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Tox. Branch II (7509C)

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Tox. Branch II (7509C)

DATA EVALUATION REPORT

Study Type: One-year oral toxicity study in dogs
(via gelatin capsule)

Chemical: DEET (N, N-diethyl-m-toluamide)

Caswell No.	346	DP Barcode Code:	D207136
MRID No.	43320101	PC Code:	N080301
EPA ID No.	N80301-051147	Submission No.:	S472821

Sponsor: DEET Joint Venture/Chemical Specialties Manufacturers Association

Testing Facility: International Research and Development Corp.
500 N. Main
Mattawan, Michigan 49071

Citation: Goldenthal, E.I. (1994) Evaluation of DEET in a one-year chronic oral toxicity study in dogs. International Research and Development Corp.; Study No. 555-021. January 30, 1994. Submitted to EPA by CSMA. EPA MRID No. 43320101

Conclusion: Groups of beagle dogs (4/sex/dose) received DEET in a gelatin capsule at dose levels of 30, 100, or 400 mg/kg/day. The control animals received white mineral oil in gelatin capsule. Each daily dose was divided into two equal administrations. One was administered in the morning, and other was given in the afternoon at one hour following the presentation of food.

Under the conditions of this study, DEET, at dosages of 30 and 100 mg/kg/day, did not produce systemic toxicity in beagle dogs. However, at 400 mg/kg/day DEET produced the following effects:

1. An increase in the incidence of ptyalism in both male and females. A male and a female dog showed signs of tremor. Most of the clinical signs were observed within 30 minutes after dosing.
2. A decrease in food intake and body weights in males and females during the first 5 weeks of the treatment.
3. A decrease in cholesterol level was seen in males.

4. Gross examination showed an increased incidence of thin males and females.
5. An increase in platelet level in female dogs was also seen.
6. Hyperplasia of uterine epithelium.

Based on the finding of the decreases in food consumption and body weights, an increase in the incidence of clinical signs, and a decrease in cholesterol levels in 400 mg/kg dogs, the LEL for chronic toxicity in dogs is 400 mg/kg; NOEL, 100 mg/kg.

This study meets the data requirements for a chronic toxicity study in dogs (Guideline No. 83-1b) and is classified as minimum.

The report alluded to seeing clinical signs such as unusual head movement, compulsive biting and scratching, and convulsion in dogs which received DEET in gelatin capsules at dose levels of 125 mg/kg or above in two other dose range-finding studies in dogs. Tox. Branch II requests that these studies be submitted for review.

Methods and Materials

Test article: Technical DEET (98.3%) was "a mixture consisting of equal parts of four representative production runs" supplied by four manufacturers (McLaughlin Gormley King Co, Miles Lab., Virginia Chemical Co., and Morflex Chemical Co.). The test article was a clear liquid (Lot No. A-1-96) and assigned the ID No. IRDC 8812B at the testing laboratory. The test article was found to be stable at room temperature.

Test animals: Twenty male and 20 female purebred beagle dogs (≈5-6 months of age) were obtained from Ridgman Farms, Mt. Horeb, Wisconsin. During the acclimation period, the dogs were given a physical examination. Stool flotation tests were performed on all dogs. Prior to the initiation of the study, an ophthalmology examination and hematology, clinical chemistry, and urinalysis measurements were performed. Only healthy animals were selected for the study.

Study Design

1. Dose selection: The dosage selection for this study was based on the results of six dose-range finding studies. Three dose-range finding studies used dietary administration; in these 3 studies dietary concentrations ranging from 300 to 10,000 ppm were employed. No compound-related systemic

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4. Gross examination showed an increased incidence of thin males and females.
5. An increase in platelet level in female dogs was also seen.
6. Hyperplasia of uterine epithelium.

The decreases in food consumption and body weights were transient, and a decrease in cholesterol levels was closely associated with the decreases in food consumption and body weight. All of The six findings in the 400 mg/kg dogs appeared to be of marginal biological significance, and 400 mg/kg could be established as NOEL/LEL.

This study meets the data requirements for a chronic toxicity study in dogs (Guideline No. 83-1b) and is classified as minimum.

The report alluded to seeing clinical signs such as unusual head movement, compulsive biting and scratching, and convulsion in dogs which received DEET in gelatin capsules at dose levels of 125 mg/kg or above in two other dose range-finding studies in dogs. Tox. Branch II requests that these studies be submitted for review.

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toxicity was seen, but diet rejection occurred at concentrations above 3,000 ppm (MRID No. 43514202). The dietary concentration of 3,000 ppm corresponded to a dosage of approximately 92 mg/kg.

The other 3 dose-range finding studies used gelatin capsule as a means of administering DEET. In the first two studies, DEET was administered as a single bolus daily dose, which ranged from 62.5 to 500 mg/kg/day, via gelatin capsule. It was reported that at dose levels of 125 mg/kg/day and above, a wide array of severe clinical signs including unusual head movements, compulsive biting and scratching, and convulsions were observed immediately after dosing (p. 13-14 of this report). These two studies have not been submitted to the Agency. Tox. Branch II is interesting in learning more about the effects of DEET in dogs found in these two dose-range finding studies. In the third gelatin capsule study, each daily dose was divided into two equal doses, which were administered once in the morning and once in the afternoon following a one-hour feeding period. This study was submitted to the Agency, and it was reviewed (MRID No. 43514201). The dosages employed in this study were 50, 100, 200, and 400 mg/kg. There was no acute effect seen in this dosing regimen. At 400 mg/kg, unusual head movements and decreases in body weight and food consumption were seen.

Based on the results of these dose-range finding studies, dosages of 30, 100, and 400 mg/kg were selected for the chronic toxicity study. The experimenters also decided to apply the divided daily dose regimen because it minimized the potential acute effects, allowed for a higher daily dose, and more closely simulated the exposure patterns under normal use conditions of DEET as an insect repellent.

2. Animal assignments: Sixteen male and 16 female beagle dogs were selected for this study. The body weights of males were in the range of 6.6 to 9.9 kg; females, 5.6 to 8.7 kg. The selected animals were divided into 4 treatment groups and a control group "... with the intent of developing groups with similar body weight means and standard deviation..." as follows:

Dosage Levels mg/kg	Number of Animals	
	Males	Female
(control) 0	4	4
30	4	4
100	4	4
400	4	4

Data excerpted from the report; p. 15 (MRID No. 43320101)

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3. Test article preparation and administration: With a glass syringe, an appropriate amount of DEET was placed into a gelatin capsule, which has a volume of approximately 7 ml. For the control group, an appropriate amount of white mineral oil was placed into the capsule. The volume of DEET or white mineral oil placed into a capsule was based on a test animal's most recent body weight measurement.

The stability of DEET in the capsule was analyzed after storing the prepared capsule for 14 days at room temperature. At the end of the 14 days, aliquots of DEET from the capsule and that from the stock solution were analyzed and compared. The results indicated that DEET was stable in the gelatin capsule for at least 14 days.

Each animal was dosed twice daily in equally divided doses of 30, 100, and 400 mg/kg/day. The animals were dosed one hour following feeding, 7 days/week, throughout the study. Food was normally offered at approximately 8:00 am and 1:00 pm. The control dogs received white mineral oil in similar treatment schedules.

4. Physical examinations: Physical examinations were conducted on each dog at pretest, 3, 6, 9, and 12 months of study. The examinations included auscultation of the thoracic cavity and respiratory tract and palpitation of the thoracic cage and abdomen.
5. Clinical observations: The test animals were observed for any clinical signs of toxicity, moribundity, and mortality twice daily throughout the study.
6. Body weight and food consumption: Individual body weight measurements were determined at pretest and weekly for the first 14 weeks of study and once every two weeks thereafter and at the termination of the study. Individual food consumption measurements were conducted in a similar manner as the body weight determinations.
7. Ophthalmological examination: Eye examination was conducted on each dog once during pretest period and during the last week of the study. The examination was conducted following pupillary dilatation with 1% tropicamide solution, and a binocular indirect ophthalmoscope was utilized.
8. Hematology and biochemical analyses: Blood samples were collected from the test animals following an overnight fast. Hematology and biochemical analyses were conducted using the blood samples collected prior to the initiation of the study from 20 dogs/sex, at 6 and 12 months of the study from all test dogs (16/sex).

Hematology: The following hematological parameters were measured:

erythrocyte count	hemoglobin
leukocyte count	differential leukocyte count
hematocrit	platelet
reticulocyte count	Mean corpuscular volume (MCV)
Mean corpuscular	Mean corpuscular hemoglobin
hemoglobin (MCH)	concentration (MCHC)

Clinical chemistry: The following biochemistry parameters were determined:

sodium	potassium
chloride	calcium
phosphorus	total bilirubin
aspartate aminotransferase (AST) (SGOT)	alanine aminotransferase (ALT) (SGPT)
urea nitrogen	creatinine
total protein	albumin
globulin	glucose
alkaline phosphatase	creatine phosphokinase (CPK)
cholesterol	

9. **Urinalysis:** Urine samples were collected during the fasting period, and the following parameters were examined:

color and appearance	volume
specific gravity	microscopic elements
pH	protein
glucose	ketones
bilirubin	occult blood
nitrites	urobilinogen
leukocytes	

10. **Pathology:** At the end of one year of treatment, all animals were weighed and sacrificed with pentobarbital over a 3 day period with animals from each group euthanized on each day.

- a. **Necropsy:** A thorough postmortem examination was conducted on each animal. The abdominal, thoracic, and cranial cavities were examined for abnormalities.
- b. **Organ weights:** The following organs were removed, trimmed free of fat, and weighed:

adrenals	liver
brain	ovaries

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kidneys
heart
thyroid/parathyroid

testis with epididymis
pituitary
gallbladder

- c. Histopathology: The following organs were removed, placed in the phosphate-buffered neutral formalin, and processed for microscopic examination.

adrenal
aorta
bone (femur, rib, &
sternum)
lung with bronchi
bone marrow & smears
brain
eye with optic nerve
gallbladder
GI tract:
esophagus
stomach
duodenum
jejunum
ileum
cecum
colon
rectum
ovary
testes with epididymis
trachea
uterus

kidney (2)
liver
bone marrow (femur, rib &
sternum)
heart
lymph nodes (tracheobronchial,
mesenteric, mandibular)
mammary gland
pancreas
pituitary
prostate
salivary gland
sciatic nerve
skeletal muscle (thigh)
skin
spinal cord
spleen
tissue masses
thymus
thyroid/parathyroid
urinary bladder
gross lesions

A grading system for any lesion consisting of trace, mild, moderate, and severe was used to define gradable lesions for comparison purposes.

11. Statistics: The details of statistical analysis methods were excerpted from the report and presented in Appendix A (p.16).
12. Quality assurance: A statement of no data confidentiality claim, a statement of compliance, a flagging statement, and a quality assurance statement were signed and included in the report.

Results

1. Clinical observation: The data indicated that there was an increase in the incidence of ptyalism in 400 mg/kg males (4/4) and females (3/4) during a major portion of the study; the incidence of ptyalism was not seen in the controls of either male or female dogs. There was a male dog (Animal No. 3597)

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in the 400 mg/kg group, which showed signs of tremor on 5 occasions between weeks 29 and 43. Another 400 mg/kg male (Animal No. 3601) also showed a slight tremor at week 37. A 400 mg/kg female showed signs of tremor. Emesis was seen in all dose groups at various times, and that seen in the 400 mg/kg group was more frequent. In general the clinical signs were observed within 30 minutes after dosing.

2. Survival rates: No deaths occurred during the study.
3. Physical examination: Physical examinations did not reveal a compound-related effect in any group of the treated dogs.
4. Body weights: The weekly body weight measurements are presented in Table 1 (p.10). A summary of the mean body weight values at pretest, weeks 13, 26, 40, and 52 are also presented in Table 2 (p.11). The weekly body weight data indicated that at pretest, the body weights of all test groups of both sexes were comparable, but as soon as the treatment began they dropped slightly in the 400 mg/kg males and females. The slight reduction in body weight persisted throughout the study. However, the decrease did not show statistical significance. In addition, the body weight gains as indicated by the percentage difference from pretest was substantially reduced in 400 mg/kg males and females (Table 2). As the study progressed, the body weight gain gradually improved, but it was unable to approach the level of the controls.
5. Food consumption: There was a reduction in food consumption during the first 5 weeks of treatment in 400 mg/kg males and females (Table 3, p.12). During the first 3 week in male and second week in females the decrease in food intake was statistically significant ($p \leq 0.01$). After the 5th week, the food consumption of the 400 mg/kg animals began to gradually approached that of the controls and the lower dose groups.
6. Ophthalmological examination: No treatment-related toxicity was seen in the eye examinations.
7. Hematology: In male dogs, compound-related changes in hematological parameters were not seen. In 400 mg/kg female dogs, there were slight decreases in hematocrit at termination and in increases in platelet levels at both 6 month and at terminal sacrifice (Table 4, p.13)
8. Clinical chemistry: The biochemical analysis data indicated a statistically significant increase ($P \leq 0.01$) in the alkaline phosphatase level in 400 mg/kg males at the 6 month measuring period, but at termination (12 months) the level was comparable to that of the controls (Table 5a, p.14). A statistically significant decrease in cholesterol level was

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also observed in 400 mg/kg males at 6 months ($p < 0.05$) and at termination ($p \leq 0.01$). A slight increase in potassium level was also seen in 400 mg/kg males at 6 months only (Table 5a). In females, there was a slight decrease in cholesterol level in 400 mg/kg group at the 6 months, but the decrease was not statistically significant (Table 5b, p.15).

9. Urinalysis: There were no compound-related changes in any parameters analyzed in any dose groups.
10. Macroscopic: The gross examination did not reveal any compound-related effects except that 2/4 males and 3/4 females of the 400 mg/kg appeared to be thin and the uterus in 2/4 females of the 400 mg/kg group were distended with fluid.
11. Organ weights: The relevant organ weights were excerpted from the report and presented in Table 6. Statistically significant and compound-related organ weight changes were not found in dose groups.

Table 6⁺

Summary of Selective Organ Weights in Male Dogs

mg/kg	Brain (g)	Testis with epididymis	
		Left	Right
(Control) 0	82.42	11.77	11.69
30	87.68	11.36	11.13
100	82.31	10.40	10.23
400	79.79	10.10	11.57

+: Data excerpted from the report; p. 80-83 (MRID No.43320101).

12. Histopathology: Compound-related histological changes were not found in treated males of any dose groups. An increase in the incidence of mild hyperplasia of epithelia of uterus was seen in 100 and 400 mg/kg females (Controls, 0/4; 30 mg/kg, 0/4; 100 mg/kg, 1/4; 400 mg/kg, 3/4). Uterine hyperplasia can be attributed to many effects, and, by itself, it is not considered as an adverse effect. The registrant reported that hyperplasia of the uterine epithelia seen in this study was due to the hormonal effects; however, no data were submitted to support this argument. The information on the estrous cycle could have been helpful in determining whether or not this finding was due to the hormonal effect. In the absence of any supporting data, the uterine hyperplasia seen in the 400 mg/kg females could be considered as a treatment-related effect, and this was also supported by the results of the gross examination which found 2/4 females in the 400 mg/kg group had distended uterine filled with fluid.

A single incidence of uterine hyperplasia seen in 100 mg/kg females may or may not be considered as a significant

response. Under the conditions of this study, no other effects were seen in the 100 mg/kg dogs; the single incidence of uterine hyperplasia found in 100 mg/kg females would not be considered as a significant effect.

Discussion

Groups of beagle dogs (4/sex/dose) received DEET in a gelatin capsule at dose levels of 30, 100, or 400 mg/kg/day. The control animals received white mineral oil in gelatin capsule. Each daily dose was divided into two equal administrations. One was administered in the morning, and other was given in the afternoon at one hour following the presentation of food.

Under the conditions of this study, DEET, at dosages of 30 and 100 mg/kg/day, did not produce systemic toxicity in beagle dogs. However, at 400 mg/kg/day DEET produced the following effects:

1. An increase in the incidence of ptyalism in both male and females. A male and a female dog showed signs of tremor. In general clinical signs were seen within 30 minutes after dosing.
2. A decrease in food intake and body weights in males and females during the first 5 weeks of the treatment.
3. A decrease in cholesterol level was seen in males.
4. Gross examination showed an increased incidence of thin males and females.
5. An increase in platelet level in female dogs was also seen.
6. Hyperplasia of uterine epithelium.

Some of the effects (ptyalism, decrease in cholesterol level, and thin appearance) seen in 400 mg/kg male and female dogs in this study were consistent with those seen in the 8-week dose-range finding study in dogs which were administered DEET via gelatin capsules (MRID No. 43514201). Ptyalism was not seen in dogs which received DEET in the diet. In the dose-range finding study, a decrease in testis/epididymis weight was also seen, but the testis/epididymis weights in 400 mg/kg males in the current study were comparable to those of the controls. The significance of the decrease in testis weight seen in the dose-range finding study was difficult to determine because there was no histological changes in the testis and the current study did not find a similar effect.

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Based on the finding of the decreases in food consumption and body weights, an increase incidence of clinical signs, and a decrease in cholesterol levels in 400 mg/kg dogs, the LEL for chronic toxicity in dogs is 400 mg/kg; NOEL, 100 mg/kg.

This study meets the data requirements for a chronic toxicity in dogs (Guideline No. 83-1b) and is classified as minimum.

The report alluded to seeing clinical signs such as unusual head movement, compulsive biting and scratching, and convulsion in dogs which received DEET at dose level of 125 mg/kg or above in gelatin capsules in two other dose range-finding studies in dogs. Tox. Branch II requests that these studies be submitted for review.

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TABLE 1*

A. Males: Summary of Body Weight Values*

Parameters Measured	Week of Study	0 mg/kg/day (Control)			30 mg/kg/day			100 mg/kg/day			400 mg/kg/day		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Body Weight	Pretest	8.3	1.36	4	8.5	0.95	4	8.5	0.65	4	8.5	0.66	4
Kilograms	1	8.5	1.35	4	8.7	1.04	4	8.6	0.91	4	7.9	0.62	4
	2	8.8	1.37	4	9.0	1.04	4	8.8	1.00	4	8.0	0.83	4
	3	8.9	1.37	4	8.9	0.97	4	8.8	0.94	4	7.7	0.81	4
	4	9.1	1.24	4	9.4	0.93	4	9.2	0.97	4	8.3	0.95	4
	5	9.6	1.34	4	9.5	0.86	4	9.4	1.04	4	8.3	0.68	4
	6	9.8	1.44	4	9.8	0.88	4	9.6	1.14	4	8.7	0.93	4
	7	9.9	1.55	4	9.9	0.83	4	9.8	0.96	4	8.6	1.08	4
	8	10.1	1.46	4	10.1	0.88	4	9.9	1.18	4	8.7	0.97	4
	9	10.3	1.50	4	10.3	0.90	4	10.2	1.04	4	8.7	0.95	4
	10	10.3	1.54	4	10.5	0.83	4	10.3	1.32	4	9.3	0.81	4
	11	10.4	1.55	4	10.6	0.90	4	10.3	1.31	4	9.4	0.76	4
	12	10.4	1.56	4	10.5	0.93	4	10.2	1.28	4	9.2	0.97	4
	13	10.4	1.45	4	10.5	1.02	4	10.2	1.31	4	9.2	0.77	4
	14	10.6	1.53	4	10.8	0.95	4	10.6	1.35	4	9.6	0.84	4
	16	10.7	1.68	4	10.8	0.93	4	10.6	1.39	4	9.7	1.02	4
	18	11.1	1.68	4	11.1	1.02	4	11.1	1.34	4	10.1	1.03	4
	20	10.8	1.64	4	11.1	1.15	4	10.7	1.37	4	9.7	1.06	4
	22	11.1	1.70	4	11.0	1.02	4	11.0	1.32	4	9.9	0.85	4
	24	11.2	1.75	4	11.2	1.05	4	11.0	1.25	4	10.1	0.79	4
	26	10.9	1.73	4	11.0	1.14	4	10.7	1.26	4	9.7	0.83	4
	28	11.4	1.78	4	11.4	1.25	4	11.1	1.29	4	10.4	0.86	4
	30	11.4	1.68	4	11.6	1.22	4	11.3	1.17	4	10.4	0.89	4
	32	11.4	1.99	4	11.7	1.22	4	11.4	1.31	4	10.8	0.96	4
	34	11.3	1.85	4	11.6	1.14	4	11.3	1.30	4	10.7	1.15	4
	36	11.3	1.86	4	11.7	1.16	4	11.3	1.30	4	10.5	1.12	4
	38	11.2	1.77	4	11.5	1.28	4	11.1	1.24	4	10.7	1.08	4
	40	11.4	1.85	4	11.7	1.28	4	11.2	1.15	4	10.7	0.97	4
	42	11.4	1.75	4	11.8	1.26	4	11.2	1.32	4	10.6	0.97	4
	44	11.6	1.96	4	11.9	1.40	4	11.4	1.25	4	10.9	1.25	4
	46	11.6	1.74	4	12.0	1.29	4	11.4	1.13	4	11.0	1.16	4
	48	11.4	1.68	4	11.7	1.25	4	11.2	1.10	4	10.9	1.08	4
	50	11.4	1.73	4	11.7	1.21	4	11.2	1.16	4	10.9	0.91	4
	52	11.4	1.81	4	11.6	1.26	4	11.1	1.39	4	10.9	1.19	4

555-021

B.

Females: Summary of Body Weight Values*

Parameters Measured	Week of Study	0 mg/kg/day (Control)			30 mg/kg/day			100 mg/kg/day			400 mg/kg/day		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Body Weight	Pretest	7.2	0.75	4	6.9	1.07	4	6.8	0.72	4	7.0	1.28	4
Kilograms	1	7.2	0.98	4	7.1	1.07	4	7.1	0.49	4	6.5	1.31	4
	2	7.6	1.04	4	7.2	1.10	4	7.3	0.50	4	6.6	1.08	4
	3	7.5	0.99	4	7.3	1.23	4	7.2	0.49	4	6.5	1.17	4
	4	7.8	1.01	4	7.6	1.35	4	7.6	0.48	4	6.7	1.18	4
	5	7.9	1.07	4	7.8	1.44	4	7.7	0.46	4	6.8	1.29	4
	6	8.0	1.07	4	7.9	1.48	4	7.8	0.56	4	7.0	1.25	4
	7	8.0	0.93	4	8.1	1.52	4	7.9	0.50	4	7.0	1.07	4
	8	8.2	0.99	4	8.1	1.66	4	8.0	0.49	4	7.1	1.23	4
	9	8.4	0.99	4	8.2	1.61	4	8.0	0.36	4	7.4	1.47	4
	10	8.4	1.08	4	8.3	1.71	4	8.3	0.50	4	7.4	1.51	4
	11	8.4	1.17	4	8.3	1.72	4	8.3	0.41	4	7.3	1.26	4
	12	8.3	1.27	4	8.3	1.74	4	8.3	0.47	4	7.2	1.23	4
	13	8.4	1.26	4	8.2	1.74	4	8.2	0.38	4	7.3	1.44	4
	14	8.6	1.26	4	8.5	1.78	4	8.4	0.39	4	7.5	1.33	4
	16	8.6	1.48	4	8.4	1.90	4	8.5	0.37	4	7.4	1.36	4
	18	9.1	1.35	4	8.7	1.79	4	8.8	0.39	4	7.7	1.28	4
	20	8.9	1.54	4	8.5	1.89	4	8.6	0.24	4	7.6	1.29	4
	22	9.0	1.43	4	8.5	1.86	4	8.7	0.40	4	7.7	1.19	4
	24	9.1	1.42	4	8.7	1.85	4	8.9	0.30	4	7.8	1.40	4
	26	8.7	1.30	4	8.5	1.78	4	8.8	0.53	4	7.7	1.47	4
	28	9.1	1.08	4	8.9	1.97	4	8.8	0.44	4	7.7	1.46	4
	30	9.2	1.08	4	8.9	1.81	4	9.1	0.47	4	8.0	1.42	4
	32	9.2	1.12	4	8.8	1.77	4	9.0	0.74	4	8.2	1.51	4
	34	9.2	1.38	4	8.5	1.72	4	8.8	0.44	4	8.1	1.49	4
	36	9.1	1.26	4	8.7	1.87	4	8.7	0.68	4	8.1	1.50	4
	38	9.0	1.18	4	8.6	2.07	4	8.6	0.72	4	8.1	1.53	4
	40	9.1	1.24	4	8.9	2.02	4	8.8	0.67	4	8.3	1.66	4
	42	9.4	1.41	4	8.9	1.94	4	8.8	0.51	4	8.4	1.66	4
	44	9.5	1.56	4	9.0	1.87	4	8.9	0.47	4	8.7	1.54	4
	46	9.5	1.44	4	9.0	1.92	4	9.0	0.61	4	8.9	1.46	4
	48	9.3	1.49	4	8.9	1.95	4	8.9	0.48	4	8.7	1.44	4
	50	9.4	1.36	4	9.0	2.83	4	9.0	0.45	4	8.7	1.68	4
	52	9.3	1.29	4	8.7	1.98	4	8.9	0.58	4	8.7	1.58	4

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S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

+Data excerpted from the report; p. 51-54 (NR10 No. 43320101).

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TABLE 2*

Dosage Level mg/kg/day	Mean Body Weights, kg (% Difference from Pretest)				
	Male				
	Pretest	Week 13	Week 26	Week 40	Week 52
0 (Control)	8.3	10.4 (+25.3)	10.9 (+31.3)	11.4 (+37.3)	11.4 (+37.3)
30	8.5	10.5 (+23.5)	11.0 (+29.4)	11.7 (+37.6)	11.6 (+36.5)
100	8.5	10.2 (+20.0)	10.7 (+25.9)	11.2 (+31.8)	11.1 (+30.6)
400	8.5	9.2 (+8.2)	9.7 (+14.1)	10.7 (+25.9)	10.9 (+28.2)
	Female				
	Pretest	Week 13	Week 26	Week 40	Week 52
0 (Control)	7.2	8.4 (+16.7)	8.7 (+20.8)	9.1 (+26.4)	9.3 (+29.2)
30	6.9	8.2 (+18.8)	8.5 (+23.2)	8.9 (+29.0)	8.7 (+26.1)
100	6.8	8.2 (+20.6)	8.8 (+29.4)	8.8 (+29.4)	8.9 (+30.9)
400	7.0	7.3 (+4.3)	7.7 (+10.0)	8.3 (+18.6)	8.7 (+24.3)

*;Data excerpted from the report; p. 22. (NRID No. 43320101).

TABLE 3⁺

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Males: Summary of Food Consumption Values

Parameters Measured	Week of Study	0 mg/kg/day (Control)			30 mg/kg/day			100 mg/kg/day			400 mg/kg/day		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Food Consumption g/animal/day	1	280	62.0	4	301	38.0	4	298	54.7	4	161 ²	17.1	4
	2	320	46.6	4	305	38.1	4	295	31.7	4	227 ¹	38.8	4
	3	290	38.2	4	310	50.6	4	304	32.6	4	217 ¹	13.5	4
	4	337	43.1	4	339	21.6	4	301	52.7	4	275	49.9	4
	5	332	58.7	4	328	43.5	4	331	62.5	4	260	33.6	4
	6	327	57.9	4	341	35.3	4	323	39.3	4	301	64.8	4
	7	318	76.6	4	330	52.4	4	317	58.6	4	294	35.7	3
	8	327	53.9	4	361	43.8	4	340	53.2	4	288	20.7	4
	9	360	65.5	4	343	31.1	4	334	28.8	4	323	64.2	4
	10	330	40.6	4	354	41.5	4	306	41.9	4	351	35.2	4
	11	327	66.7	4	318	56.7	4	305	36.2	4	314	29.8	4
	12	329	70.7	4	344	47.0	4	312	33.1	4	297	69.0	4
	13	306	57.0	4	308	70.2	4	295	59.5	4	302	46.7	4
	14	317	57.3	4	344	79.8	4	321	49.7	4	350	39.5	4
	16	327	65.6	4	318	24.8	4	312	32.1	4	318	45.6	4
	18	349	68.4	4	362	50.7	4	342	71.0	4	330	68.9	4
	20	334	71.7	4	330	65.6	4	317	72.7	4	320	41.3	4
	22	322	47.1	4	331	53.3	4	320	70.2	4	319	27.9	4
	24	312	66.6	4	287	35.0	4	335	88.0	4	307	78.0	4
	26	304	72.8	4	309	64.0	4	288	46.7	4	344	65.1	4
	28	313	53.8	4	313	71.6	4	284	40.5	4	339	32.6	4
	30	295	36.6	4	328	37.7	4	310	36.2	4	328	56.5	4
	32	321	83.1	4	339	51.7	4	296	14.4	4	361	65.3	4
	34	341	70.6	4	332	52.6	4	325	42.6	4	348	43.9	4
	36	318	46.8	4	318	45.4	4	314	24.1	4	299	38.1	4
	38	319	57.8	4	324	41.0	4	299	32.2	4	331	15.1	4
	40	313	60.8	4	337	62.9	4	278	15.0	4	296	32.9	4
	42	331	68.7	4	346	68.2	4	320	21.5	4	332	43.0	4
	44	309	64.5	4	308	46.8	4	314	29.8	4	317	25.6	4
	46	334	68.8	4	353	45.7	4	309	23.3	4	311	24.9	4
	48	306	58.1	4	330	36.2	4	311	31.4	4	287	22.9	4
	50	349	62.4	4	341	57.2	4	327	9.2	4	351	20.7	4
	52	320	68.3	4	315	66.8	4	271	27.0	4	316	37.3	4

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Females: Summary of Food Consumption Values

Parameters Measured	Week of Study	0 mg/kg/day (Control)			30 mg/kg/day			100 mg/kg/day			400 mg/kg/day		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Food Consumption g/animal/day	1	256	22.2	4	257	49.7	4	244	32.6	4	186	38.5	4
	2	274	32.6	4	241	47.1	4	246	13.7	4	197 ¹	24.2	4
	3	276	43.5	4	266	53.3	4	234	27.1	4	224	44.7	4
	4	281	37.2	4	262	49.0	4	257	18.6	4	267	71.1	4
	5	285	29.5	4	280	59.5	4	250	19.1	4	259	71.2	4
	6	286	47.3	4	262	51.9	4	309	63.1	4	258	54.2	4
	7	259	38.5	4	255	48.0	4	236	7.6	4	216	39.9	4
	8	287	24.5	4	277	67.6	4	261	9.8	4	274	37.1	4
	9	291	33.9	4	293	61.8	4	265	22.3	4	285	58.8	4
	10	301	27.6	4	271	71.7	4	267	19.5	4	290	98.5	4
	11	279	43.2	4	243	43.1	4	250	36.6	4	247	25.0	4
	12	288	24.8	4	256	49.7	4	246	17.7	4	242	31.1	4
	13	269	55.6	4	208	42.3	4	229	27.5	4	263	45.1	4
	14	295	65.9	4	205	100.4	4	255	25.2	4	274	43.2	4
	16	298	38.7	4	254	72.5	4	275	58.6	4	263	53.9	4
	18	313	60.0	4	286	81.7	4	286	48.3	4	282	39.1	4
	20	276	51.9	4	238	61.6	4	238	32.1	4	287	49.8	4
	22	290	52.5	4	238	38.9	4	229	15.0	4	241	49.3	4
	24	292	49.2	4	212	48.1	4	286	153.2	4	308	144.0	4
	26	251	90.8	4	255	54.3	4	223	71.6	4	291	113.9	4
	28	250	53.1	4	235	46.8	4	267	49.8	4	315	133.4	4
	30	297	62.2	4	263	39.8	4	245	69.3	4	289	37.8	4
	32	315	73.3	4	224	35.6	4	226	74.4	4	327	108.3	4
	34	267	42.6	4	221	58.5	4	234	58.0	4	282	52.3	4
	36	302	37.1	4	227	77.1	4	230	52.1	4	267	26.5	4
	38	273	31.9	4	243	75.8	4	209	52.5	4	283	43.0	4
	40	288	61.5	4	249	46.6	4	228	39.7	4	263	46.9	4
	42	303	41.6	4	272	38.7	4	232	52.5	4	295	46.7	4
	44	298	43.7	4	267	40.9	4	242	12.8	4	278	30.6	4
	46	271	28.6	4	267	28.8	4	247	25.5	4	298	58.4	4
	48	286	53.5	4	259	43.4	4	248	17.7	4	283	58.8	4
	50	318	57.4	4	278	42.6	4	267	20.4	4	295	35.0	4
	52	245	96.4	4	228	41.0	4	213	32.2	4	258	51.1	4

S.D. - Standard Deviation

*No statistical significance observed

N - Number of Animals

¹Significantly different from the control group; $p \leq 0.05$ ²Significantly different from the control group; $p \leq 0.01$

+: Data excerpted from the report; p. 55-58 (NRID No. 43320101).

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TABLE 4⁺

Males: Summary of Hematological Values*

Parameter Measured	Measurement Interval	0 mg/kg/day (Control)			30 mg/kg/day			100 mg/kg/day			400 mg/kg/day		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Leukocytes x10 ⁶ /cumm	Pretest	11.2	2.41	4	11.5	3.51	4	12.0	1.85	4	11.8	2.93	4
	6 Month	9.9	1.27	4	8.8	1.06	4	10.1	1.71	4	11.4	0.56	4
	Terminal	9.0	1.89	4	8.8	0.81	4	10.0	1.64	4	11.2	1.23	4
Erythrocytes x10 ⁶ /cumm	Pretest	6.04	0.444	4	6.20	0.366	4	5.98	0.743	4	6.00	0.396	4
	6 Month	6.97	1.028	4	6.56	0.444	4	6.74	0.473	4	6.17	0.671	4
	Terminal	7.05	0.681	4	6.90	0.937	4	6.53	0.607	4	6.03	0.462	4
Hemoglobin g/dl	Pretest	13.9	0.94	4	13.9	0.53	4	13.9	1.30	4	13.9	0.98	4
	6 Month	16.1	1.86	4	15.1	0.74	4	15.8	0.72	4	14.5	1.34	4
	Terminal	16.5	1.15	4	15.9	1.79	4	15.6	0.92	4	14.6	1.15	4
Hematocrit %	Pretest	40.3	3.14	4	40.6	2.09	4	40.2	4.08	4	40.6	2.47	4
	6 Month	48.1	6.65	4	45.0	2.01	4	46.7	1.90	4	42.9	4.51	4
	Terminal	47.1	3.97	4	45.7	6.08	4	44.0	2.53	4	40.8	3.98	4
MCV microns ³	Pretest	66.7	0.52	4	65.5	0.71	4	67.3	2.14	4	67.7	1.47	4
	6 Month	69.1	1.18	4	68.7	1.64	4	69.4	3.38	4	69.5	1.22	4
	Terminal	66.9	1.06	4	66.3	1.35	4	67.6	3.45	4	67.5	1.75	4
MCH Picograms	Pretest	22.9	0.35	4	22.4	0.53	4	23.4	0.97	4	23.2	0.43	4
	6 Month	23.2	0.78	4	23.1	0.60	4	23.4	1.10	4	23.5	0.72	4
	Terminal	23.5	0.67	4	23.0	0.64	4	24.0	0.95	4	24.2	0.90	4
MCHC %	Pretest	34.4	0.58	4	34.2	0.59	4	34.7	0.63	4	34.3	0.37	4
	6 Month	33.6	0.92	4	33.6	0.40	4	33.8	0.42	4	33.7	0.59	4
	Terminal	35.1	0.65	4	34.8	0.76	4	35.6	0.49	4	35.8	1.20	4
Platelets x10 ³ /cmm	Pretest	387	62.7	4	445	82.1	4	390	85.1	4	361	67.2	4
	6 Month	283	49.4	4	286	37.8	4	302	41.0	4	355	45.9	4
	Terminal	300	40.2	4	284	32.2	4	313	42.4	4	330	54.7	4

Females: Summary of Hematological Values

Parameters Measured	Measurement Interval	0 mg/kg/day (Control)			30 mg/kg/day			100 mg/kg/day			400 mg/kg/day		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Leukocytes x10 ⁶ /cumm	Pretest	11.4	1.47	4	11.1	3.76	4	10.2	1.76	4	11.0	2.77	4
	6 Month	9.8	1.10	4	11.7	2.41	4	9.5	1.37	4	8.7	0.85	4
	Terminal	10.9	1.14	4	8.8	1.51	4	8.4	0.90	4	10.8	2.44	4
Erythrocytes x10 ⁶ /cumm	Pretest	6.23	0.193	4	6.50	0.414	4	6.30	0.305	4	6.28	0.526	4
	6 Month	6.38	0.404	4	6.53	0.435	4	6.81	0.855	4	5.96	0.239	4
	Terminal	6.45	0.175	4	6.71	0.614	4	7.00	1.117	4	5.40	0.546	4
Hemoglobin g/dl	Pretest	14.4	0.30	4	14.8	0.69	4	13.8	0.79	4	13.7	1.25	4
	6 Month	15.6	0.57	4	15.2	0.64	4	15.8	1.77	4	13.7 ²	0.17	4
	Terminal	15.8	0.79	4	15.7	1.12	4	16.2	2.30	4	13.1	1.33	4
Hematocrit %	Pretest	41.8	1.80	4	43.3	1.79	4	41.4	1.44	4	40.6	3.99	4
	6 Month	44.8	1.56	4	45.4	2.60	4	46.5	5.55	4	39.7	1.11	4
	Terminal	43.9	2.20	4	44.4	3.13	4	46.5	7.47	4	34.7 ¹	3.77	4
MCV microns ³	Pretest	67.1	1.69	4	66.7	1.78	4	65.7	1.32	4	64.5	1.80	4
	6 Month	70.3	2.47	4	69.5	2.26	4	68.4	1.23	4	66.7	0.93	4
	Terminal	68.1	2.62	4	66.3	2.27	4	66.4	0.80	4	64.2	1.28	4
MCH Picograms	Pretest	23.1	0.66	4	22.8	0.48	4	22.0	0.60	4	21.8 ¹	0.48	4
	6 Month	24.4	0.91	4	23.3	1.01	4	23.3	0.57	4	23.0	0.75	4
	Terminal	24.4	1.21	4	23.4	0.71	4	23.2	0.44	4	24.2	0.68	4
MCHC %	Pretest	34.5	0.93	4	34.2	0.32	4	33.4	0.88	4	33.9	0.31	4
	6 Month	34.7	0.41	4	33.6	0.91	4	34.1	1.14	4	34.5	0.68	4
	Terminal	35.9	0.77	4	35.3	0.37	4	34.9	0.74	4	37.8	1.09	4
Platelets x10 ³ /cmm	Pretest	351	63.0	4	369	122.5	4	453	45.9	4	431	101.7	4
	6 Month	297	60.1	4	301	74.0	4	315	24.2	4	446 ²	71.3	4
	Terminal	263	58.9	4	286	67.2	4	322	29.3	4	449 ²	56.2	4

555-021

S.D. - Standard Deviation
N - Number of Animals¹Significantly different from the control group; p<0.05²Significantly different from the control group; p<0.01

+: Data excerpted from the report; p. 57-66 (NRID No. 43320101).

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TABLE 5a⁺

Males: Summary of Biochemical Values

Parameters Measured	Measurement Interval	0 mg/kg/day (Control)			30 mg/kg/day			100 mg/kg/day			400 mg/kg/day		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Sodium mEq/l	Pretest	144	0.6	4	144	0.6	4	143	0.5	4	143	1.0	4
	6 Month	149	3.7	4	149	1.3	4	148	3.1	4	147	2.0	4
	Terminal	152	1.9	3	153	3.8	4	150	1.4	4	154	3.0	4
Potassium mEq/l	Pretest	4.9	0.15	4	4.8	0.21	4	4.8	0.17	4	4.8 ¹	0.17	4
	6 Month	4.7	0.32	4	4.5	0.25	4	4.6	0.26	4	5.8 ¹	0.98	4
	Terminal	4.5	0.18	3	4.5	0.19	4	4.6	0.50	4	4.3	0.15	4
Chloride mEq/l	Pretest	113	1.3	4	110	1.9	4	110	1.0	4	113	2.2	4
	6 Month	118	2.7	4	118	0.6	4	117	1.7	4	118	3.1	4
	Terminal	122	2.0	3	122	2.8	4	120	1.7	4	121	3.4	4
Calcium mg/dl	Pretest	11.4	0.28	4	11.7	0.34	4	11.3	0.30	4	11.5	0.24	4
	6 Month	11.2	0.43	4	11.1	0.19	4	10.9 ¹	0.28	4	10.9	0.24	4
	Terminal	10.5	0.15	4	10.6	0.39	4	10.0 ¹	0.15	4	10.1	0.21	4
Phosphorus mg/dl	Pretest	7.1	0.51	4	7.0	0.50	4	7.5	0.75	4	7.0	0.64	4
	6 Month	4.4	0.81	4	4.7	0.31	4	4.5	0.79	4	4.7	0.61	4
	Terminal	3.7	0.17	4	4.0	0.16	4	4.6	0.41	4	4.1	0.95	4
Alkaline Phosphatase U/L	Pretest	140	39.3	4	129	10.5	4	114	24.1	4	141 ¹	24.9	4
	6 Month	78	27.0	4	54	14.5	4	64	16.8	4	116 ¹	12.0	4
	Terminal	131	82.1	4	55	14.6	4	64	15.5	4	129	9.6	4
Creatinine mg/dl	Pretest	0.7	0.08	4	0.7	0.00	4	0.7	0.05	4	0.7	0.05	4
	6 Month	0.9	0.10	4	1.0	0.06	4	1.0	0.16	4	0.9	0.14	4
	Terminal	1.0	0.05	4	1.0	0.05	4	1.0	0.08	4	1.0	0.17	4
Total Protein g/dl	Pretest	7.7	0.51	4	8.0	0.68	4	7.3	1.85	4	6.1	1.07	4
	6 Month	6.2	0.45	4	6.0	0.15	4	6.0	0.17	4	6.0	0.37	4
	Terminal	6.6	0.21	4	6.3	0.60	4	6.2	0.22	4	6.0	0.51	4
Albumin g/dl	Pretest	2.8	0.10	4	2.8	0.10	4	2.8	0.13	4	2.9	0.24	4
	6 Month	3.0	0.25	4	2.9	0.05	4	2.8	0.13	4	3.0	0.21	4
	Terminal	3.1	0.10	4	3.1	0.10	4	2.9	0.15	4	3.1	0.17	4
Globulin g/dl	Pretest	5.0	0.51	4	5.3	0.78	4	4.5	1.83	4	3.2	0.97	4
	6 Month	3.2	0.22	4	3.1	0.19	4	3.2	0.18	4	3.1	0.31	4
	Terminal	3.4	0.15	4	3.2	0.60	4	3.3	0.26	4	3.0	0.47	4
Cholesterol mg/dl	Pretest	211	47.3	4	218	17.2	4	186	24.9	4	203 ²	32.5	4
	6 Month	176	26.3	4	166	13.0	4	138	24.5	4	118 ²	15.4	4
	Terminal	172	31.9	4	149	22.2	4	125	29.2	4	112 ²	22.0	4
Glucose mg/dl	Pretest	112	3.4	4	114	8.7	4	111	6.6	4	117	9.0	4
	6 Month	104	12.4	4	109	6.8	4	111	7.9	4	104	9.1	4
	Terminal	94	6.8	4	96	9.9	4	93	10.6	4	96	16.4	4

555-021

S.D. - Standard Deviation
N - Number of Animals¹Significantly different from the control group; $p \leq 0.05$ ²Significantly different from the control group; $p \leq 0.01$

+: Data excerpted from the report; p. 67-69 (NRID No. 43320101).

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TABLE 56*

Females: Summary of Biochemical Values*

Parameters Measured	Measurement Interval	0 mg/kg/day (Control)			30 mg/kg/day			100 mg/kg/day			400 mg/kg/day		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Sodium mEq/l	Pretest	148	1.0	4	149	2.6	4	147	1.3	4	148	2.4	4
	6 Month	149	2.3	4	149	1.6	4	148	1.2	4	148	1.3	4
	Terminal	152	1.5	3	154	2.5	4	152	1.7	4	153	2.1	4
Potassium mEq/l	Pretest	4.9	0.17	4	4.7	0.22	4	4.9	0.29	4	4.6	0.15	4
	6 Month	4.4	0.37	4	4.5	0.25	4	4.7	0.38	4	4.8	0.19	4
	Terminal	4.4	0.32	3	4.3	0.43	4	4.5	0.28	4	4.5	0.19	4
Chloride mEq/l	Pretest	114	0.5	4	116	2.4	4	114	2.5	4	116	0.8	4
	6 Month	119	4.0	4	117	1.7	4	116	3.1	4	118	0.6	4
	Terminal	121	2.9	3	123	3.0	4	120	2.8	4	122	1.7	4
Calcium mg/dl	Pretest	11.3	0.28	4	11.1	0.19	4	10.9	0.10	4	11.0	0.31	4
	6 Month	11.3	0.26	4	11.0	0.44	4	11.1	0.53	4	10.8	0.33	4
	Terminal	10.4	0.41	4	10.4	0.46	4	10.2	0.40	4	10.2	0.13	4
Phosphorus mg/dl	Pretest	6.9	0.56	4	6.6	0.60	4	7.0	0.42	4	6.6	0.52	4
	6 Month	4.3	0.18	4	4.5	0.87	4	4.4	0.23	4	4.4	0.78	4
	Terminal	4.1	0.20	4	4.1	0.43	4	4.1	0.28	4	4.3	0.44	4
Alkaline Phosphatase U/L	Pretest	140	28.0	4	123	19.2	4	143	26.3	4	115	17.1	4
	6 Month	103	43.7	4	61	7.2	4	89	17.4	4	90	24.8	4
	Terminal	117	55.0	4	75	16.8	4	102	29.0	4	133	45.2	4
Creatinine mg/dl	Pretest	0.8	0.06	4	0.7	0.00	4	0.7	0.15	4	0.8	0.05	4
	6 Month	0.9	0.12	4	0.8	0.05	4	1.0	0.14	4	0.9	0.10	4
	Terminal	1.0	0.15	4	0.9	0.05	4	1.0	0.10	4	1.0	0.08	4
Total Protein g/dl	Pretest	7.1	0.35	4	7.0	0.13	4	6.8	0.32	4	6.8	0.44	4
	6 Month	6.1	0.17	4	5.9	0.23	4	5.8	0.17	4	6.0	0.54	4
	Terminal	6.0	0.30	4	6.2	0.29	4	5.8	0.28	4	6.2	0.42	4
Albumin g/dl	Pretest	2.9	0.08	4	3.0	0.14	4	2.8	0.24	4	2.8	0.21	4
	6 Month	3.1	0.13	4	3.1	0.17	4	3.0	0.24	4	3.0	0.19	4
	Terminal	3.1	0.10	4	3.3	0.22	4	3.1	0.19	4	3.0	0.26	4
Globulin g/dl	Pretest	4.2	0.33	4	4.0	0.19	4	4.0	0.13	4	4.0	0.46	4
	6 Month	3.0	0.17	4	2.8	0.13	4	2.9	0.21	4	3.0	0.39	4
	Terminal	2.9	0.37	4	2.9	0.17	4	2.8	0.25	4	3.3	0.24	4
Cholesterol mg/dl	Pretest	205	51.1	4	189	25.1	4	172	28.6	4	191	23.1	4
	6 Month	188	46.9	4	157	15.5	4	160	23.6	4	123	19.6	4
	Terminal	170	52.3	4	132	7.0	4	154	25.6	4	169	36.1	4
Glucose mg/dl	Pretest	116	9.0	4	114	5.0	4	115	7.1	4	118	7.5	4
	6 Month	107	3.4	4	108	9.3	4	109	7.8	4	100	5.4	4
	Terminal	93	10.0	4	98	9.4	4	93	7.5	4	94	8.1	4

555-021

S.D. - Standard Deviation *No statistical significance observed
 N - Number of Animals

+: Data excerpted from the report; p. 70-72 (NRID No. 43320101).

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