+ - Moderate occ - Occasional
 4+ - Marked

(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 25. Urinalysis Values for Male and Female Rats at Three Months.

Rat No.	Sex	Volume (ml.)	Appearance	pH	Specific Gravity	Albumin	Bilirubin	Glucose	Occ. Blood	Microscopic						Cal-cium Ox.	Bact-eria	Blad-der Worms
										WBC	RBC	Epi. Cells	Amor. Urates	Amn. Urates	Triplic. Epos.			
<u>Control:</u>																		
14164	M	8	LS;cl	6.8	1.053	N	N	N	N					F	M		M	
14169	M	7	S;cl	7.3	1.055	N	N	N	N					F	F		F	
14172	M	11	LS;cl	9.0	1.035	N	N	N	N					F	F		F	
14176	M	5	S;cl	6.5	1.066	N	N	N	N			1-2		F	F		F	
14179	M	4	S;cl	7.8	1.058	N	N	N	N					F	F		F	
14191	M	7	S;cl	6.9	1.052	N	N	N	N					F	F		F	
14147	F	1	S;C	6.1	1.080	N	N	N	N					F	F		F	
14151	F	2	S;C	6.3	1.069	N	N	N	N					F	F		F	
14154	F	2	S;cl	7.4	1.065	N	N	N	N			occ		F	F		M	
14156	F	2	S;cl	6.1	1.065	N	N	N	N					F	F		F	
14158	F	1	S;C	6.0	1.080	N	N	N	N			1-2		F	F		F	
14161	F	2	S;C	6.7	1.065	N	N	N	N	occ		occ		F	F		F	
<u>100 ppm.:</u>																		
14203	M	7	S;cl	6.7	1.058	N	N	N	N					F	F		M	
14206	M	7	LS;cl	7.0	1.048	N	N	N	N					F	F		M	
14210	M	6	S;cl	9.0	1.055	N	N	N	N			2-3		F	F		F	
14215	M	3	DS;cl	6.0	1.080	N	N	N	N					F	F		F	
14213	M	9	S;cl	9.0	1.045	N	N	N	N					F	F		F	
14219	M	6	LS;cl	6.3	1.049	N	N	N	N			occ		F	F		F	
14183	F	1	S;C	6.0	1.080	N	N	N	N					F	F		F	
14186	F	6	LS;cl	8.0	1.045	N	N	N	N					F	F		F	
14190	F	6	S;cl	7.0	1.035	N	N	N	N			1-2		F	F		M	
14195	F	6	LS;cl	6.2	1.035	N	N	N	N					F	F		M	
14197	F	1	S;C	7.7	1.072	N	N	N	N					F	M		F	
14200	F	2	S;cl	6.0	1.065	N	N	N	N	occ				F	M		F	

Code: S - Straw C - Clear N - Negative F - Few
 LS - Light Straw cl - Cloudy 1+ - Trace-to-Slight M - Many
 DS - Dark Straw 2+ - Slight-to-Moderate L - Loaded
 3+ - Moderate occ - Occasional
 4+ - Marked

000155

LS - Light Straw cl - Cloudy
 DS - Dark Straw

000155

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

M - Many
 L - Loaded
 occ - Occasional

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Ninety-Day Feeding Study in the Rat.

TABLE 25. Continued. Urinalysis Values for Male and Female Rats at Three Months.

Rat No.	Sex	Volume (ml.)	Appearance	pH	Specific Gravity	Albu- min	Bili- rubin	Glu- cose	Occ. Blood	Microscopic									
										WBC	RBC	Epi. Cells	Amor. Urates	Amn. Urates	Triple Phos.	Cal- cium Ox.	Bact- eria	Blad- der Worms	
<u>1000 ppm.:</u>																			
14244	M	10	LS;cl	7.0	1.035	N	N	N	3+*			occ		F	F		M	F	
14247	M	6	S;cl	6.8	1.057	N	N	N	N						F		M	F	
14252	M	5	S;cl	6.6	1.065	N	N	N	N		2-3			F	F		F	F	
14255	M	4	S;C	6.0	1.065	N	N	N	N			occ	F	F	F		F	F	
14257	M	10	LS;cl	7.0	1.037	N	N	N	N		2-3			F	M		M	M	
14260	M	3	S;cl	6.7	1.073	N	N	N	N			1-2		F	M		F		
14224	F	5	S;cl	9.0	1.045	N	N	N	N					F	F		M		
14227	F	2	S;C	6.7	1.068	N	N	N	N				F		F		F		
14232	F	3	S;cl	5.9	1.057	N	N	N	N	occ				F	F		M		
14236	F	2	S;C	6.0	1.075	N	N	N	N	1-2			F	F	F		F		
14238	F	2	S;cl	6.5	1.065	N	N	N	N					F	F		F		
14240	F	1	S;C	6.2	1.078	N	N	N	N					F	F		F		
<u>5000 ppm.:</u>																			
14283	M	2	Am;Cl	6.2	1.075	N	N	N	N	occ			F	F	F		F		
14287	M	4	S;cl	6.8	1.073	N	N	N	N					F	F		F	F	
14291	M	6	S;cl	8.8	1.045	2+	N	N	N					F	M		M	F	
14294	M	2	DS;cl	7.7	1.080	N	N	N	N					F	M		F	F	
14297	M	4	DS;C	6.1	1.075	N	N	N	N			occ		F	F		F	F	
14300	M	4	S;cl	6.8	1.065	N	N	N	N				F	F	F		F	M	
14266	F	1	S;C	7.0	1.080	N	N	N	N					F	F		F		
14269	F	2	S;cl	6.2	1.068	N	N	N	N	occ				F	M		F		
14272	F	1	DS;C	5.8	1.065	N	N	N	N			occ	F	F	M		F		
14276	F	1	DS;C	6.6	1.065	N	N	N	N			1-2		F	M		F		
14278	F	2	S;C	6.3	1.065	N	N	N	N	1-2				F	M		F		
14281	F	1	DS;C	6.0	1.080	N	N	N	N	1-2			F		F		M		

Code: S - Straw C - Clear N - Negative F - Few
 LS - Light Straw cl - Cloudy 1+ - Trace-to-Slight M - Many
 DS - Dark Straw 2+ - Slight-to-Moderate L - Loaded
 Am - Amber 3+ - Moderate occ - Occasional
 4+ - Marked * Repeat 3+

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000156

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(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 26. Necropsy Observations. Thirty-Day Interim Sacrifice.

Animal Number	Sex	Organ	Comment
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Rats were normal except as noted below:

Control:

14165	M	thymus	Few petechial hemorrhages.
14146	F	uterus	Mild hydrouterus.

100 ppm.:

14202	M	lung	Moderate pneumonia.
14208	M	lung	Mild pneumonia.
14185	F	uterus	Mild hydrouterus.

2500 ppm.:

14288	M	spleen	Slightly enlarged.
14262	F	spleen	Slightly enlarged.

125-016

000157

(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 26. Continued. Necropsy Observations. Sixty-Day Interim Sacrifice.

Animal Number	Sex	Organ	Comment
<u>Rats were normal except as noted below:</u>			
<u>Control:</u>			
14149	F	lung	Few scattered gray areas.
<u>100 ppm.:</u>			
14221	M	liver lung	Pale. Gray pinpoint areas scattered throughout.
<u>5000 ppm.:</u>			
14289	M	liver testes	Slightly pale. Left testis approximately twice the size of right.
14293	M	liver	Pale.
14295	M	liver	Pale yellow in color.

125-016

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(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 26. Continued. Necropsy Observations. Ninety-Day Terminus* Sacrifice.

Animal Number	Sex	Organ	Comment
<u>Rat were normal except as noted below:</u>			
<u>Control:</u>			
14175	M	lung	Mild pneumonia.
14153	F	lung	Mild pneumonia.
<u>100 ppm.:</u>			
14214	M	lung	Mild pneumonia.
<u>1000 ppm.:</u>			
14252	M	liver	Slightly yellowish.
14254	M	lung	Mild pneumonia.
14227	F	abdominal cavity	6 mm. firm hemorrhagic area in abdominal fat.
14233	F	lung	Mild pneumonia.
14237	F	lung	Mild pneumonia.
<u>5000 ppm.:</u>			
14284	M	liver	Slight yellowish cast.
14286	M	lung	mild pneumonia.
14291	M	liver	Slight yellowish cast.
14294	M	liver	Slight yellowish cast.
14297	M	liver	Slight yellowish cast.
14266	F	lung	Moderate pneumonia and bronchiectasis.
14274	F	kidney	Hydronephrosis, right kidney.

125-016

000159

(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 26. Continued. Necropsy Observations. 21-Day Compound Withdrawal.

Animal Number	Sex	Organ	Comment
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Rats were normal except as noted below:

5000 ppm.:

14299	M	liver	Slightly pale.
14300	N	liver	Slightly pale.

125-016

000160

(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 27. Mean Actual (Grams) and Relative (% Body Weight) Organ Weights.

Dietary Level	Sex	Terminal	Spleen		Liver		Adrenals		Kidneys		Testes/Ovaries	
		Body Wt. Gm.	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Cm.	%
<u>30-Day Interim Sacrifice:</u>												
0	M	315	0.97	0.308	14.11	4.479	0.039	0.010	2.66	0.844	2.99	0.949
0	F	202	0.70	0.347	8.74	4.327	0.069	0.034	1.73	0.856	0.089	0.040
100	M	268	0.70	0.261	11.65	4.347	0.044	0.020	2.22	0.828	2.69	1.003
100	F	212	0.69	0.326	7.28	3.434	0.054	0.025	1.56	0.736	0.092	0.040
500	M	243	0.62	0.255	10.06	4.136	0.037	0.015	2.20	0.946	2.74	1.127
500	F	188	0.47	0.250	8.26	4.394	0.054	0.029	1.86	0.990	0.097	0.050
2500	M	277	1.12	0.404	15.68	5.661	0.044	0.016	2.80	1.011	2.74	0.989
2500	F	173	0.59	0.341	8.65	5.000	0.068	0.039	1.85	1.069	0.123	0.070
<u>60-Day Interim Sacrifice:</u>												
0	M	355	0.76	0.214	13.02	3.668	0.062	0.017	2.62	0.738	3.07	0.865
0	F	233	0.52	0.22	8.25	3.541	0.070	0.030	1.72	0.738	0.133	0.060
100	M	338	0.79	0.234	10.91	3.228	0.048	0.014	2.53	0.749	3.30	0.976
100	F	230	0.52	0.226	8.00	3.478	0.065	0.028	1.70	0.739	0.132	0.060
1000	M	355	0.74	0.208	12.94	3.645	0.046	0.013	2.70	0.761	3.08	0.868
1000	F	210	0.54	0.257	7.89	3.757	0.075	0.036	1.92	0.914	0.162	0.080
5000	M	412	0.90	0.218	21.71	5.269	0.071	0.017	3.46	0.840	3.82	0.927
5000	F	232	0.62	0.267	12.04	5.190	0.067	0.029	2.36	1.017	0.145	0.060
<u>90-Day Terminal Sacrifice:</u>												
0	M	495	1.08	0.218	14.12	2.853	0.066	0.013	2.87	0.580	3.32	0.670
0	F	270	0.71	0.263	8.17	3.026	0.075	0.028	1.73	0.641	0.154	0.057
100	M	469	1.14	0.243	14.19	3.026	0.057	0.012	2.95	0.629	3.39	0.723
100	F	284	0.81	0.285	8.27	2.912	0.071	0.025	1.87	0.658	0.171	0.060
1000	M	452	0.97	0.215	15.02	3.323	0.060	0.013	3.05	0.675	3.39	0.750
1000	F	284	0.77	0.271	10.59	3.729	0.087	0.031	2.30	0.810	0.155	0.055
5000	M	425	0.98	0.231	20.38	4.795	0.057	0.013	3.33	0.783	3.37	0.793
5000	F	237	0.81	0.342	10.95	4.620	0.072	0.030	2.25	0.949	0.142	0.060
<u>21-Day Compound Withdrawal:</u>												
0	M	490	0.70	0.143	14.82	3.024	0.056	0.014	2.97	0.606	3.36	0.686
0	F	297	0.56	0.189	9.17	3.087	0.073	0.025	2.09	0.704	0.224	0.080
1000	M	507	0.91	0.179	17.41	3.434	0.065	0.013	3.36	0.663	3.59	0.709
1000	F	287	0.61	0.213	9.35	3.258	0.077	0.027	2.25	0.784	0.177	0.060
5000	M	440	0.61	0.139	16.55	3.761	0.058	0.013	3.18	0.723	3.32	0.755
5000	F	277	0.57	0.206	10.75	3.881	0.083	0.030	2.45	0.884	0.162	0.060

125-016

000161

steps/
aries

%

	Thymus		Heart		Lung		Thyroid		Brain		Pituitary	
	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%	Gm.	%
0.949	0.90	0.286	1.15	0.365	1.63	0.517	0.023	0.007	1.86	0.591	0.009	0.003
9 0.040	0.68	0.337	0.78	0.386	1.32	0.653	0.021	0.010	1.79	0.886	0.007	0.003
1.003	0.73	0.272	0.98	0.366	1.56	0.582	0.027	0.010	1.74	0.649	0.009	0.003
2 0.040	0.47	0.222	0.69	0.325	1.25	0.590	0.018	0.008	1.74	0.820	0.009	0.004
1.127	0.67	0.276	0.94	0.386	1.58	0.650	0.024	0.010	1.84	0.757	0.008	0.003
7 0.050	0.71	0.378	0.77	0.410	1.28	0.681	0.024	0.013	1.74	0.926	0.008	0.004
0.989	0.74	0.267	1.06	0.383	1.65	0.596	0.018	0.006	1.96	0.708	0.006	0.002
3 0.070	0.59	0.341	0.68	0.393	1.34	0.774	0.018	0.010	1.80	1.040	0.004	0.002
0.865	0.64	0.180	1.41	0.397	1.91	0.538	0.026	0.007	1.61	0.454	0.014	0.004
3 0.060	0.57	0.244	0.86	0.369	1.16	0.498	0.024	0.010	1.79	0.768	0.011	0.005
0.976	0.79	0.234	1.17	0.346	1.70	0.503	0.027	0.008	1.88	0.556	0.010	0.003
2 0.060	0.50	0.217	0.76	0.330	1.44	0.626	0.036	0.016	1.75	0.761	0.012	0.005
0.868	0.66	0.186	1.09	0.307	1.92	0.501	0.022	0.007	2.00	0.563	0.010	0.003
2 0.080	0.56	0.267	0.81	0.386	1.41	0.671	0.033	0.016	1.87	0.890	0.010	0.005
0.927	0.90	0.218	1.36	0.330	2.06	0.500	0.030	0.007	1.98	0.481	0.012	0.003
5 0.060	0.56	0.241	0.85	0.366	1.34	0.578	0.025	0.011	1.86	0.802	0.013	0.006
0.670	0.66	0.130	1.37	0.277	2.02	0.408	0.028	0.006	1.92	0.388	0.014	0.003
4 0.057	0.51	0.189	0.84	0.311	1.37	0.507	0.025	0.009	1.82	0.674	0.013	0.005
0.723	0.64	0.136	1.42	0.303	2.11	0.450	0.027	0.006	1.99	0.424	0.011	0.002
1 0.060	0.52	0.185	0.87	0.306	1.40	0.493	0.024	0.008	1.87	0.658	0.013	0.005
0.750	0.59	0.131	1.32	0.292	2.08	0.460	0.028	0.006	1.96	0.434	0.013	0.003
5 0.055	0.50	0.176	0.98	0.345	1.48	0.521	0.031	0.011	1.89	0.665	0.013	0.005
0.793	0.66	0.155	1.29	0.304	1.91	0.449	0.025	0.006	2.00	0.471	0.010	0.002
2 0.060	0.50	0.211	0.85	0.359	1.54	0.650	0.022	0.009	1.85	0.781	0.010	0.004
0.686	0.79	0.161	1.32	0.269	2.47	0.504	0.035	0.007	2.07	0.422	0.010	0.002
4 0.080	0.52	0.175	0.89	0.300	1.53	0.515	0.026	0.009	1.87	0.630	0.012	0.004
0.709	0.84	0.166	1.51	0.298	2.29	0.452	0.036	0.007	2.12	0.418	0.014	0.003
7 0.060	0.58	0.202	0.84	0.293	1.63	0.568	0.029	0.010	1.95	0.680	0.014	0.005
0.755	0.67	0.152	1.28	0.291	1.82	0.414	0.030	0.007	2.01	0.457	0.012	0.003
2 0.060	0.62	0.224	0.93	0.336	1.60	0.578	0.030	0.010	1.90	0.686	0.012	0.005

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(b) (4)
Ninety-Day Feeding Study in the Rat.

TABLE 28. Organ Weights, Grams

Animal No. & Group	Terminal Sex	Terminal Weight Grams	Spleen	Liver	Adrenals	Kidneys	Testes/Ovaries	Thymus	Heart	Lung	Thyroid	Brain	Pituitary
<u>30-DAY INTERIM SACRIFICE:</u>													
<u>Control:</u>													
14162	M	270	1.09	12.02	0.024	2.35	3.06	0.75	0.90	1.44	0.020	1.84	0.007
14165	M	360	0.92	17.02	0.051	3.11	2.81	0.93	1.43	1.68	0.024	1.83	0.010
14168	M	315	0.89	13.30	0.043	2.52	3.10	1.01	1.12	1.76	0.025	1.92	0.008
14142	F	205	0.52	8.63	0.079	1.79	0.084	0.79	0.79	1.30	0.022	8.80	0.008
14145	F	175	0.99	8.11	0.056	1.50	0.063	0.53	0.71	1.22	0.020	1.78	0.006
14146	F	225	0.60	9.49	0.071	1.91	0.120	0.71	0.85	1.45	0.021	1.80	0.007
<u>100 ppm.:</u>													
14202	M	275	0.94	12.51	0.044	2.39	2.76	0.81	0.93	1.84	0.025	1.90	0.009
14205	M	300	0.67	13.42	0.050	2.41	3.11	0.69	1.07	1.47	0.027	1.72	0.008
14208	M	230	0.50	9.02	0.038	1.86	2.19	0.70	0.93	1.37	0.029	1.61	0.010
14182	F	280	0.57	7.75	0.060	1.61	0.110	0.60	0.72	1.30	0.030	1.70	0.010
14185	F	190	1.10	7.81	0.053	1.67	0.092	0.41	0.65	1.36	0.012	1.72	0.010
14188	F	165	0.40	6.28	0.048	1.42	0.075	0.39	0.70	1.08	0.012	1.79	0.007
<u>500 ppm.:</u>													
14242	M	225	0.49	9.49	0.028	2.16	2.33	0.50	0.99	1.76	0.033	1.73	0.006
14245	M	270	0.79	11.02	0.046	2.52	2.82	0.93	1.03	1.60	0.023	2.00	0.010
14248	M	235	0.59	9.66	0.036	2.21	2.56	0.58	0.79	1.38	0.016	1.78	0.007
14222	F	205	0.50	9.20	0.052	1.96	0.084	0.60	0.81	1.31	0.028	1.71	0.007
14225	F	160	0.40	7.08	0.051	1.59	0.083	0.45	0.70	1.14	0.026	1.71	0.007
14228	F	200	0.50	8.51	0.060	2.04	0.123	0.87	0.80	1.38	0.018	1.79	0.009
<u>2500 ppm.:</u>													
14282	M	255	0.71	14.75	0.061	2.49	2.29	0.65	0.96	1.46	0.026	1.93	0.005
14285	M	290	0.90	15.29	0.051	2.90	2.83	0.88	1.02	1.40	0.019	2.01	0.006
14288	M	285	1.76	16.99	0.019	3.00	3.10	0.70	1.20	2.08	0.010	1.94	0.007
14262	F	195	0.99	10.35	0.079	2.12	0.100	0.67	0.76	1.41	0.021	1.81	0.003
14265	F	170	0.47	7.78	0.056	1.70	0.117	0.61	0.65	1.14	0.013	1.75	0.002
14268	F	155	0.32	7.82	0.068	1.74	0.153	0.50	0.63	1.47	0.020	1.83	0.006

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(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 28. Continued. Organ Weights, Grams.

Animal No. & Group	Sex	Terminal Weight Grams	Spleen	Liver	Adrenals	Kidneys	Testes/Ovaries	Thymus	Heart	Lung	Thyroid	Brain	Pituitary
<u>21-DAY COMPOUND WITHDRAWAL:</u>													
<u>Control:</u>													
14177	M	420	0.60	11.80	0.050	2.67	3.30	0.58	1.18	2.43	0.030	2.21	0.010
14179	M	520	0.65	14.98	0.064	3.02	3.29	0.88	1.41	2.23	0.034	2.07	0.010
14180	M	530	0.85	17.68	0.055	3.22	3.50	0.90	1.38	2.75	0.042	1.93	0.010
14158	F	280	0.42	8.48	0.071	1.98	0.185	0.41	0.93	1.57	0.041	1.80	0.011
14159	F	320	0.53	9.34	0.072	2.15	0.248	0.64	0.90	1.50	0.018	1.92	0.010
14161	F	290	0.73	9.70	0.075	2.15	0.239	0.51	0.85	1.52	0.020	1.90	0.014
<u>1000 ppm.:</u>													
14258	M	560	1.05	18.65	0.064	3.65	3.80	0.90	1.70	2.23	0.035	2.15	0.014
14259	M	470	0.63	17.40	0.068	3.20	3.55	0.83	1.41	2.30	0.034	2.00	0.015
14260	M	490	1.05	16.17	0.062	3.23	3.41	0.80	1.41	2.34	0.038	2.22	0.012
14238	F	280	0.68	8.90	0.081	2.26	0.180	0.52	0.80	2.11	0.027	1.98	0.015
14239	F	290	0.57	9.63	0.069	2.40	0.192	0.61	0.91	1.42	0.023	1.81	0.010
14240	F	290	0.59	9.52	0.081	2.09	0.160	0.60	0.82	1.35	0.037	2.06	0.017
<u>5000 ppm.:</u>													
14298	M	340	0.55	11.10	0.051	2.80	3.32	0.58	1.05	1.64	0.018	2.01	0.012
14299	M	535	0.78	22.95	0.074	3.75	3.40	0.75	1.60	2.09	0.044	2.13	0.014
14300	M	445	0.50	15.61	0.048	2.98	3.25	0.68	1.20	1.72	0.028	1.90	0.010
14278	F	280	0.57	11.10	0.087	2.30	0.124	0.61	0.88	1.70	0.029	1.78	0.009
14279	F	260	0.53	10.13	0.085	2.52	0.160	0.60	0.92	1.32	0.034	1.93	0.014
14230	F	290	0.62	11.01	0.077	2.52	0.203	0.65	1.00	1.78	0.028	1.98	0.013

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(b) (4)
Ninety-Day Feeding Study in the Rat.

TABLE 28. Continued. Organ Weights, Grams.

Animal No. & Group	Sex	Terminal Weight Grams	Spleen	Liver	Adrenals	Kidneys	Testes/Ovaries	Thymus	Heart	Lung	Thyroid	Brain	Pituitary
<u>60-DAY INTERIM SACRIFICE:</u>													
<u>Control:</u>													
14167	M	340	0.81	13.13	0.058	2.60	3.14	0.69	1.16	1.67	0.027	1.81	0.014
14170	M	385	0.71	14.70	0.069	2.90	2.89	0.70	1.48	2.03	0.027	1.20	0.017
14178	M	340	0.75	11.24	0.059	2.36	3.19	0.52	1.58	2.02	0.025	1.81	0.011
14143	F	200	0.49	7.28	0.059	1.55	0.170	0.49	0.75	1.07	0.015	1.87	0.01
14149	F	260	0.47	8.88	0.071	1.90	0.100	0.69	0.98	1.22	0.031	1.74	0.009
14152	F	240	0.59	8.58	0.080	1.71	0.130	0.53	0.84	1.19	0.027	1.75	0.014
<u>100 ppm.:</u>													
14217	M	325	0.79	11.78	0.051	2.69	3.32	0.83	1.13	1.60	0.037	2.01	0.010
14220	M	340	0.79	10.52	0.053	2.31	3.31	0.96	1.22	1.81	0.025	1.71	0.009
14221	M	350	0.79	10.44	0.041	2.59	3.27	0.59	1.15	1.69	0.019	1.92	-
14184	F	215	0.41	0.062	0.062	1.61	0.144	0.45	0.70	1.15	0.044	1.79	0.012
14193	F	235	0.54	8.29	0.064	1.66	0.135	0.47	0.80	1.78	0.023	1.73	0.013
14194	F	240	0.61	7.70	0.069	1.82	0.116	0.58	0.78	1.38	0.042	1.73	0.010
<u>1000 ppm.:</u>													
14246	M	320	0.62	11.75	0.050	2.57	2.70	0.60	1.12	1.95	0.024	1.91	0.010
14251	M	360	0.79	14.00	0.048	3.09	3.17	0.62	1.11	1.81	0.029	1.99	0.012
14253	M	385	0.81	13.08	0.041	2.45	3.37	0.77	1.05	2.01	0.014	2.09	0.008
14223	F	215	0.55	8.24	0.081	1.89	0.138	0.58	0.89	1.40	0.042	1.82	0.010
14230	F	220	0.65	8.01	0.076	2.01	0.200	0.50	0.88	1.62	0.038	1.90	0.009
14234	F	195	0.41	7.42	0.068	1.85	0.149	0.60	0.66	1.21	0.018	1.90	0.010
<u>5000 ppm.:</u>													
14289	M	450	0.71	26.05	0.070	3.49	1.69, 2.95	1.00	1.40	1.89	0.029	1.90	0.014
14293	M	355	1.34	16.75	0.067	3.33	3.32	0.91	1.38	2.19	0.036	1.96	0.013
14295	M	430	0.66	22.33	0.075	3.56	3.49	0.78	1.29	2.11	0.025	2.08	0.009
14263	F	265	0.50	13.71	0.074	2.46	0.168	0.68	0.87	1.29	0.021	1.80	0.019
14270	F	200	0.55	10.29	0.063	2.20	0.079	0.50	0.80	1.44	0.033	1.88	0.012
14275	F	230	0.80	12.11	0.065	2.41	0.188	0.50	0.89	1.30	0.022	1.90	0.007

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(b) (4)
Ninety-Day Feeding Study in the Rat.

TABLE 28. Continued. Organ Weights, Grams.

Animal No. & Group	Sex	Terminal Weight Grams	Spleen	Liver	Adrenals	Kidneys	Testes/ Ovaries	Thymus	Heart	Lung	Thyroid	Brain	Pituitary
<u>90-DAY TERMINAL SACRIFICE:</u>													
<u>Control:</u>													
14163	M	410	1.10	11.63	0.061	2.29	2.80	0.52	1.22	2.00	0.040	1.88	0.009
14164	M	545	1.22	17.92	0.059	3.71	3.58	1.09	1.90	2.38	0.051	2.02	0.017
14166	M	420	0.91	12.83	0.053	2.51	3.22	0.43	1.13	1.64	0.019	1.88	0.014
14169	M	460	1.11	14.18	0.063	3.10	3.65	0.71	1.23	1.78	0.036	2.01	0.012
14171	M	430	1.32	13.81	0.066	2.79	3.37	0.59	1.40	2.09	0.021	1.81	0.014
14172	M	490	1.10	15.47	0.078	3.10	3.19	0.95	1.38	2.07	0.024	1.91	0.013
14173	M	800	0.99	11.91	0.058	2.39	3.15	0.41	1.12	2.03	0.020	1.80	0.014
14174	M	450	1.00	15.12	0.080	3.02	3.31	0.69	1.38	1.60	0.019	1.85	0.015
14175	M	545	1.28	17.71	0.065	3.12	3.49	0.60	1.58	2.92	0.026	2.00	0.015
14176	M	400	0.75	10.48	0.081	2.65	3.42	0.58	1.39	1.68	0.025	2.08	0.012
14144	F	325	1.00	9.90	0.096	2.49	0.242	0.60	1.05	1.71	0.031	1.85	0.014
14147	F	255	0.51	7.11	0.065	1.52	0.134	0.52	0.80	1.00	0.015	1.70	0.013
14148	F	280	0.76	8.62	0.060	1.70	0.155	0.39	0.71	1.35	0.024	1.80	0.013
14150	F	300	0.75	9.80	0.084	1.92	0.167	0.51	0.98	1.52	0.031	1.92	0.013
14151	F	250	0.71	7.50	0.051	1.61	0.104	0.60	0.75	1.21	0.031	1.65	
14153	F	255	0.69	7.88	0.080	1.58	0.147	0.60	0.83	1.61	0.023	1.85	
14154	F	275	0.72	8.39	0.073	1.72	0.140	0.51	0.78	1.48	0.030	1.82	0.014
14155	F	255	0.81	8.32	0.090	1.60	0.170	0.53	0.85	1.37	0.024	1.80	0.016
14156	F	290	0.78	8.63	0.090	1.89	0.154	0.38	0.89	1.40	0.023	1.89	0.012
14157	F	210	0.39	5.58	0.055	1.23	0.123	0.41	0.73	1.05	0.018	1.89	0.008

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(b) (4)
Ninety-Day Feeding Study in the Rat.

TABLE 28. Continued. Organ Weights, Grams.

Animal No. & Group	Terminal Sex Weight Grams	Spleen	Liver	Adrenals	Kidneys	Testes/ Ovaries	Thymus	Heart	Lung	Thyroid	Brain	Pituitary	
<u>90-DAY TERMINAL SACRIFICE:</u>													
<u>100 ppm.:</u>													
14203	M	455	1.49	14.08	0.051	2.50	3.05	0.41	1.43	2.28	0.019	1.85	0.007
14204	M	560	0.99	17.48	0.061	3.38	3.70	0.60	1.73	2.10	0.025	1.93	0.014
14206	M	465	1.20	14.60	0.067	3.25	3.50	0.60	1.38	2.72	0.024	2.08	0.011
14207	M	435	1.20	12.02	0.060	3.05	3.93	0.82	1.22	1.74	0.023	2.08	0.009
14209	M	400	1.21	12.07	0.054	2.72	3.19	0.44	1.28	1.90	0.025	1.82	0.009
14210	M	520	1.24	15.48	0.053	2.79	3.10	1.11	1.39	2.20	0.021	1.90	0.010
14211	M	470	1.48	13.78	0.035	3.10	3.42	0.36	1.43	1.95	0.039	2.19	0.011
14213	M	380	1.03	11.20	0.051	2.61	3.43	0.53	1.20	1.62		2.09	0.009
14214	M	485	1.02	14.03	0.061	2.89	3.50	0.60	1.46	2.71	0.027	2.09	0.013
14215	M	420	0.70	12.49	0.056	2.80	3.33	0.90	1.30	2.08	0.028	2.00	0.011
14216	M	535	0.90	15.90	0.055	3.29	3.32	0.59	1.50	2.02	0.036	1.97	0.013
14218	M	520	1.41	17.65	0.081	3.02	3.74	0.72	1.71	2.21	0.022	1.83	0.015
14219	M	450	1.00	13.65	0.055	2.95	2.85	0.54	1.40	1.90	0.029	2.08	0.010
14183	F	310	0.64	8.78	0.076	1.93	0.210	0.50	0.80	1.52	0.028	1.78	0.014
14186	F	345	0.81	9.62	0.093	2.15	0.203	0.58	1.14	1.34	0.034	2.02	0.014
14187	F	280	0.81	8.00	0.074	1.77	0.186	0.44	0.79	1.21	0.026	1.90	0.013
14189	F	265	1.10	8.40	0.081	1.91	0.183	0.81	0.83	1.42	0.027	1.73	0.015
14190	F	255	0.70	7.58	0.067	1.58	0.165	0.33	0.71	1.29	0.023	1.75	0.011
14191	F	290	1.22	7.51	0.061	1.96	0.168	0.56	0.92	1.43	0.016	1.89	0.012
14192	F	245	0.68	7.58	0.069	1.80	0.161	0.30	0.72	1.43	0.023	1.91	0.011
14195	F	280	0.71	8.50	0.093	2.01	0.161	0.60	0.93	1.30	0.026	1.88	0.014
14196	F	270	0.89	8.59	0.064	1.80	0.177	0.48	0.89	1.53	0.028	1.92	0.008
14197	F	260	0.54	7.32	0.049	1.72	0.116	0.49	0.88	1.28	0.022	1.77	0.012
14198	F	295	1.00	8.40	0.055	1.79	0.181	0.42	0.79	1.60	0.014	1.82	0.013
14199	F	280	0.76	8.83	0.050	1.81	0.170	0.61	1.01	1.41	0.019	1.81	0.015
14200	F	285	0.81	8.80	0.077	1.98	0.119	0.71	0.81	1.37	0.023	1.87	0.014
14201	F	310	0.68	7.88	0.084	1.99	0.198	0.48	0.93	1.50	0.020	2.09	0.013

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(014)

Ninety-Day Feeding Study in the Rat.

TABLE 28. Continued. Organ Weights, Grams.

Animal No. & Group	Sex	Terminal Weight Grams	Spleen	Liver	Adrenals	Kidneys	Testes/Ovaries	Thymus	Heart	Lung	Thyroid	Brain	Pituitary
<u>90-DAY TERMINAL SACRIFICE:</u>													
<u>1000 ppm.:</u>													
14243	M	455	1.09	12.68	0.054	2.87	3.39	0.27	1.30	1.92	0.019	1.82	0.030
14244	M	535	0.97	17.13	0.065	3.51	3.60	0.98	1.50	2.94	0.026	1.98	0.012
14247	M	475	0.99	16.20	0.053	3.00	3.40	0.41	1.31	2.21	0.031	2.25	0.010
14249	M	470	1.17	15.88	0.082	3.21	3.58	0.68	1.51	1.65	0.034	1.93	0.012
14250	M	440	0.89	16.13	0.057	3.01	3.30	0.42	1.32	1.98	0.031	1.91	0.013
14252	M	470	0.79	16.61	0.067	3.42	3.80	0.60	1.39	1.93	0.029	1.89	Missed
14254	M	460	1.18	15.50	0.058	3.23	3.41	0.59	1.31	2.75	0.017	1.81	0.012
14255	M	410	1.00	12.80	0.053	2.60	3.30	0.79	1.21	2.00	0.026	2.01	0.012
14256	M	385	1.01	12.39	0.055	2.58	2.81	0.35	1.10	1.71	0.024	1.98	0.008
14257	M	415	0.63	14.90	0.055	3.03	3.29	0.78	1.21	1.68	0.040	1.99	0.009
14224	F	290	0.69	12.38	0.107	2.60	0.172	0.40	0.90	1.49	0.027	1.81	0.011
14226	F	270	0.51	8.91	0.066	2.21	0.097	0.22	1.40	1.39	0.037	1.89	0.005
14227	F	295	0.50	9.40	0.073	2.49	0.127	0.35	0.85	1.52	Missed	1.90	0.009
14229	F	305	0.89	10.75	0.075	2.10	0.186	0.61	0.98	1.35	Missed	1.91	0.012
14231	F	320	0.77	11.55	0.097	2.55	0.206	0.37	1.09	1.83	0.026	2.08	0.010
14232	F	280	0.77	11.00	0.096	2.17	0.201	0.80	0.68	1.24	0.040	1.90	0.014
14233	F	230	1.22	14.39	0.116	2.89	0.171	0.68	1.12	1.65	0.031	1.99	0.019
14235	F	325	0.84	8.14	Missed	1.73	0.130	0.31	0.70	1.20	0.022	1.68	0.014
14236	F	275	0.61	10.52	0.074	2.21	0.144	0.50	0.91	1.33	0.028	1.92	0.017
14237	F	250	0.88	8.81	0.077	2.08	0.117	0.75	1.00	1.79	0.034	1.85	0.016

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Ninety-Day Feeding Study in the Rat.

TABLE 28. Continued. Organ Weights, Grams.

Animal No. & Group	Sex	Terminal Weight Grams	Spleen	Liver	Adrenals	Kidneys	Testes/Ovaries	Thymus	Heart	Lung	Thyroid	Brain	Pituitary
90-DAY TERMINAL SACRIFICE:													
5000 ppm.:													
14283	M	429	1.30	19.57	0.058	3.30	3.30	0.58	1.21	1.88	0.024	2.04	0.010
14284	M	525	1.02	25.68	0.065	3.91	2.87	1.32	1.43	2.35	0.035	2.09	0.015
14286	M	345	0.98	15.13	0.059	2.62	3.21	0.69	0.91	2.18	0.023	2.08	0.008
14287	M	425	1.11	20.11	0.050	3.30	3.39	0.80	1.30	1.98	0.029	2.10	0.011
14290	M	430	0.90	21.49	0.059	3.38	3.60	0.42	1.58	1.61	0.027	1.92	0.012
14291	M	410	0.51	21.65	0.060	3.18	3.20	0.59	1.17	2.02	0.031	1.83	0.010
14292	M	390	1.19	19.82	0.050	3.20	3.49	0.63	1.20	1.42	0.019	2.02	0.009
14294	M	395	0.77	18.30	0.054	3.30	3.40	0.30	1.38	2.09	0.021	1.90	0.008
14296	M	430	1.12	19.82	0.054	3.31	3.60	0.79	1.42	1.60	0.023	1.92	0.010
14297	M	480	0.91	22.19	0.058	3.80	3.61	0.51	1.28	1.92	0.017	2.05	0.011
14264	F	220	0.90	9.84	0.063	2.00	0.146	0.41	0.78	1.38	0.020	1.78	0.010
14266	F	225	0.83	11.40	0.077	2.03	0.122		0.80	2.93	0.018	1.88	0.011
14267	F	250	0.48	10.85	0.067	2.28	0.178	0.58	0.72	1.28	0.019	1.80	0.012
14269	F	220	0.58	11.01	0.068	2.25	0.092	0.53	0.83	1.13	0.024	1.91	0.011
14271	F	270	1.08	11.91	0.072	2.78		0.57	0.98	1.40	0.018	1.79	
14272	F	215	0.67	9.57	0.083	1.80	0.130	0.58	0.70	1.32	0.032	1.91	0.010
14273	F	240	0.70	11.75	0.062	2.38	0.180	0.42	0.90	1.21	0.018	1.98	0.007
14274	F	240	1.51	10.41	0.059	2.45	0.107	0.51	0.83	1.60	0.015	1.81	0.008
14276	F	250	0.48	11.30	0.085	2.12	0.144	0.43	1.03	1.61	0.031	1.81	0.013
14277	F	235	0.83	11.41	0.079	2.40	0.182	0.48	0.95	1.51	0.025	1.78	

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Ninety-Day Feeding Study in the Rat.

TABLE 29. Incidence of Histopathologic Lesions.

Tissue and Lesion	30 Day				60 Day			
	Interim Sacrifice		Interim Sacrifice		Control		5000 ppm.	
	Control	2500 ppm.	Control	5000 ppm.	M	F	M	F
brain - no lesion	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3
- glial nodules								
spinal cord - no lesion	3/3	3/3	2/2	3/3	3/3	3/3	3/3	3/3
peripheral nerve - no lesion	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3
eye - no lesion	3/3	3/3	3/3	3/3	3/3	3/3	3/3	2/2
pituitary - no lesion	2/2	3/3	2/2	1/1	3/3	2/2	3/3	2/2
thyroid - no lesion	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3
parathyroid - no lesion			1/1		3/3	3/3	2/2	1/1
adrenal - no lesion	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3
- ossification								
lung - no lesion	3/3	2/3	3/3	2/3	3/3	2/3	3/3	3/3
- chronic respiratory disease		1/3		1/3		1/3		
heart - no lesion	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3
- arteritis								
spleen - no lesion	3/3	3/3	2/3	3/3	3/3	3/3	3/3	3/3
- hematopoiesis			1/3					
lymph node - no lesion	3/3	3/3	3/3	3/3	2/2	3/3	3/3	3/3
thymus - no lesion	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3
bone marrow - no lesion	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3
salivary gland - no lesion	3/3	3/3	3/3	3/3	3/3	2/2	3/3	3/3
stomach - no lesion	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3
small intestine - no lesion	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3
large intestine - no lesion	3/3	3/3	3/3	3/3	3/3	3/3	2/3	3/3
- nematodes								1/3

90 Day						21 Day			
Terminal Sacrifice						Withdrawal			
Control		1000 ppm.		5000 ppm.		Control		5000 ppm.	
M	F	M	F	M	F	M	F	M	F
10/10	10/10			9/10	10/10	3/3	3/3	3/3	3/3
				1/10					
8/8	9/9			9/9	9/9	3/3	3/3	3/3	3/3
9/9	9/9			9/9	8/8	3/3	3/3	3/3	3/3
10/10	9/9			9/9	9/9	3/3	3/3	3/3	3/3
9/9	3/3			8/8	1/1	3/3	3/3	3/3	3/3
10/10	9/9			10/10	9/9	3/3	3/3	3/3	3/3
5/5	6/6			3/3	2/2	1/1	1/1	3/3	1/1
10/10	10/10			9/10	10/10	3/3	3/3	3/3	3/3
				1/10					
5/10	9/10			7/10	7/10	2/3	1/3	2/3	1/3
5/10	1/10			3/10	3/10	1/3	2/3	1/3	2/3
9/10	10/10			10/10	10/10	3/3	3/3	3/3	3/3
1/10									
10/10	10/10			9/9	10/10	3/3	3/3	3/3	3/3
9/9	8/8			8/8	10/10	3/3	2/2	3/3	3/3
9/9	9/9			9/9	8/8	3/3	3/3	3/3	3/3
10/10	10/10			9/9	10/10	3/3	3/3	3/3	3/3
9/9	9/9			9/9	8/8	3/3	3/3	3/3	3/3
10/10	10/10			10/10	10/10	3/3	3/3	3/3	3/3
10/10	10/10			10/10	10/10	3/3	3/3	3/3	3/3
10/10	10/10			10/10	9/10	3/3	3/3	3/3	3/3
				1/10					

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Ninety-Day Feeding Study in the Rat.

TABLE 29. Continued. Incidence of Histopathologic Lesions.

Tissue and Lesion	30 Day				60 Day			
	Interim Sacrifice		Interim Sacrifice		Interim Sacrifice		Interim Sacrifice	
	Control	2500 ppm.	Control	2500 ppm.	Control	5000 ppm.	Control	5000 ppm.
	M	F	M	F	M	F	M	F
pancreas - no lesion	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3
pancreatitis, focal								
liver - no lesion	2/3	3/3	0/3	2/3	2/3	2/3	0/3	0/3
- portal inflammatory infiltrate	1/3			1/3	1/3	1/3	1/3	1/3
- centrilobular change			3/3				3/3	2/2
kidney - no lesion	3/3	3/3	3/3	2/3	3/3	3/3	3/3	3/3
- focal nephritis				1/3				
- hyaline droplets								
urinary bladder - no lesion	2/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3
- siminal plug	1/3							
estives or ovaries - no lesion	3/3	3/3	3/3	3/3	3/3	3/3	2/3	3/3
- edema							1/3	
prostate or uterus - no lesion	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3
- hydrometra								
skeletal muscle - no lesion	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3
skin - no lesion	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3
bone - no lesion	3/3	3/3	3/3	3/3	2/3	3/3	3/3	3/3

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90 Day Terminal Sacrifice						21 Day Withdrawal			
Control		1000 ppm.		5000 ppm.		Control		5000 ppm.	
M	F	M	F	M	F	M	F	M	F
10/10	10/10			10/10	10/10	2/3	3/3	3/3	3/3
						1/3			
7/10	5/10	7/10	6/10	1/10	2/10	2/3	2/3	0/3	0/3
3/10	5/10	3/10	4/10	1/10	8/10	1/3	1/3	1/3	3/3
1/10				9/10	2/10			2/3	
8/10	10/10			10/10	9/10	3/3	3/3	3/3	2/3
					1/10				1/3
2/10									
6/8	9/9			10/10	9/9	1/2	3/3	3/3	3/3
2/8						1/2			
10/10	10/10			10/10	10/10	3/3	3/3	3/3	3/3
10/10	9/10			10/10	10/10	3/3	3/3	2/2	2/2
	1/10								
9/9	10/10			10/10	9/9	3/3	3/3	3/3	3/3
9/9	10/10			9/9	6/6	3/3	3/3	3/3	3/3
10/10	10/10			10/10	10/10	2/3	3/3	3/3	3/3

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Ninety-Day Feeding Study in the Rat.

TABLE 30. Histopathologic Observations. Thirty-Day Interim Sacrifice.

Animal Number	Sex	Tissue	Comment
<u>Control:</u>			
14162	M	liver	Mild portal lymphocytic infiltrate.
14165	M		No lesion.
14168	M	urinary bladder	Seminal plug.
14142	F		No lesion.
14145	F	lung	Small focus of pneumonic consolidation.
14146	F		No lesion.
<u>2500 ppm.:</u>			
14282	M	liver	Slight hypertrophy of centrilobular hepatocytes.
14285	M	liver	Slight hypertrophy of centrilobular hepatocytes with loss of coarse cytoplasmic granularity.
14288	M	liver spleen	Slight hypertrophy of centrilobular hepatocytes with loss of usual coarse granularity. Moderate hematopoietic activity.
14252	F	liver kidney	Mild portal lymphocytic infiltrate. Mild focal interstitial lymphocytic infiltrate.
14265	F	lung	Moderate peribronchial lymphoid hyperplasia.
14268	F		No lesion.

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(b) (4) Ninety-Day Feeding Study in the Rat.

TABLE 30. Continued. Histopathologic Observations. Sixty-Day Interim Sacrifice.

Animal Number	Sex	Tissue	Comment
<u>Control:</u>			
14167	M		No lesion.
14170	M		No lesion.
14178	M	liver	Slight portal lymphocytic infiltrate.
14143	F		No lesion.
14149	F	liver lung	Slight portal lymphocytic infiltrate. Few small scattered foci of pneumonic consolidation.
14152	F		No lesion.
<u>5000 ppm.:</u>			
14289	M	large intestine testes liver	Nematodes. One testis was edematous and had reduced spermatogenic activity. Hypertrophy of hepatocytes which was more pronounced in the centrilobular area; hepatocytes appeared to have higher glycogen content than controls.
14293	M	liver	Moderate hypertrophy of hepatocytes, predominately centrilobular with loss of coarse granularity. Moderate portal lymphocytic infiltrate with scattered small nodules of proliferated reticuloendothelial cells in liver parenchyma.
14295	M	liver	Hypertrophy of hepatocytes, primarily centrilobular, hepatocytes appeared to contain more glycogen than control.
14263	F	liver	Slight hypertrophy of hepatocytes, predominately centrilobular.
14270	F	liver	Slight portal lymphocytic infiltrate.
14275	F	liver	Slight hypertrophy of centrilobular hepatocytes.
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Ninety-Day Feeding Study in the Rat.

TABLE 39. Continued. Histopathologic Observations. Ninety-Day Terminal Sacrifice.

Animal Number	Sex	Tissue	Comment
<u>Control:</u>			
14163	M	lung	Moderate perivascular lymphocytic cuffing.
14164	M	urinary bladder	Seminal plug.
14166	M		No lesion.
14169	M	kidney	Small numbers of hyaline droplets in epithelium of convoluted tubules.
		liver	Slight portal lymphocytic infiltrate and bile duct proliferation.
14171	M	lung	Moderate perivascular lymphocytic cuffing with localized pneumonitis.
14172	M	urinary bladder	Seminal plug.
		lung	Slight perivascular lymphocytic cuffing, peribronchial lymphoid hyperplasia.
14173	M	lung	Slight peribronchial lymphoid hyperplasia.
		kidney	Moderate numbers of hyaline droplets in epithelium of convoluted tubules.
14174	M		No lesion.
14175	M	liver	Slight portal lymphocytic infiltrate, centrilobular hepatocytes less coarsely granular.
		lung	Slight perivascular lymphocytic cuffing.
14176	M	liver	Slight portal lymphocytic infiltrate.
		heart	Moderate mural necrosis and perivascular inflammatory infiltrate of a coronary vessel.
14144	F		No lesion.
14147	F		No lesion.
14148	F	liver	Slight portal lymphocytic infiltrate and bile duct proliferation.

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Ninety-Day Feeding Study in the Rat.

TABLE 30. Continued. Histopathologic Observations. Ninety-Day Terminal Sacrifice.

Animal Number	Sex	Tissue	Comment
<u>Control (cont'd):</u>			
14150	F		No lesion.
14151	F	liver	Slight portal lymphocytic infiltrate.
14153	F	lung liver	Small area of chronic pneumonitis, Slight portal lymphocytic infiltrate.
14154	F	uterus liver	Hydometra. Slight portal lymphocytic infiltrate.
14155	F	liver	Slight portal lymphocytic infiltrate.
14156	F		No lesion.
14157	F		No lesion.

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(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 30. Continued. Histopathologic Observations. Ninety-Day Terminal Sacrifice.

Animal Number	Sex	Tissue	Comment
<u>1000 ppm., Liver Only:</u>			
14243	M		No lesion.
14244	M		No lesion.
14247	M		Slight portal lymphocytic infiltrate.
14249	M		No lesion.
14250	M		No lesion.
14252	M		No lesion.
14254	M		No lesion.
14255	M		No lesion.
14256	M		Slight portal lymphocytic infiltrate.
14257	M		Slight portal lymphocytic infiltrate.
14224	F		No lesion.
14226	F		No lesion.
14227	F		No lesion.
14229	F		Slight portal lymphocytic infiltrate.
14231	F		No lesion.
14232	F		Slight portal lymphocytic infiltrate.
14233	F		Slight portal lymphocytic infiltrate.
14235	F		Slight portal lymphocytic infiltrate.
14236	F		No lesion.
14237	F		No lesion.

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Ninety-Day Feeding Study in the Rat.

TABLE 30, Continued. Histopathologic Observations. Ninety-Day Terminal Sacrifice.

Animal Number	Sex	Tissue	Comment
<u>5000 ppm.:</u>			
14283	M	liver	Centrolobular hepatocytes slightly hypertrophied cytoplasm less coarsely granular than in hepatocytes at periphery of lobules.
14284	M	liver lung	Centrolobular hepatocytes less coarsely granular than those at periphery. Slight peribronchial lymphoid hyperplasia.
14286	M	brain lung liver	Glial nodules in medulla, structure resembling <u>Sarcosporidia</u> also present. Slight perivascular lymphocytic cuffing, area of pneumonic consolidation. Centrolobular hepatocytes less granular than those at periphery of lobule, slight portal lymphocytic infiltrate.
14287	M	adrenal liver	Area of osteoid and bone in cortex of one adrenal Cytoplasm of centrolobular hepatocytes less coarsely granular than cytoplasm of hepatocytes at periphery, slight portal lymphocytic infiltrate.
14290	M		No lesion.
14291	M	liver	Cytoplasm of centrolobular hepatocytes less coarsely granular than cytoplasm of hepatocytes at periphery of lobules.
14292	M	liver lung	Centrolobular hepatocytes less coarsely granular than those at periphery of lobules. Slight peribronchial lymphoid hyperplasia.
14294	M	liver	Centrolobular hepatocytes less coarsely granular than those at periphery of lobule.
14296	M	liver	Marked portal lymphocytic infiltrate, centrolobular hepatocytes slightly less granular than those at periphery of lobule.

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(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 30. Continued. Histopathologic Observations. Ninety-Day Terminal Sacrifice.

Animal Number	Sex	Tissue	Comment
5000 ppm. (cont'd):			
14297	M	liver	Centrolobular hepatocytes less coarsely granular than those at periphery of lobule.
14264	F	liver	Moderate portal lymphocytic infiltrate.
14266	F	liver	Centrolobular hepatocytes less coarsely granular than those at periphery, mild portal lymphocytic infiltrate.
		lung	Chronic murine pneumonia of moderate severity.
14267	F	liver	Mild portal lymphocytic infiltrate.
14269	F	liver	Slight portal lymphocytic infiltrate.
14271	F	kidney	Moderate interstitial lymphocytic infiltrate.
		liver	Mild portal lymphocytic infiltrate.
14272	F	liver	Mild portal lymphocytic infiltrate.
14273	F	liver	Mild portal lymphocytic infiltrate.
		large intestine	Nematodes.
14274	F	liver	Mild portal lymphocytic infiltrate, centrolobular hepatocytes less coarsely granular than those at periphery.
14276	F	lung	Moderate perivascular lymphocytic cuffing.
14277	F	lung	Moderate perivascular lymphocytic cuffing.

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(b) (4)

Ninety-Day Feeding Study in the Rat.

TABLE 30. Continued. Histopathologic Observations, 21-Day Compound Withdrawal.

Animal Number	Sex	Tissue	Comment
<u>Control:</u>			
14177	M		No lesion.
14179	M	pancreas	Small area of necrosis and chronic inflammation.
14180	M	lung liver urinary bladder	Moderate peribronchial lymphoid hyperplasia. Slight portal lymphocytic infiltrate. Seminal plug.
14158	F		No lesion.
14159	F	lung	Moderate peribronchial lymphoid hyperplasia.
14161	F	liver lung	Slight portal lymphocytic infiltrate. Slight perivascular lymphocytic cuffing.
<u>5000 ppm.:</u>			
14298	M	liver lung	Slight portal lymphocytic infiltrate. Mild peribronchial lymphoid hyperplasia.
14299	M	urinary bladder liver	Seminal plug. Centrolobular hepatocytes appeared slightly hypertrophied.
14300	M	liver	Centrolobular hepatocytes appeared slightly hypertrophied.
14278	F	kidney liver lung	Slight interstitial lymphocytic infiltrate, few calcified tubules. Moderate lymphocytic inflammatory infiltrate, primarily in portal areas. Moderate peribronchial lymphoid hyperplasia.
14279	F	liver	Mild portal lymphocytic infiltrate, few scattered vacuolated hepatocytes.
14280	F	lung liver	Slight peribronchial lymphoid hyperplasia. Slight portal lymphocytic infiltrate.

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